Medicines Information Services

Information on drug therapy
Information on any aspect of drug therapy can be obtained from Regional and District Medicines Information Services. Details regarding the local services provided within your Region can be obtained by telephoning the following numbers.

**England**
- Birmingham: (0121) 424 7298
- Bristol: (0117) 342 2867
- Ipswich: (01473) 704 431
- Leeds: (0113) 206 5377
- Leicester: (0116) 258 6491
- Liverpool: (0151) 794 8113/7, or (0151) 794 8118

**London**
- Guy's Hospital: (020) 7188 8750, or (020) 7188 3849, or (020) 7188 3855
- Northwick Park Hospital: (020) 8869 2761, or (020) 8869 3973

**Wales**
- Cardiff: (029) 2074 2979, or (029) 2074 2251

**Scotland**
- Aberdeen: (01224) 552 316
- Dundee: (01382) 632 351, or (01382) 660 111 Extn 32351
- Edinburgh: (0131) 242 2920
- Glasgow: (0141) 211 4407

**Northern Ireland**
- Belfast: (028) 9504 0558

**Republic of Ireland**
- Dublin: (01) 473 0589, or (01) 453 7941 Extn 2348

**Proprietary Manufacturers**
Telephone numbers and email addresses of proprietary manufacturers listed in BNF Publications are shown in the Index of proprietary manufacturers p. 1417

**UK Teratology Information Service**
Information on drug and chemical exposures in pregnancy.
Tel: 0344 892 0909
www.uktis.org

**UK Drugs in Lactation Advisory Service (UKDILAS)**
Information on the compatibility of drugs with breastfeeding.
Tel: (0116) 258 6491, or (0121) 424 7298
www.ukmi.nhs.uk/ukdilas

**Medicines in Dentistry Specialist Advisory Service**
Information on drug therapy relating to dental treatment.
Liverpool: (0151) 794 8206

**Driver and Vehicle Licensing Agency (DVLA)**
Information on the national medical guidelines of fitness to drive is available from:
www.gov.uk/government/publications/at-a-glance

**Patient Information Lines**
NHS Urgent Care Services 111

**Poisons Information Services**
UK National Poisons Information Service 0344 892 0111
www.toxbase.org

**Sport**
- Information regarding the use of medicines in sport is available from UK Anti-Doping:
  - www.ukad.org.uk
  - Tel: (020) 7842 3450
  - ukad@ukad.org.uk

- UK Anti-Doping Fleetbank House
  2-6 Salisbury Square
  London
  EC4Y 8AE
- Information about the prohibited status of specific medicines based on the current World Anti-Doping Agency Prohibited List is available from Global Drug Reference Online: www.globaldro.com/UK/search

**Travel Immunisation**
Up-to-date information on travel immunisation requirements may be obtained from:
- National Travel Health Network and Centre (for healthcare professionals only) 0845 602 6712 Monday – Friday (closed Wednesday afternoons and Bank Holidays): 09:00 – 11:45 and 13:00 – 15:45
- Travel Medicine Team, Health Protection Scotland (0141) 300 1100 (14:00 – 16:00 hours weekdays)
  www.travax.nhs.uk (for registered users of the NHS website Travax only)
- Welsh Government Switchboard English language 0300 0603300 (09.00 – 17.30 hours weekdays only)
- Welsh Government Switchboard Yr iaith Gymraeg 0300 0604400 (09.00 – 17.30 hours weekdays only)
- Department of Health and Social Services (Belfast)
  (028) 9052 2118 (weekdays)

**List of Registered Medical Practitioners**
Details on whether doctors are registered and hold a licence to practise medicine in the UK can be obtained from the General Medical Council.
Tel: (0161) 923 6602
www.gmc-uk.org/register
Access the BNF your way

The British National Formulary (BNF) and BNF for Children are updated monthly online via MedicinesComplete, ensuring healthcare professionals always have the latest prescribing advice.

**ONLINE**

**BNF on MedicinesComplete**  
Access BNF and BNF for Children on MedicinesComplete and receive the very latest drug information through monthly online updates.

**FormularyComplete**  
Create, edit and manage your own local formulary content built upon the trusted prescribing advice of the BNF and BNF for Children.

**BNF on Evidence Search**  
Search the BNF and BNF for Children alongside other authoritative clinical and non-clinical evidence and best practice at http://evidence.nhs.uk from NICE.

**PRINT**

Eligible health professionals will now receive one print copy a year – the September issue – to supplement online access. If you are entitled to an NHS copy please refer to page ii for full details on distribution, call 01268 495 609 or email bnf@binleys.com.
How to purchase

Buy direct from Pharmaceutical Press by visiting
www.pharmpress.com/bnf

For enquiries about the BNF or BNFC in print, contact
direct@macmillan.co.uk
Tel: +44 (0) 1256 302 699

For enquiries concerning MedicinesComplete,
FormularyComplete, or bulk orders of the print edition, contact
pharmpress-support@rpharms.com
Tel: +44 (0) 20 7572 2266

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Available for iOS, Android and Blackberry

For pricing information please visit the website at
www.pharmpress.com/bnf

For international sales contact your local sales agent.
Contact details at www.pharmpress.com/agents

Stay up to date – sign up to the BNF eNewsletter at www.bnf.org/newsletter
In Wales, contact NHS Wales Shared Services Partnership—Contractor Services:
Tel: 01792 607420
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ni.bnf@hscni.net

About BNF content
The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. **BNF for Children** should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from Medicines Information Services.

Please refer to digital versions of BNF for the most up-to-date content. BNF is published in print but interim updates are issued and published in the digital versions of BNF. The publishers work to ensure that the information is as accurate and up-to-date as possible at the date of publication, but knowledge and best practice in this field change regularly. BNF’s accuracy and currency cannot be guaranteed and neither the publishers nor the authors accept any responsibility for errors or omissions. While considerable efforts have been made to check the material in this publication, it should be treated as a guide only. Prescribers, pharmacists and other healthcare professionals are advised to check [www.bnf.org](http://www.bnf.org) for information about key updates and corrections.

Pharmaid
Numerous requests have been received from lower income countries for BNFs. The Pharmaid scheme of the Commonwealth Pharmacists Association will dispatch old BNFs to certain Commonwealth countries. For more information on this scheme see [http://commonwealthpharmacy.org/what-we-do/pharmaid/](http://commonwealthpharmacy.org/what-we-do/pharmaid/). If you would like to donate your copy email: admin@commonwealthpharmacy.org

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**BNF**

In England, NICE purchases print editions of the BNF (September editions only) for distribution within the NHS. For details of who is eligible to receive a copy and further contact details, please refer to the NICE website: [www.nice.org.uk/mpc/BritishNationalFormulary.jsp](http://www.nice.org.uk/mpc/BritishNationalFormulary.jsp). If you are entitled to an NHS copy of BNF, please call (0) 1268 495 609 or email: bnf@binleys.com.

In Scotland, email:
nss.psd-bnf@nhs.net
The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society. It is published under the authority of a Joint Formulary Committee which comprises representatives of the two professional bodies, the UK Health Departments, the Medicines and Healthcare products Regulatory Agency, and a national guideline producer. The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the Group includes representatives of the British Dental Association and a representative from the UK Health Departments. The Nurse Prescribers’ Advisory Group advises on the content relevant to nurses and includes representatives from different parts of the nursing community and from the UK Health Departments.

The BNF aims to provide prescribers, pharmacists, and other healthcare professionals with sound up-to-date information about the use of medicines.

The BNF includes key information on the selection, prescribing, dispensing and administration of medicines. Medicines generally prescribed in the UK are covered and those considered less suitable for prescribing are clearly identified. Little or no information is included on medicines promoted for purchase by the public.

Information on drugs is drawn from the manufacturers’ product literature, medical and pharmaceutical literature, UK health departments, regulatory authorities, and professional bodies. Advice is constructed from clinical literature and reflects, as far as possible, an evaluation of the evidence from diverse sources. The BNF also takes account of authoritative national guidelines and emerging safety concerns. In addition, the editorial team receives advice on all therapeutic areas from expert clinicians; this ensures that the BNF’s recommendations are relevant to practice.

The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. BNF for Children should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services, see Medicines Information Services (see inside front cover).

It is important to use the most recent BNF information for making clinical decisions. The print edition of the BNF is updated in March and September each year. Monthly updates are provided online via Medicines Complete and the NHS Evidence portal. The more important changes are listed under Changes; changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies.

The BNF Publications website (www.bnf.org) includes additional information of relevance to healthcare professionals. Other digital formats of the BNF—including versions for mobile devices and integration into local formularies—are also available.

BNF Publications welcomes comments from healthcare professionals. Comments and constructive criticism should be sent to:

British National Formulary,
Royal Pharmaceutical Society,
66–68 East Smithfield
London
E1W 1AW
editor@bnf.org

The contact email for manufacturers or pharmaceutical companies wishing to contact BNF Publications is manufacturerinfo@bnf.org
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The British Dental Association has contributed to the advice on medicines for dental practice through its representatives on the Dental Advisory Group.
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How BNF Publications are constructed

Overview

The BNF is an independent professional publication that addresses the day-to-day prescribing information needs of healthcare professionals. Use of this resource throughout the health service helps to ensure that medicines are used safely, effectively, and appropriately.

Hundreds of changes are made between print editions, and are published monthly in a number of digital formats. The most clinically significant updates are listed under Changes p. xix.

The BNF is unique in bringing together authoritative, independent guidance on best practice with clinically validated drug information. Validation of information follows a standardised process, reviewing emerging evidence, best-practice guidelines, and advice from a network of clinical experts. Where the evidence base is weak, further validation is undertaken through a process of peer review. The process and its governance are outlined in greater detail in the sections that follow.

Joint Formulary Committee

The Joint Formulary Committee (JFC) is responsible for the content of the BNF. The JFC includes pharmacy, medical, nursing and lay representatives; there are also representatives from the Medicines and Healthcare products Regulatory Agency (MHRA), the UK Health Departments, and a national guideline producer. The JFC decides on matters of policy and reviews amendments to the BNF in the light of new evidence and expert advice.

Dental Advisory Group

The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the group includes representatives from the British Dental Association and a representative from the UK Health Departments.

Nurse Prescribers’ Advisory Group

The Nurse Prescribers’ Advisory Group oversees the list of drugs approved for inclusion in the Nurse Prescribers’ Formulary; the group includes representatives from a range of nursing disciplines and stakeholder organisations.

Expert advisers

The BNF uses about 60 expert clinical advisers (including doctors, pharmacists, nurses, and dentists) throughout the UK to help with clinical content. The role of these expert advisers is to review existing text and to comment on amendments drafted by the clinical writers. These clinical experts help to ensure that the BNF remains reliable by:

- commenting on the relevance of the text in the context of best clinical practice in the UK;
- checking draft amendments for appropriate interpretation of any new evidence;
- providing expert opinion in areas of controversy or when reliable evidence is lacking;
- providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breast-feeding, children, the elderly, palliative care, and the emergency treatment of poisoning.

In addition to consulting with regular advisers, the BNF calls on other clinical specialists for specific developments when particular expertise is required.

The BNF works closely with a number of expert bodies that produce clinical guidelines. Drafts or pre-publication copies of guidelines are often received for comment and assimilation into the BNF.

Editorial team

BNF clinical writers have all worked as pharmacists or possess a pharmacy degree and a further, relevant postgraduate qualification, and have a sound understanding of how drugs are used in clinical practice. As a team, the clinical writers are responsible for editing, maintaining, and updating BNF content. They follow a systematic prioritisation process in response to updates to the evidence base in order to ensure the most clinically important topics are reviewed as quickly as possible. In parallel the team of clinical writers undertakes a process of rolling revalidation, aiming to review all of the content in the BNF over a 3- to 4-year period.

Amendments to the text are drafted when the clinical writers are satisfied that any new information is reliable and relevant. A set of standard criteria define when content is referred to expert advisers, the Joint Formulary Committee or other advisory groups, or submitted for peer review.

Clinical writers prepare the text for publication and undertake a number of validation checks on the knowledge at various stages of the production process.

Sources of BNF information

The BNF uses a variety of sources for its information; the main ones are shown below.

Summaries of product characteristics

The BNF reviews summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are the principal source of product information and are carefully processed. Such processing involves:

- verifying the approved names of all relevant ingredients including 'non-active' ingredients (the BNF is committed to using approved names and descriptions as laid down by the Human Medicine Regulations 2012);
- comparing the indications, cautions, contra-indications, and side-effects with similar existing drugs. Where these are different from the expected pattern, justification is sought for their inclusion or exclusion;
- seeking independent data on the use of drugs in pregnancy and breast-feeding;
- incorporating the information into the BNF using established criteria for the presentation and inclusion of the data;
- checking interpretation of the information by a second clinical writer before submitting to a content manager; changes relating to doses receive a further check;
- identifying potential clinical problems or omissions and seeking further information from manufacturers or from expert advisers;
- constructing, with the help of expert advisers, a comment on the role of the drug in the context of similar drugs.

Much of this processing is applicable to the following sources as well.

Literature

Clinical writers monitor core medical and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in the BNF and the paper is noted, the new information is assessed for reliability (using tools based on SIGN methodology) and relevance to UK clinical practice. If necessary, new text is drafted and discussed with expert advisers and the Joint Formulary Committee. The BNF enjoys a close working relationship with a number of national information providers.

In addition to the routine process, which is used to identify ‘triggers’ for changing the content, systematic literature searches are used to identify the best quality evidence available to inform an update. Clinical writers receive training in critical appraisal, literature evaluation, and search strategies.
Consensus guidelines
The advice in the BNF is checked against consensus guidelines produced by expert bodies. The quality of the guidelines is assessed using adapted versions of the AGREE II tool. A number of bodies make drafts or pre-publication copies of the guidelines available to the BNF; it is therefore possible to ensure that a consistent message is disseminated. The BNF routinely processes guidelines from the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

Reference sources
Textbooks and reference sources are used to provide background information for the review of existing text or for the construction of new text. The BNF team works closely with the editorial team that produces Martindale: The Complete Drug Reference. The BNF has access to Martindale information resources and each team keeps the other informed of significant developments and shifts in the trends of drug usage.

Peer review
Although every effort is made to identify the most robust data available, inevitably there are areas where the evidence base is weak or contradictory. While the BNF has the valuable support of expert advisers and the Joint Formulary Committee, the recommendations made may be subject to a further level of scrutiny through peer review to ensure they reflect best practice.

Content for peer review is posted on bnf.org and interested parties are notified via a number of channels, including the BNF e-newsletter.

Statutory information
The BNF routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescriptions only Medicines Order. Official compendia such as the British Pharmacopoeia and its addenda are processed routinely to ensure that the BNF complies with the relevant sections of the Human Medicines Regulations 2012.

The BNF maintains close links with the Home Office (in relation to controlled drug regulations) and the Medicines and Healthcare products Regulatory Agency (including the British Pharmacopoeia Commission). Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug are issued by the UK health departments are processed as a matter of routine.

Relevant professional statements issued by the Royal Pharmaceutical Society are included in the BNF as are guidelines from bodies such as the Royal College of General Practitioners.

Medicines and devices
NHS Prescription Services (from the NHS Business Services Authority) provides non-clinical, categorical information (including prices) on the medicines and devices included in the BNF.

Comments from readers
Readers of the BNF are invited to send in comments. Numerous letters and emails are received by the BNF team. Such feedback helps to ensure that the BNF provides practical and clinically relevant information. Many changes in the presentation and scope of the BNF have resulted from comments sent in by users.

Comments from industry
Close scrutiny of BNF by the manufacturers provides an additional check and allows them an opportunity to raise issues about BNF’s presentation of the role of various drugs; this is yet another check on the balance of BNF’s advice. All comments are looked at with care and, where necessary, additional information and expert advice are sought.

Market research
Market research is conducted at regular intervals to gather feedback on specific areas of development.

Assessing the evidence
From January 2016, recommendations made in BNF publications have been evidence graded to reflect the strength of the recommendation. The addition of evidence grading is to support clinical decision making based on the best available evidence.

The BNF aims to revalidate all content over a rolling 3- to 4-year period and evidence grading will be applied to recommendations as content goes through the revalidation process. Therefore, initially, only a small number of recommendations will have been graded.

Grading system
The BNF has adopted a five level grading system from A to E, based on the former SIGN grading system. This grade is displayed next to the recommendation within the text.

Evidence used to make a recommendation is assessed for validity using standardised methodology tools based on AGREE II and assigned a level of evidence. The recommendation is then given a grade that is extrapolated from the level of evidence, and an assessment of the body of evidence and its applicability.

Evidence assigned a level 1- or 2- score has an unacceptable level of bias or confounding and is not used to form recommendations.

Levels of evidence
• **Level 1++**
  High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.

• **Level 1+**
  Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.

• **Level 1-**
  Meta-analyses, systematic reviews, or RCTs with a high risk of bias.

• **Level 2++**
  High quality systematic reviews of case control or cohort studies; or high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.

• **Level 2+**
  Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.

• **Level 2-**
  Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.

• **Level 3**
  Non-analytic studies, e.g. case reports, case series.

• **Level 4**
  Expert advice or clinical experience from respected authorities.

Grades of recommendation
• **Grade A:** High strength
  NICE-accredited guidelines; or guidelines that pass AGREE II assessment; or at least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
- **Grade B: Moderate strength**
  A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.

- **Grade C: Low strength**
  A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++.

- **Grade D: Very low strength**
  Evidence level 3; or extrapolated evidence from studies rated as 2+; or tertiary reference source created by a transparent, defined methodology, where the basis for recommendation is clear.

- **Grade E: Practice point**
  Evidence level 4.
How to use BNF Publications in print

How to use the BNF

This edition of the BNF continues to display the fundamental change to the structure of the content that was first shown in BNF 70. The changes were made to bring consistency and clarity to BNF content, and to the way that the content is arranged within print and digital products, increasing the ease with which information can be found. For reference, the most notable changes to the structure of the content include:

- Drug monographs – where possible, all information that relates to a single drug is contained within its drug monograph, moving information previously contained in the prescribing notes. Drug monographs have also changed structurally: additional sections have been added, ensuring greater regularity around where information is located within the publication.
- Drug class monographs – where substantial amounts of information are common to all drugs within a drug class (e.g. macrolides p. 494), a drug class monograph has been created to contain the common information.
- Medicinal forms – categorical information about marketed medicines, such as price and pack size, continues to be sourced directly from the Dictionary of Medicines and Devices provided by the NHS Business Services Authority. However, clinical information curated by the BNF team has been clearly separated from the categorical pricing and pack size information and is included in the relevant section of the drug monograph.
- Section numbering – the BNF section numbering has been removed. This section numbering tied the content to a rigid structure and enforced the retention of defunct classifications, such as mercurial diuretics, and hindered the relocation of drugs where therapeutic use had altered. It also caused constraints between the BNF and BNF for Children, where drugs had different therapeutic uses in children.
- Appendix 4 – the content has been moved to individual drug monographs. The introductory notes have been replaced with a new guidance section, Guidance on intravenous infusions p. 16.

Introduction

In order to achieve the safe, effective, and appropriate use of medicines, healthcare professionals must be able to use the BNF effectively, and keep up to date with significant changes in the BNF that are relevant to their clinical practice. This How to Use the BNF is key in reinforcing the details of the new structure of the BNF to all healthcare professionals involved with prescribing, monitoring, supplying, and administering medicines, as well as supporting the learning of students training to join these professions.

Structure of the BNF

This BNF edition continues to broadly follows the high-level structure of earlier editions of the BNF (i.e. those published before BNF 70):

Front matter, comprising information on how to use the BNF, the significant content changes in each edition, and guidance on various prescribing matters (e.g. prescription writing, the use of intravenous drugs, particular considerations for special patient populations).

Chapters, containing drug monographs describing the uses, doses, safety issues and other considerations involved in the use of drugs; drug class monographs; and treatment summaries, covering guidance on the selection of drugs. Monographs and treatment summaries are divided into chapters based on specific aspects of medical care, such as Chapter 5, Infections, or Chapter 16, Emergency treatment of poisoning; or drug use related to a particular system of the body, such as Chapter 2, Cardiovascular.

Within each chapter, content is organised alphabetically by therapeutic use (e.g. Airways disease, obstructive), with the treatment summaries first, (e.g. asthma), followed by the monographs of the drugs used to manage the conditions discussed in the treatment summary. Within each therapeutic use, the drugs are organised alphabetically by classification (e.g. Antimuscarinics, Beta 2-agonist bronchodilators) and then alphabetically within each classification (e.g. Aclidinium bromide, Glycopyrronium bromide, Ipratropium bromide).

Appendices, covering interactions, borderline substances, cautionary and advisory labels, and woundcare.

Back matter, covering the lists of medicines approved by the NHS for Dental and Nurse Practitioner prescribing, proprietary and specials manufacturers’ contact details, and the index. Yellow cards are also included, to facilitate the reporting of adverse events, as well as quick reference guides for life support and key drug doses in medical emergencies, for ease of access.

Navigating the BNF

The contents page provides the high-level layout of information within the BNF; and in addition, each chapter begins with a small contents section, describing the therapeutic uses covered within that chapter. Once in a chapter, location is guided by the side of the page showing the chapter number (the thumbnail), alongside the chapter title. The top of the page includes the therapeutic use (the running head) alongside the page number.

Once on a page, visual cues aid navigation: treatment summary information is in black type, with therapeutic use titles similarly styled in black, whereas the use of colour indicates drug-related information, including drug classification titles, drug class monographs, and drug monographs.

Although navigation is possible by browsing, primarily access to the information is via the index, which covers the titles of drug class monographs, drug monographs, and treatment summaries. The index also includes the names of branded medicines and other topics of relevance, such as abbreviations, guidance sections, tables, and images.

Content types

Treatment summaries

Treatment summaries are of three main types:

- an overview of delivering a drug to a particular body system (e.g. Skin conditions, management p. 1074)
- a comparison between a group or groups of drugs (e.g. beta-adrenoceptor blockers (systemic) p. 139)
- an overview of the drug management or prophylaxis of common conditions intended to facilitate rapid appraisal of options (e.g. Hypertension p. 132, or Malaria, prophylaxis p. 560).

In order to select safe and effective medicines for individual patients, information in the treatment summaries must be used in conjunction with other prescribing details about the drugs and knowledge of the patient’s medical and drug history.

Monographs

Overview

In earlier editions (i.e. before BNF 70), a systematically administered drug with indications for use in different body systems was split across the chapters relating to those body systems. So, for example, codeine phosphate p. 421 was found in chapter 1, for its antimotility effects and chapter 4 for its analgesic effects. However, the monograph in chapter
1 contained only the dose and some selected safety precautions.

Now, all of the information for the systemic use of a drug is contained within one monograph, so codeine phosphate p. 421 is now included in chapter 4. This carries the advantage of providing all of the information in one place, so the user does not need to flick back and forth across several pages to find all of the relevant information for that drug.

Cross references are included in chapter 4, where the management of diarrhoea is discussed, to the drug monograph to assist navigation.

Where drugs have systemic and local uses, for example, chloramphenicol p. 524, and the considerations around drug use are markedly different according to the route of administration, the monograph is split, as with earlier editions, into the relevant chapters.

This means that the majority of drugs are still placed in the same chapters and sections as earlier editions, and although there may be some variation in order, all of the relevant information will be easier to locate.

One of the most significant changes to the monograph structure is the increased granularity, with a move from around 9 sections to over 20 sections; sections are only included when relevant information has been identified. The following information describes these sections and their uses in more detail.

Nomenclature

Monograph titles follow the convention of recommended international non-proprietary names (rINNs), or, in the absence of a rINN, British Approved Names. Relevant synonyms are included below the title and, in some instances a brief description of the drug action is included. Over future editions these drug action statements will be rolled out for all drugs.

In some monographs, immediately below the nomenclature or drug action, there are a number of cross references or flags used to signpost the user to any additional information they need to consider about a drug.

This is most common for drugs formulated in combinations, where users will be signposted to the monographs for the individual ingredients (e.g. senna with ispaghula husk p. 59) or for drugs that are related to a drug class monograph (see Drug class monographs, below).

Indication and dose

User feedback has highlighted that one of the main uses of the BNF is identifying indications and doses of drugs.

Therefore, indication and dose information has been promoted to the top of the monograph and highlighted by a coloured panel to aid quick reference.

The indication and dose section is more highly structured than in earlier editions, giving greater clarity around which doses should be used for which indications and by which route. In addition, if the dose varies with a specific preparation or formulation, that dosing information has been moved out of the preparations section and in to the indication and dose panel, under a heading of the preparation name.

Doses are either expressed in terms of a definite frequency (e.g. 1 g 4 times daily) or in the total daily dose format (e.g. 6 g daily in 3 divided doses); the total daily dose should be divided into individual doses (in the second example, the patient should receive 2 g 3 times daily).

Doses for specific patient groups (e.g. the elderly) may be included if they are different to the standard dose. Doses for children can be identified by the relevant age range and may vary according to their age or body-weight.

In earlier editions of the BNF, age ranges and weight ranges overlapped. For clarity and to aid selection of the correct dose, wherever possible these age and weight ranges now do not overlap. When interpreting age ranges it is important to understand that a patient is considered to be 64 up until the point of their 65th birthday, meaning that an age range of adult 18 to 64 is applicable to a patient from the day of their 18th birthday until the day before their 65th birthday. All age ranges should be interpreted in this way. Similarly, when interpreting weight ranges, it should be understood that a weight of up to 30 kg is applicable to a patient up to 10 kg, but not including, the point that they tip the scales at 30 kg and a weight range of 35 to 59 kg is applicable to a patient as soon as they tip the scales at 35 kg right up until, but not including, the point that they tip the scales at 60 kg. All weight ranges should be interpreted in this way.

In all circumstances, it is important to consider the patient in question and their physical condition, and select the dose most appropriate for the individual.

Other information relevant to Indication and dose

The dose panel also contains, where known, an indication of pharmacokinetic considerations that may affect the choice of dose, and dose equivalence information, which may aid the selection of dose when switching between drugs or preparations.

The BNF includes unlicensed use of medicines when the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience. When the BNF recommends an unlicensed medicine or the ‘off-label’ use of a licensed medicine, this is shown below the indication and dose panel in the unlicensed use section.

Minimising harm and drug safety

The drug chosen to treat a particular condition should minimise the patient’s susceptibility to adverse effects and, where co-morbidities exist, have minimal detrimental effects on the patient’s other diseases. To achieve this, the Contra-indications, Cautions and Side-effects of the relevant drug should be reviewed.

The information under Cautions can be used to assess the risks of using a drug in a patient who has co-morbidities that are also included in the Cautions for that drug—if a safer alternative cannot be found, the drug may be prescribed while monitoring the patient for adverse-effects or deterioration in the co-morbidity. Contra-indications are far more restrictive than Cautions and mean that the drug should be avoided in a patient with a condition that is contra-indicated.

The impact that potential side-effects may have on a patient’s quality of life should also be assessed. For instance, in a patient who has difficulty sleeping, it may be preferable to avoid a drug that frequently causes insomnia.

Clinically relevant Side-effects for drugs are included in the monographs or class monographs. Side-effects are listed in order of frequency, where known, and arranged alphabetically. The frequency of side-effects follows the regulatory standard:

- Very common — occurs more frequently than 1 in 10 administrations of a drug
- Common — occurs between 1 in 10 and 1 in 100 administrations of a drug
- Uncommon — between 1 in 100 and 1 in 1,000 administrations of a drug
- Rare — between 1 in 1,000 and 1 in 10,000 administrations of a drug
- Very rare — occurs less than 1 in 10,000 administrations of a drug
- Frequency not known

An exhaustive list of side-effects is not included, particularly for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is generally not listed, unless the drug carries an increased risk of such reactions,
Typical layout of a monograph and associated medicinal forms

1. Class Monographs and drug monographs
In most cases, all information that relates to an individual drug is contained in its drug monograph and there is no symbol. Class monographs have been created where substantial amounts of information are common to all drugs within a drug class, these are indicated by a flag symbol in a circle:

Drug monographs with a corresponding class monograph are indicated by a tab with a flag symbol:

The page number of the corresponding class monograph is indicated within the tab. For further information, see How to use BNF Publications

2. Drug classifications
Used to inform users of the class of a drug and to assist in finding other drugs of the same class. May be based on pharmacological class (e.g. opioids) but can also be associated with the use of the drug (e.g. cough suppressants)

3. Review date
The date of last review of the content

4. Specific preparation name
If the dose varies with a specific preparation or formulation it appears under a heading of the preparation name

5. Evidence grading
Evidence grading to reflect the strengths of recommendations will be applied as content goes through the revalidation process. A five level evidence grading system based on the former SIGN grading system has been adopted. The grades A, B, C, D, E are displayed next to the recommendations within the text, and are preceded by the symbol: ✶

For further information, see How BNF Publications are constructed
- **HEPATIC IMPAIRMENT** advice on the use of a drug in hepatic impairment
- **RENAL IMPAIRMENT** advice on the use of a drug in renal impairment
- **PRE-TREATMENT SCREENING** covers one off tests required to assess the suitability of a patient for a particular drug
- **MONITORING REQUIREMENTS** specifies any special monitoring requirements, including information on monitoring the plasma concentration of drugs with a narrow therapeutic index
- **EFFECTS ON LABORATORY TESTS** for drugs that can interfere with the accuracy of seemingly unrelated laboratory tests
- **TREATMENT CESSION** specifies whether further monitoring or precautions are advised when the drug is withdrawn
- **DIRECTIONS FOR ADMINISTRATION** practical information on the preparation of intravenous drug infusions; general advice relevant to other routes of administration
- **PRESCRIBING AND DISPENSING INFORMATION** practical information around how a drug can be prescribed and dispensed including details of when brand prescribing is necessary
- **HANDLING AND STORAGE** includes information on drugs that can cause adverse effects to those who handle them before they are taken by, or administered to, a patient; advice on storage conditions
- **PARENT AND CARER ADVICE** for drugs with a special need for counselling
- **PROFESSION SPECIFIC INFORMATION** provides details of the restrictions certain professions such as dental practitioners or nurse prescribers need to be aware of when prescribing on the NHS
- **NATIONAL FUNDING/ACCESS DECISIONS** details of NICE Technology Appraisals and SMC advice
- **LESS SUITABLE FOR PRESCRIBING** preparations that are considered by the Joint Formulary Committee to be less suitable for prescribing
- **EXCEPTION TO LEGAL CATEGORY** advice and information on drugs which may be sold without a prescription under specific conditions

### Legal categories

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPN</td>
<td>This symbol has been placed against those preparations that are available only on a prescription issued by an appropriate practitioner. For more detailed information see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition)</td>
</tr>
</tbody>
</table>
| CD1 CD2 CD3 CD4-1 CD4-2 CD5 | These symbols indicate that the preparations are subject to the prescription requirements of the Misuse of Drugs Act

For regulations governing prescriptions for such preparations, see Controlled Drugs and Drug Dependence

Not all monographs include all possible sections; sections are only included when relevant information has been identified

### MEDICINAL FORMS

**Form**
- CAUTIONARY AND ADVISORY LABELS if applicable
- EXCIPIENTS clinically important but not comprehensive
- ELECTROLYTES if clinically significant quantities occur

**Preparation name** *(Manufacturer/Non-proprietary)*
- Drug name and strength pack sizes *(POM)*
- Prices

**Combinations available** this indicates a combination preparation is available and a cross reference page number is provided to locate this preparation
when the information is included under Allergy and cross sensitivity.

The Important safety advice section in the BNF, delineated by a coloured outline box, highlights important safety concerns, often those raised by regulatory authorities or guideline producers. Safety warnings issued by the Commission on Human Medicines (CHM) or Medicines and Healthcare products Regulatory Agency (MHRA) are found here.

Drug selection should aim to minimise drug interactions. If it is necessary to prescribe a potentially serious combination of drugs, patients should be monitored appropriately. The mechanisms underlying drug interactions are explained in Appendix 1, followed by details of drug interactions.

Use of drugs in specific patient populations

Drug selection should aim to minimise the potential for drug accumulation, adverse drug reactions, and exacerbation of pre-existing hepatic or renal disease. If it is necessary to prescribe drugs whose effect is altered by hepatic or renal disease, appropriate drug dose adjustments should be made, and patients should be monitored adequately. The general principles for prescribing are outlined under Prescribing in hepatic impairment p. 19, and Prescribing in renal impairment p. 19. Information about drugs that should be avoided or used with caution in hepatic disease or renal impairment can be found in drug monographs under Hepatic impairment and Renal impairment (e.g. Fluconazole p. 548).

Similarly, drug selection should aim to minimise harm to the fetus, nursing infant, and mother. The infant should be monitored for potential side-effects of drugs used by the mother during pregnancy or breast-feeding. The general principles for prescribing are outlined under Prescribing in pregnancy p. 21 and Prescribing in breast-feeding p. 21. The Treatment Summaries provide guidance on the drug treatment of common conditions that can occur during pregnancy and breast-feeding (e.g. Asthma p. 225). Information about the use of specific drugs during pregnancy and breast-feeding can be found in their drug monographs under Pregnancy, and Breast-feeding (e.g. Fluconazole p. 548). A section, Conception and contraception, containing information around considerations for females of childbearing potential or men who might father a child (e.g. isotretinoin p. 1122) has been included.

Administration and monitoring

When selecting the most appropriate drug, it may be necessary to screen the patient for certain genetic markers or metabolic states. This information is included within a section called Pre-treatment screening (e.g. abacavir p. 596). This section covers one-off tests required to assess the suitability of a patient for a particular drug.

Once the drug has been selected, it needs to be given in the most appropriate manner. A Directions for administration section contains the information about intravenous administration previously located in Appendix 4. This provides practical information on the preparation of intravenous drug infusions, including compatibility of drugs with standard intravenous infusion fluids, method of dilution or reconstitution, and administration rates. In addition, general advice relevant to other routes of administration is provided within this section (e.g. fentanyl p. 424).

After selecting and administering the most appropriate drug by the most appropriate route, patients should be monitored to ensure they are achieving the expected benefits from drug treatment without any unwanted side-effects. The Monitoring section specifies any special monitoring requirements, including information on monitoring the plasma concentration of drugs with a narrow therapeutic index (e.g. theophylline p. 256). Monitoring may, in certain cases, be affected by the impact of a drug on laboratory tests (e.g. hydroxocobalamin p. 899), and this information is included in Effects on laboratory tests.

In some cases, when a drug is withdrawn, further monitoring or precautions may be advised (e.g. clonidine hydrochloride p. 136): these are covered under Treatment cessation.

Choice and supply

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (see Taking Medicines to Best Effect). Taking the time to explain to the patient (and carers) the rationale and the potential adverse effects of treatment may improve adherence. For some medicines there is a special need for counselling (e.g. appropriate posture during administration of doxycycline p. 521); this is shown in Patient and carer advice.

Other information contained in the latter half of the monograph also helps prescribers and those dispensing medicines choose medicinal forms (by indicating information such as flavour or when branded products may not be interchangeable (e.g. diltiazem hydrochloride p. 148), assess the suitability of a drug for prescribing, understand the NHS funding status for a drug (e.g. sildena p. 744), or assess when a patient may be able to purchase a drug without prescription (e.g. loperamide hydrochloride p. 63).

Medicinal forms

In the BNF, preparations follow immediately after the monograph for the drug that is their main ingredient. In earlier editions, when a particular preparation had safety information, dose advice or other clinical information specific to the product, it was contained within the preparations section. This information has been moved to the relevant section in the main body of the monograph under a heading of the name of the specific medicinal form (e.g. peppermint oil p. 43).

The medicinal forms (formerly preparations) section provides information on the type of formulation (e.g. tablet), the amount of active drug in a solid dosage form, and the concentration of active drug in a liquid dosage form. The legal status is shown for prescription-only medicines and controlled drugs, as well as pharmacy medicines and medicines on the general sales list. Practitioners are reminded, by a statement under the heading of Medicinal Forms that not all products containing a specific drug ingredient may be similarly licensed. To be clear on the precise licensing status of specific medicinal forms, practitioners should check the product literature for the particular product being prescribed or dispensed.

Details of all medicinal forms available on the dm+d for each drug in BNF Publications appears online on MedicinesComplete. In print editions, due to space constraints, only certain branded products are included in detail. Where medicinal forms are listed they should not be inferred as equivalent to the other brands listed under the same form heading. For example, all the products listed under a heading of Modified release capsule will be available as modified release capsules, however, the brands listed under that form heading may have different release profiles, the available strengths may vary and/or the products may have different licensing information. As with earlier editions of the BNF, practitioners must ensure that the particular product being prescribed or dispensed is appropriate.

As medicinal forms are derived from dm+d data, some drugs may appear under names derived from that data; this may vary slightly from those in previous BNF versions, e.g. sodium acid phosphate, is now sodium dihydrogen phosphate anhydrous.

Patients should be prescribed a preparation that complements their daily routine, and that provides the right dose of drug for the right indication and route of administration. When dispensing liquid preparations, a
sugar-free preparation should always be used in preference to one containing sugar. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries.

In earlier editions, the BNF only included excipients and electrolyte information for proprietary medicines. This information is now covered at the level of the dose form (e.g. tablet). It is not possible to keep abreast of all of the generic products available on the UK market, and so this information serves as a reminder to the healthcare professional that, if the presence of a particular excipient is of concern, they should check the product literature for the particular product being prescribed or dispensed.

Cautionary and advisory labels that pharmacists are recommended to add when dispensing are included in the medicinal forms section. Details of these labels can be found in Appendix 3, Guidance for cautionary and advisory labels p. 1383. As these labels have now been applied at the level of the dose form, a full list of medicinal products with their relevant labels would be extensive. This list has therefore been removed, but the information is retained within the monograph.

In the case of compound preparations, the prescribing information for all constituents should be taken into account.

**Prices in the BNF**

Basic NHS net prices are given in the BNF to provide an indication of relative cost. Where there is a choice of suitable preparations for a particular disease or condition the relative cost may be used in making a selection. Cost-effective preparations for a particular disease or condition the relative indication of relative cost. Where there is a choice of suitable preparations the relative price information published by the NHS updated structure, drug class monographs have been created.

In earlier editions of the BNF, information relating to a class of drugs sharing the same properties (e.g. tetracyclines p. 520), was contained within the prescribing notes. In the updated structure, drug class monographs have been created to contain the common information; this ensures such information is easier to find, and has a more regularised structure.

For consistency and ease of use, the class monograph follows the same structure as a drug monograph. Class monographs are indicated by the presence of a flag (e.g. beta-adrenoceptor blockers (systemic) p. 139). If a drug monograph has a corresponding class monograph, that needs to be considered in tandem, in order to understand the full information about a drug, the monograph is also indicated by a flag (e.g. metoprolol tartrate p. 145). Within this flag, the page number of the drug class monograph is provided (e.g. 1234), to help navigate the user to this information. This is particularly useful where occasionally, due to differences in therapeutic use, the drug monograph may not directly follow the drug class monograph (e.g. sotalol hydrochloride p. 102).

**Evidence grading**

The BNF has adopted a five level evidence grading system (see How BNF Publications are constructed p. ix). Recommendations that are evidence graded can be identified by a symbol appearing immediately before the recommendation. The evidence grade is displayed at the end of the recommendation.

**Other content**

Nutrition

Appendix 2, Borderline substances p. 1348, includes tables of ACBS-approved enteral feeds and nutritional supplements based on their energy and protein content. There are separate tables for specialised formulae for specific clinical conditions. Classified sections on foods for special diets and nutritional supplements for metabolic diseases are also included.

Wound dressings

A table on wound dressings in Appendix 4, Wound management products and elasticated garments p. 1386, allows an appropriate dressing to be selected based on the appearance and condition of the wound. Further information about the dressing can be found by following the cross-reference to the relevant classified section in the Appendix.

Advanced wound contact dressings have been classified in order of increasing absorbency.

**Other useful information**

**Finding significant changes in the BNF**

- **Changes**, provides a list of significant changes, dose changes, classification changes, new names, and new preparations that have been incorporated into the BNF, as well as a list of preparations that have been discontinued and removed from the BNF. Changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies. So many changes are made for each update of the BNF, that not all of them can be accommodated in the Changes section. We encourage healthcare professionals to regularly review the prescribing information on drugs that they encounter frequently;

- **Changes to the Dental Practitioners’ Formulary**, are located at the end of the Dental List;

- **E-newsletter**, the BNF & BNFC e-newsletter service is available free of charge. It alerts healthcare professionals to details of significant changes in the clinical content of these publications and to the way that this information is delivered. Newsletters also review clinical case studies, provide tips on using these publications effectively, and highlight forthcoming changes to the publications. To sign up for e-newsletters go to [www.bnf.org](http://www.bnf.org).

- An e-learning programme developed in collaboration with the Centre for Pharmacy Postgraduate Education (CPPE), enables pharmacists to identify and assess how significant changes in the BNF affect their clinical practice. The module can be found at [www.cppe.ac.uk](http://www.cppe.ac.uk).

**Using other sources for medicines information**

The BNF is designed as a digest for rapid reference. Less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to
specialist literature. *BNF for Children* should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services.
Changes

Monthly updates are provided online via MedicinesComplete and the NHS Evidence portal. The changes listed below are cumulative (from one print edition to the next).

**Significant changes**
Significant changes that will appear in the print edition of BNF 73 (March–September 2017):
- Alirocumab p. 195: for treating primary hypercholesterolaemia and mixed dyslipidaemia [NICE guidance].
- Anal fissure p. 87: updated guidance on management.
- Azacitidine p. 811: for treating acute myeloid leukaemia with more than 30% bone marrow blasts [NICE guidance].
- Belimumab p. 773: for treating active autoantibody-positive systemic lupus erythematosus [NICE guidance].
- Bosutinib p. 859: for previously treated chronic myeloid leukaemia [NICE guidance].
- Cabazitaxel p. 825: for hormone-relapsed metastatic prostate cancer treated with docetaxel [NICE guidance].
- Camagozifloxin p. 641: increased risk of lower extremity amputations in high cardiovascular risk patients [MHRA/CHM advice].
- Camagozifloxin p. 641, dapaglogifloxin p. 642, and empaglogifloxin p. 643 as monotherapies for treating type 2 diabetes [NICE guidance].
- Ceritinib p. 861 for previously treated anaplastic lymphoma kinase-positive non-small cell lung cancer [NICE guidance].
- Ciclosporin p. 766 for treating dry eye disease that has not improved despite treatment with artificial tears [NICE guidance].
- Coeliac disease p. 34: new guidance on management.
- Dementia p. 281: updated guidance on management.
- Etonogestrel p. 740 (Nexplanon®) contraceptive implants: reports of device in vasculature and lung [MHRA/CHM advice].
- Exocrine pancreatic insufficiency p. 83: updated guidance on management.
- Idelalisib p. 868: updated indications and advice on minimising the risk of infection [MHRA/CHM advice]
- Lumacaftor with ivacaftor p. 275 for treating cystic fibrosis homozygous for F508del mutation [NICE guidance].
- Naloxegol p. 61 for treating opioid-induced constipation [NICE guidance].
- Nivolumab p. 787: (as monotherapy) for treating advanced (unresectable or metastatic) melanoma [NICE guidance] and nivolumab in combination with ipilimumab p. 786 for treating advanced melanoma [NICE guidance].
- Oral prostogestogen-only contraceptives: updated guidance on starting routine, see desogestrel p. 737, norethisterone p. 699 and levonorgestrel p. 737.
- Panobinostat p. 834 for treating multiple myeloma after at least 2 previous treatments [NICE guidance].
- Paraffin-based skin emollients on dressings or clothing: fire risk [MHRA/CHM advice].
- Pemetrexed p. 819: maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin [NICE guidance].
- Pomalidomide p. 855: risk of hepatitis B reactivation [MHRA/CHM advice].
- Ramucirumab p. 791: for previously treated locally advanced or metastatic non-small-cell lung cancer [NICE guidance].
- Riociguat p. 176: not for use in pulmonary hypertension associated with idiopathic interstitial pneumonias [MHRA/CHM advice].
- Risk of death and severe harm from error with injectable phenytoin [NHS Improvement Patient Safety Alert], see phenytoin p. 302.
- Risk of severe harm and death due to withdrawing insulin from pen devices [NHS Improvement Patient Safety Alert], see insulin p. 648.
- Short bowel syndrome p. 44: new guidance on management.
- Warfarin sodium p. 131: reports of calciphylaxis [MHRA/CHM advice].

**Dose changes**
Changes in dose statements made since the publication of the print edition of BNF 72 (September 2016–March 2017):
- Etoricoxib p. 996 [rheumatoid arthritis and ankylosing spondylitis].
- Metronidazole p. 499 [acute ulcerative gingivitis and acute oral infections].
- Olaparib p. 881 [with concomitant use of potent or moderate CYP3A4 inhibitors].

**Classification changes**
Classification changes made since the publication of the print edition of BNF 72 (September 2016–March 2017):

**New names**
Name changes made since the publication of the print edition of BNF 72 (September 2016–March 2017):

**Deleted preparations**
Preparations discontinued since the publication of the print edition of BNF 72 (September 2016–March 2017):

**New preparations**
New preparations included since the publication of the print edition of BNF 72 (September 2016–March 2017):
Guidance on prescribing

General guidance
Medicines should be prescribed only when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy, when the risk to both mother and fetus must be considered. It is important to discuss treatment options carefully with the patient to ensure that the patient is content to take the medicine as prescribed. In particular, the patient should be helped to distinguish the adverse effects of prescribed drugs from the effects of the medical disorder. When the beneficial effects of the medicine are likely to be delayed, the patient should be advised of this.

Taking medicines to best effect
Difficulties in adherence to drug treatment occur regardless of age. Factors contributing to poor compliance with prescribed medicines include:

- prescription not collected or not dispensed;
- purpose of medicine not clear;
- perceived lack of efficacy;
- real or perceived adverse effects;
- patients’ perception of the risk and severity of side-effects may differ from that of the prescriber;
- instructions for administration not clear;
- physical difficulty in taking medicines (e.g. swallowing the medicine, handling small tablets, or opening medicine containers);
- unattractive formulation (e.g. unpleasant taste);
- complicated regimen.

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (‘concordance’). The prescriber should be sensitive to religious, cultural, and personal beliefs that can affect a patient’s acceptance of medicines.

Taking the time to explain to the patient (and relatives) the rationale and the potential adverse effects of treatment may improve adherence. Reinforcement and elaboration of the physician’s instructions by the pharmacist and other members of the healthcare team also helps. Advising the patient of the possibility of alternative treatments may encourage the patient to seek advice rather than merely abandon unacceptable treatment.

Simplifying the drug regimen may help; the need for frequent administration may reduce adherence, although there appears to be little difference in adherence between once-daily and twice-daily administration. Combination products reduce the number of drugs taken at the expense of the ability to titrate individual doses.

Biological medicines

Biological medicines are medicines that are made by or derived from a biological source using biotechnology processes, such as recombinant DNA technology. The size and complexity of biological medicines, as well as the way they are produced, may result in a degree of natural variability in molecules of the same active substance, particularly in different batches of the medicine. This variation is maintained within strict acceptable limits. Examples of biological medicines include insulins and monoclonal antibodies. Biological medicines must be prescribed by brand name and the brand name specified on the prescription should be dispensed in order to avoid inadvertent switching. Automatic substitution of brands at the point of dispensing is not appropriate for biological medicines.

Biosimilar medicines

A biosimilar medicine is a biological medicine that is highly similar and clinically equivalent (in terms of quality, safety, and efficacy) to an existing biological medicine that has already been authorised in the European Union (known as the reference biological medicine or originator medicine). The active substance of a biosimilar medicine is similar, but not identical, to the originator biological medicine. Once the patent for a biological medicine has expired, a biosimilar medicine may be authorised by the European Medicines Agency (EMA). A biosimilar medicine is not the same as a generic medicine, which contains a simpler molecular structure that is identical to the originator medicine.

Therapeutic equivalence

Biosimilar medicines should be considered to be therapeutically equivalent to the originator biological medicine within their authorised indications.

Simplifying the drug regimen may help; the need for frequent administration may reduce adherence, although there appears to be little difference in adherence between once-daily and twice-daily administration. Combination products reduce the number of drugs taken at the expense of the ability to titrate individual doses.

Safety monitoring

Biosimilar medicines are subject to a black triangle status (▼) at the time of initial authorisation. It is important to report suspected adverse reactions using the Yellow Card Scheme (see Adverse reactions to drugs p. 12). For all biological medicines, adverse reaction reports should clearly state the brand name and the batch number of the suspected medicine.

UK Medicines Information centres have developed a validated tool to determine potential safety issues associated with all new medicines. These ‘in-use product safety assessment reports’ will be published for new biosimilar medicines as they become available, see www.ukmi.nhs.uk/activities/patientsafety/default.asp?pageRef=20.

National funding/access decisions

The Department of Health has confirmed that, in England, NICE can decide to apply the same remit, and the resulting technology appraisal guidance, to relevant biosimilar medicines which appear on the market subsequent to their originator biological medicine. In other circumstances, where a review of the evidence for a particular biosimilar medicine is necessary, NICE will consider producing an evidence summary (see Evidence summary: new medicines, www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/evidence-summaries-new-medicines).

National information

Guidance on prescribing

Availability
The following drugs are available as a biosimilar medicine:

- Epoetin alfa p. 887
- Epoetin zeta p. 890
- Etanercept p. 973
- Filgrastim p. 903
- Follitropin alfa p. 682
- Infliximab p. 976
- Insulin glargine p. 651
- Somatropin p. 685

Complementary and alternative medicine
An increasing amount of information on complementary and alternative medicine is becoming available. The scope of the BNF is restricted to the discussion of conventional medicines but reference is made to complementary treatments if they affect conventional therapy (e.g. interactions with St John’s wort). Further information on herbal medicines is available at www.mhra.gov.uk.

Abbreviation of titles
In general, titles of drugs and preparations should be written in full. Unofficial abbreviations should not be used as they may be misinterpreted.

Non-proprietary titles
Where non-proprietary (‘generic’) titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where there is a demonstrable difference in clinical effect between each manufacturer’s version of the formulation, making it important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated. Non-proprietary titles should not be invented for the purposes of prescribing generically since this can lead to confusion, particularly in the case of compound and modified-release preparations. Titles used as headings for monographs may be used freely in the United Kingdom but in other countries may be subject to restriction.

Many of the non-proprietary titles used in this book are titles of monographs in the European Pharmacopoeia, British Pharmacopoeia, or British Pharmaceutical Codex 1973. In such cases the preparations must comply with the standard (if any) in the appropriate publication, as required by the Human Medicines Regulations 2012.

Proprietary titles
Names followed by the symbol® are or have been used as proprietary names in the United Kingdom. These names may in general be applied only to products supplied by the owners of the trade marks.

Marketing authorisation and BNF advice
In general the doses, indications, cautions, contra-indications, and side-effects in the BNF reflect those in the manufacturers’ data sheets or Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). The BNF does not generally include proprietary medicines that are not supported by a valid Summary of Product Characteristics or when the marketing authorisation holder has not been able to supply essential information. When a preparation is available from more than one manufacturer, the BNF reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisations. Unlicensed products can be obtained from ‘special-order’ manufacturers or specialist importing companies.

Where an unlicensed drug is included in the BNF, this is indicated in square brackets after the entry. When the BNF suggests a use (or route) that is outside the licensed indication of a product (‘off-label’ use), this too is indicated. Unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

The doses stated in the BNF are intended for general guidance and represent, unless otherwise stated, the usual range of doses that are generally regarded as being suitable for adults.

Prescribing unlicensed medicines
Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber’s professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines, and also inform the patient or the patient’s carer that the prescribed medicine is unlicensed.

Oral syringes
An oral syringe is supplied when oral liquid medicines are prescribed in doses other than multiples of 5 mL. The oral syringe is marked in 0.5 mL divisions from 1 to 5 mL to measure doses of less than 5 mL (other sizes of oral syringe may also be available). It is provided with an adaptor and an instruction leaflet. The 5–5 mL spoon is used for doses of 5 mL (or multiples thereof).

Important
To avoid inadvertent intravenous administration of oral liquid medicines, only an appropriate oral or enteral syringe should be used to measure an oral liquid medicine (if a medicine spoon or graduated measure cannot be used); these syringes should not be compatible with intravenous or other parenteral devices. Oral or enteral syringes should be clearly labelled ‘Oral’ or ‘Enteral’ in a large font size; it is the healthcare practitioner’s responsibility to label the syringe with this information if the manufacturer has not done so.

Excipients
Branded oral liquid preparations that do not contain fructose, glucose, or sucrose are described as ‘sugar-free’ in the BNF. Preparations containing hydrogenated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked ‘sugar-free’ since there is evidence that they do not cause dental caries. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible.

Where information on the presence of aspartame, gluten, sulfites, tartrazine, arachis (peanut) oil or sesame oil is available, this is indicated in the BNF against the relevant preparation.

Information is provided on selected excipients in skin preparations, in vaccines, and on selected preservatives and excipients in eye drops and injections.

The presence of benzyl alcohol and polyoxyl castor oil (polyethoxylated castor oil) in injections is indicated in the BNF. Benzyl alcohol has been associated with a fatal toxic syndrome in preterm neonates, and therefore, parenteral preparations containing the preservative should not be used in neonates. Polyoxyl castor oils, used as vehicles in intravenous injections, have been associated with severe anaphylactoid reactions.

The presence of propylene glycol in oral or parenteral medicines is indicated in the BNF; it can cause adverse effects if its elimination is impaired, e.g. in renal failure, in neonates and young children, and in slow metabolisers of the substance. It may interact with disulfiram p. 459 and metronidazole p. 499.

The lactose content in most medicines is too small to cause problems in most lactose-intolerant patients. However in severe lactose intolerance, the lactose content should be...
determined before prescribing. The amount of lactose varies according to manufacturer, product, formulation, and strength. **Important** In the absence of information on excipients in the BNF and in the product literature (available at www.medicines.org.uk/emc), contact the manufacturer (see Index of Proprietary Manufacturers) if it is essential to check details.

**Extemporaneous preparation**
A product should be dispensed extemporaneously only when no product with a marketing authorisation is available. The BP direction that a preparation must be freshly prepared indicates that it must be made not more than 24 hours before it is issued for use. The direction that a preparation should be recently prepared indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15–25°C. The term water used without qualification means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled purified water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation (Water for injections).

**Drugs and driving**
Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk. A new offence of driving, attempting to drive, or being in charge of a vehicle, with certain specified controlled drugs in excess of specified limits, came into force on 2nd March 2015. This offence is an addition to the existing rules on drug impaired driving and fitness to drive, and applies to two groups of drugs—commonly abused drugs, including amphetamines, cannabis, cocaine, and ketamine p. 1189, and drugs used mainly for medical reasons, such as opioids and benzodiazepines. Anyone found to have any of the drugs (including related drugs, for example, apomorphine hydrochloride p. 390) above specified limits in their blood will be guilty of an offence, whether their driving was impaired or not. This also includes prescribed drugs which metabolise to those included in the offence, for example, selegiline hydrochloride p. 399. However, the legislation provides a statutory "medical defence" for patients taking drugs for medical reasons in accordance with instructions, if their driving was not impaired—it continues to be an offence to drive if actually impaired. Patients should therefore be advised to continue taking their medicines as prescribed, and when driving, to carry suitable evidence that the drug was prescribed, or sold, to treat a medical or dental problem, and that it was taken according to the instructions given by the prescriber, or information provided with the medicine (e.g. a repeat prescription form or the medicine’s patient information leaflet). Further information is available from the Department for Transport at www.gov.uk/government/collections/drug-driving.

**Patents**
In the BNF, certain drugs have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters Patent, their inclusion in this Formulary neither conveys, nor implies, licence to manufacture.

**Health and safety**
When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Substances such as corticosteroids, some antimicrobials, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution. Contact with the skin and inhalation of dust should be avoided.

**Safety in the home**
Patients must be warned to keep all medicines out of the reach of children. All solid dose and all oral and external liquid preparations must be dispensed in a reclosable child-resistant container unless:

- the medicine is in an original pack or patient pack such as to make this inadvisable;
- the patient will have difficulty in opening a child-resistant container;
- a specific request is made that the product shall not be dispensed in a child-resistant container;
- no suitable child-resistant container exists for a particular liquid preparation.

All patients should be advised to dispose of unwanted medicines by returning them to a supplier for destruction.

**Labelling of prescribed medicines**
There is a legal requirement for the following to appear on the label of any prescribed medicine:

- name of the patient;
- name and address of the supplying pharmacy;
- date of dispensing;
- name of the medicine;
- directions for use of the medicine;
- precautions relating to the use of the medicine.

The Royal Pharmaceutical Society recommends that the following also appears on the label:

- the words ‘Keep out of the sight and reach of children’;
- where applicable, the words ‘Use this medicine only on your skin’.

A pharmacist can exercise professional skill and judgement to amend or include more appropriate wording for the name of the medicine, the directions for use, or the precautions relating to the use of the medicine.

**Non-proprietary names of compound preparations**
Non-proprietary names of compound preparations which appear in the BNF are those that have been compiled by the British Pharmacopoeia Commission or another recognised body; whenever possible they reflect the names of the active ingredients.

Prescribers should avoid creating their own compound names for the purposes of generic prescribing; such names do not have an approved definition and can be misrepresented.

Special care should be taken to avoid errors when prescribing compound preparations; in particular the hyphen in the prefix ‘co-’ should be retained.

Special care should also be taken to avoid creating generic names for modified-release preparations where the use of these names could lead to confusion between formulations with different lengths of action.

**EEA and Swiss prescriptions**
Pharmacists can dispense prescriptions issued by doctors and dentists from the European Economic Area (EEA) or Switzerland (except prescriptions for controlled drugs in Schedules 1, 2, or 3, or for drugs without a UK marketing authorisation). Prescriptions should be written in ink or otherwise so as to be indelible, should be dated, should state the name of the patient, should state the address of the prescriber, should contain particulars indicating whether the prescriber is a doctor or dentist, and should be signed by the prescriber.
Security and validity of prescriptions
The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions. In particular, prescription forms should:
- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

Patient group direction (PGD)
In most cases, the most appropriate clinical care will be provided on an individual basis by a prescriber to a specific individual patient. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit patient care without compromising safety.

A Patient Group Direction is a written direction relating to the supply and administration (or administration only) of a licensed prescription-only medicine (including some Controlled Drugs in specific circumstances) by certain classes of healthcare professionals; the Direction is signed by a doctor (or dentist) and by a pharmacist. Further information on Patient Group Directions is available in Health Service Circular HSC 2000/026 (England), HDL (2001) 7 (Scotland), and WHC (2000) 116 (Wales); see also the Human Medicines Regulations 2012.

NICE and Scottish Medicines Consortium
Advice issued by the National Institute for Health and Care Excellence (NICE) is included in the BNF when relevant. The BNF also includes advice issued by the Scottish Medicines Consortium (SMC) when a medicine is restricted or not recommended for use within NHS Scotland. If advice within a NICE Single Technology Appraisal differs from SMC advice, the Scottish Executive expects NHS Boards within NHS Scotland to comply with the SMC advice. Details of the advice together with updates can be obtained from www.nice.org.uk and from www.scottishmedicines.org.uk.
Prescription writing

Shared care
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Requirements
Prescriptions should be written legibly in ink or otherwise so as to be indelible (it is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink), should be dated, should state the name and address of the patient, the address of the prescriber, an indication of the type of prescriber, and should be signed in ink by the prescriber (computer-generated facsimile signatures do not meet the legal requirement). The age and the date of birth of the patient should preferably be stated, and it is a legal requirement (computer-generated facsimile signatures do not meet the legal requirement). The age and the date of birth of the patient should preferably be stated, and it is a legal requirement. Wherever appropriate the prescriber should state the current requirements for prescription-only medicines. Prescriptions for controlled drugs have additional legal requirements.

Wherever appropriate the prescriber should state the current weight of the child to enable the dose prescribed to be calculated. Consideration should also be given to including the dose per unit mass e.g. mg/kg or the dose per m² body-surface area e.g. mg/m² where this would reduce error.

The following should be noted:

- The strength or quantity to be contained in capsules, lozenges, tablets etc. should be stated by the prescriber. In particular, strength of liquid preparations should be clearly stated (e.g. 125 mg/5 mL).
- The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg. Quantities of 1 gram or more should be written as 1 g etc. Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g. Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg. When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not 0.5 mL. Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.
- 'Micrograms' and 'nanograms' should not be abbreviated. Similarly ‘units’ should not be abbreviated.
- The term 'millilitre' (ml or mL) is used in medicine and pharmacy, and cubic centimetre, c.c., or cm³ should not be used. (The use of capital ‘L’ in mL is a printing convention throughout the BNF; both ‘mL’ and ‘ml’ are recognised SI abbreviations).
- Dose and dose frequency should be stated; in the case of preparations to be taken ‘as required’ a minimum dose interval should be specified. Care should be taken to ensure children receive the correct dose of the active drug. Therefore, the dose should normally be stated in terms of the mass of the active drug (e.g. ‘125 mg 3 times daily’); terms such as ‘5 mL’ or ‘1 tablet’ should be avoided except for compound preparations. When doses other than multiples of 5 mL are prescribed for oral liquid preparations the dose-volume will be provided by means of an oral syringe, (except for preparations intended to be measured with a pipette). Suitable quantities:
  - Elixirs, Linctuses, and Paediatric Mixtures (5 mL dose), 50, 100, or 150 mL
  - Adult Mixtures (10 mL dose), 200 or 300 mL
  - Ear Drops, Eye drops, and Nasal Drops, 10 mL (or the manufacturer’s pack)
  - Eye Lotions, Gargles, and Mouthwashes, 200 mL
- The names of drugs and preparations should be written clearly and not abbreviated, using approved titles only; avoid creating generic titles for modified-release preparations).
- The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given then the quantity to be supplied needs to be stated. When several items are ordered on one form the box can be marked with the number of days of treatment provided the quantity is added for any item for which the amount cannot be calculated.
- Although directions should preferably be in English without abbreviation, it is recognised that some Latin abbreviations are used.

Sample prescription

<table>
<thead>
<tr>
<th>Pharmacy Stamp</th>
<th>Age</th>
<th>Title, Forename, Surname &amp; Address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1yr 0mths</td>
<td>Master Peter Patient</td>
</tr>
<tr>
<td></td>
<td>2/4/2010</td>
<td>Flat 1, 50 Standhope Street, Newtown TW22 1ST</td>
</tr>
</tbody>
</table>

Please don’t stamp over age box

Number of days of treatment
N.B. Ensure dose is stated

<table>
<thead>
<tr>
<th>Endorsements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin oral suspension</td>
</tr>
</tbody>
</table>
125mg/ml sugar-free |
125mg three times daily |
Supply 100ml |
[No more items on this prescription] |

Date: 02/07/11

Prescribing by dentists

Until new prescribing arrangements are in place for NHS prescriptions, dentists should use form FP10D (GP14 in Scotland, WP10D in Wales) to prescribe only those items listed in the Dental Practitioners’ Formulary. The Human Medicines Regulations 2012 does not set any limitations upon the number and variety of substances which the dentist may administer to patients in the surgery or may order by private prescription—provided the relevant legal requirements are observed the dentist may use or order whatever is required for the clinical situation. There is no statutory requirement for the dentist to communicate with a patient’s medical practitioner when prescribing for dental use. There are, however, occasions when this would be in the patient’s interest and such communication is to be encouraged. For legal requirements relating to prescriptions...
of Controlled Drugs, see Controlled drugs and drug dependence p. 8.

**Computer-issued prescriptions**

For computer-issued prescriptions, the following advice, based on the recommendations of the Joint GP Information Technology Committee, should also be noted:

1. The computer must print out the date, the patient’s surname, one forename, other initials, and address, and may also print out the patient’s title and date of birth. The age of children under 12 years and of adults over 60 years must be printed in the box available; the age of children under 5 years should be printed in years and months. A facility may also exist to print out the age of patients between 12 and 60 years.

2. The doctor’s name must be printed at the bottom of the prescription form; this will be the name of the doctor responsible for the prescription (who will normally sign it). The doctor’s surgery address, reference number, and Primary Care Trust (PCT, Health Board in Scotland, Local Health Board in Wales) are also necessary. In addition, the surgery telephone number should be printed.

3. When prescriptions are to be signed by general practitioner registrars, assistants, locums, or deputising doctors, the name of the doctor printed at the bottom of the form must still be that of the responsible principal.

4. Names of medicines must come from a dictionary held in the computer memory, to provide a check on the spelling and to ensure that the name is written in full. The computer can be programmed to recognise both the non-proprietary and the proprietary name of a particular drug and to print out the preferred choice, but must not print out both names. For medicines not in the dictionary, separate checks are required—the user must be warned that no check was possible and the entire prescription must be entered in the lexicon.

5. The dictionary may contain information on the usual doses, formulations, and pack sizes to produce standard predetermined prescriptions for common preparations, and to provide a check on the validity of an individual prescription on entry.

6. The prescription must be printed in English without abbreviation; information may be entered or stored in abbreviated form. The dose must be in numbers, the frequency in words, and the quantity in numbers in brackets, thus: 40 mg four times daily (112). It must also be possible to prescribe by indicating the length of treatment required.

7. The BNF recommendations should be followed as listed above.

8. Checks may be incorporated to ensure that all the information required for dispensing a particular drug has been filled in. For instructions such as ‘as directed’ and ‘when required’, the maximum daily dose should normally be specified.

9. Numbers and codes used in the system for organising and retrieving data must never appear on the form.

10. Supplementary warnings or advice should be written in full, should not interfere with the clarity of the prescription itself, and should be in line with any warnings or advice in the BNF; numerical codes should not be used.

11. A mechanism (such as printing a series of nonspecific characters) should be incorporated to cancel out unused space, or wording such as ‘no more items on this prescription’ may be added after the last item. Otherwise the doctor should delete the space manually.

12. To avoid forgery the computer may print on the form the number of items to be dispensed (somewhere separate from the box for the pharmacist). The number of items per form need be limited only by the ability of the printer to produce clear and well-demarcated instructions with sufficient space for each item and a spacer line before each fresh item.

13. Handwritten alterations should only be made in exceptional circumstances—it is preferable to print out a new prescription. Any alterations must be made in the doctor’s own handwriting and countersigned; computer records should be updated to fully reflect any alteration. Prescriptions for drugs used for contraceptive purposes (but which are not promoted as contraceptives) may need to be marked in handwriting with the symbol ⊥, (or endorsed in another way to indicate that the item is prescribed for contraceptive purposes).

14. Prescriptions for controlled drugs can be printed from the computer, but the prescriber’s signature must be handwritten (See Controlled Drugs and Drug Dependence; the prescriber may use a date stamp).

15. The strip of paper on the side of the FP10SS (GP10SS in Scotland, WP10SS in Wales) may be used for various purposes. But care should be taken to avoid including confidential information. It may be advisable for the patient’s name to appear at the top, but this should be preceded by ‘confidential’.

16. In rural dispensing practices prescription requests (or details of medicines dispensed) will normally be entered in one surgery. The prescriptions (or dispensed medicines) may then need to be delivered to another surgery or location; if possible the computer should hold up to 10 alternatives.

17. Prescription forms that are reprinted or issued as a duplicate should be labelled clearly as such.
Emergency supply of medicines

Emergency supply requested by member of the public
Pharmacists are sometimes called upon by members of the public to make an emergency supply of medicines. The Human Medicines Regulations 2012 allows exemptions from the Prescription Only requirements for emergency supply to be made by a person lawfully conducting a retail pharmacy business provided:

- that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:
  - that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;
  - that treatment with the prescription-only medicine has on a previous occasion been prescribed for the person requesting it;
  - as to the dose that it would be appropriate for the person to take;
- that no greater quantity shall be supplied than will provide 5 days’ treatment of phenobarbital p. 313, phenobarbital sodium, or Controlled Drugs in Schedules 4 or 5 (doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation) or 30 days’ treatment for other prescription-only medicines, except when the prescription-only medicine is:
  - insulin, an ointment or cream, or a preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;
  - an oral contraceptive when a full cycle may be supplied;
  - an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;
- that an entry shall be made in the prescription book stating:
  - the date of supply;
  - the name, quantity and, where appropriate, the pharmaceutical form and strength;
  - the name and address of the patient;
  - the nature of the emergency;
- that the container or package must be labelled to show:
  - the date of supply;
  - the name, quantity and, where appropriate, the pharmaceutical form and strength;
  - the name of the patient;
  - the words 'Emergency supply’;
  - the words 'Keep out of the reach of children’ (or similar warning);
- that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital p. 315 or phenobarbital sodium for the treatment of epilepsy: for details see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition); (Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation).
- that an entry shall be made in the prescription book stating:
  - the date of supply;
  - the name, quantity and, where appropriate, the pharmaceutical form and strength;
  - the name and address of the practitioner requesting the emergency supply;
  - the name and address of the patient;
  - the date on the prescription;
  - when the prescription is received the entry should be amended to include the date on which it is received.

Royal Pharmaceutical Society’s guidelines
1. The pharmacist should consider the medical consequences of not supplying a medicine in an emergency.
2. If the pharmacist is unable to make an emergency supply of a medicine the pharmacist should advise the patient how to obtain essential medical care.

For conditions that apply to supplies made at the request of a patient see Medicines, Ethics and Practice, London Pharmaceutical Press, (always consult latest edition).
Controlled drugs and drug dependence

Regulations and classification
The Misuse of Drugs Act, 1971 prohibits certain activities in relation to 'Controlled Drugs', in particular their manufacture, supply, and possession. The penalties applicable to offences involving the different drugs are graded broadly according to the harmlessness attributable to a drug when it is misused and for this purpose the drugs are defined in the following three classes:

- **Class A** includes: alfentanil p. 1187, cocaine, diamorphine hydrochloride (heroin) p. 423, dipipamone hydrochloride, lysergide (LSD), methadone hydrochloride p. 464, methylenedioxymethamphetamine (MDMA, 'ecstasy'), morphine, opium, pethidine hydrochloride p. 434, phencyclidine, remifentanil p. 1188, and class B substances when prepared for injection.


- **Class C** includes: certain drugs related to the amfetamines such as benzphetamine and chlorphenetermine, buprenorphine p. 417, mazindol, mebrobamate p. 324, pemoline, pipradrol, most benzodiazipines, tramadol hydrochloride p. 435, zaleplon p. 453, zolpidem tartrate p. 454, zopiclone p. 454, androgenic and anabolic steroids, clenbuterol, chionic gonadotrophin (HCG), non-human chionic gonadotrophin, somatotropin, somatrem, and somatropin p. 685.

The Misuse of Drugs Regulations 2001 (and subsequent amendments) define the classes of person who are authorised to supply and possess controlled drugs while acting in their professional capacities and lay down the conditions under which these activities may be carried out. In the regulations drugs are divided into five schedules each specifying the requirements governing such activities as import, export, production, supply, possession, prescribing, and record keeping which apply to them.

- **Schedule 1** includes drugs such as lysergide which is not used medicinally. Possession and supply are prohibited except in accordance with Home Office authority.

- **Schedule 2** includes drugs such as diamorphine hydrochloride (heroin) p. 423, morphine p. 429, nabilone p. 402, remifentanil p. 1188, pethidine hydrochloride p. 434, secoberbital, glutethimide, the amfetamines, sodium oxybate and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for secoberbital), the need to keep registers, etc. (unless exempted in Schedule 5).

- **Schedule 3** includes the barbiturates (except secoberbital, now Schedule 2), buprenorphine p. 417, mazindol, mebrobamate p. 324, midazolam p. 318, pentazocine p. 434, phentermine, temazepam p. 451, and tramadol hydrochloride p. 435. They are subject to the special prescription requirements. Safe custody requirements do apply, except for any 5,5 disubstituted barbituric acid (e.g. phenobarbital), mazindol, mebrobamate p. 324, midazolam p. 318, pentazocine p. 434, phentermine, tramadol hydrochloride p. 435, or any stereoisomorphic form or salts of the above. Records in registers do not need to be kept (although there are requirements for the retention of invoices for 2 years).

- **Schedule 4** includes in Part I benzodiazipines (except temazepam p. 451 and midazolam p. 318, which are in Schedule 3), zaleplon p. 453, zolpidem tartrate p. 454, and zopiclone p. 454 which are subject to minimal control. Part II includes androgenic and anabolic steroids, clenbuterol, chionic gonadotrophin (HCG), non-human chionic gonadotrophin, somatotropin, somatrem, and somatropin p. 685. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements.

- **Schedule 5** includes those preparations which, because of their strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years.

Prescriptions
Preparations in Schedules 1, 2, 3, 4, and 5 of the Misuse of Drugs Regulations 2001 (and subsequent amendments) are identified throughout the BNF and BNF for children using the following symbols:

- **CD1** for preparations in Schedule 1
- **CD2** for preparations in Schedule 2
- **CD3** for preparations in Schedule 3
- **CD4** for preparations in Schedule 4 (Part I)
- **CD4-1** for preparations in Schedule 4 (Part II)
- **CD5** for preparations in Schedule 5

The principal legal requirements relating to medical prescriptions are listed below (see also Department of Health Guidance).

**Prescription requirements** Prescriptions for Controlled Drugs that are subject to prescription requirements (all preparations in Schedules 2 and 3) must be indelible and must be signed by the prescriber, be dated, and specify the prescriber's address. A machine-written prescription is acceptable, but the prescriber's signature must be handwritten. Advanced electronic signatures can be accepted for Schedule 2 and 3 Controlled Drugs where the Electronic Prescribing Service (EPS) is used. All prescriptions for Controlled Drugs that are subject to the prescription requirements must always state:

- the name and address of the patient;
- in the case of a preparation, the form, (the dosage form e.g. tablets must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name e.g. MST Continus or whether only one form is available), and where appropriate the strength of the preparation (when more than one strength of a preparation exists the strength required must be specified);
- for liquids, the total volume in millilitres (in both words and figures) of the preparation to be supplied; for dosage units, the number (in both words and figures) of dosage units to be supplied; in any other case, the total quantity (in both words and figures) of the Controlled Drug to be supplied;
- the dose (the instruction ‘one as directed’ constitutes a dose but ‘as directed’ does not);
- the words ‘for dental treatment only’ if issued by a dentist.

A pharmacist is not allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. In the case of a prescription for a Controlled Drug in Schedule 2 or 3, a pharmacist can amend the prescription if it specifies the total quantity only in words or in figures or if it contains minor typographical errors, provided that such amendments are indelible and clearly attributable to the pharmacist (implementation date for N. Ireland not confirmed). Failure to comply with the regulations concerning the writing of prescriptions will
Guidance (June 3) must be written on specially designated forms provided by
Private prescriptions for Controlled Drugs in Schedules 2, 3, or 4 is valid for 28 days
from the date stated thereon (the prescriber may forward-date the prescription; the start date may also be specified in
the body of the prescription).

Instalments and ‘repeats’
A prescription may order a Controlled Drug to be dispensed
by instalments; the amount of instalments and the intervals
to be observed must be specified. A total of 14 days’
treatment by instalment of any drug listed in Schedule 2 of
the Misuse of Drugs Regulations, buprenorphine p. 417, and
diazepam p. 321 may be prescribed in England. In England,
forms FP10 (MDA) (blue) and FP10H (MDA) (blue) should be
used. In Scotland, forms GP10 (peach), HBP (blue), or HBPA
(pink) should be used. In Wales a total of 14 days’ treatment
by instalment of any drug listed in Schedules 2–5 of the
Misuse of Drugs Regulations may be prescribed. In Wales,
form WP10 (MDA) or form WP10HP (AD) should be used.
Instalment prescriptions must be dispensed in accordance
with the directions in the prescription. However, the Home
Office has approved specific wording which may be included
in an instalment prescription to cover certain situations; for
example, if a pharmacy is closed on the day when an
instalment is due. For details, see Medicines, Ethics and
Practice, London, Pharmaceutical Press (always consult
latest edition) or see Drug Misuse and Dependence: UK
Guidelines on Clinical Management (2007), available at
Prescriptions ordering ‘repeats’ on the same form are not
permitted for Controlled Drugs in Schedules 2 or 3.

Private prescriptions
Private prescriptions for Controlled Drugs in Schedules 2 and
3 must be written on specially designated forms provided by
Primary Care Trusts in England, Health Boards in Scotland,
Local Health Boards in Wales, or the Northern Ireland
Central Services Agency; in addition, prescriptions must
specify the prescriber’s identification number. Prescriptions to
be supplied by a pharmacist in hospital are exempt from the
requirements for private prescriptions.

Department of Health guidance
Guidance (June 2006) issued by the Department of Health in
England on prescribing and dispensing of Controlled Drugs
requires:

- in general, prescriptions for Controlled Drugs in
Schedules 2, 3, and 4 to be limited to a supply of up to
30 days’ treatment; exceptionally, to cover a justifiable
clinical need and after consideration of any risk, a
prescription can be issued for a longer period, but the
reasons for the decision should be recorded on the
patient’s notes;
- the patient’s identifier to be shown on NHS and private
prescriptions for Controlled Drugs in Schedules 2 and 3.

Further information is available at www.gov.uk/dh.

See sample prescription:

Dependence and misuse
The most serious drugs of addiction are cocaine,
diamorphine hydrochloride (heroin) p. 423, morphine
p. 429, and the synthetic opioids. For arrangements for
prescribing of diamorphine, dipipanone, or cocaine for
addicts, see Prescribing of diamorphine (heroin),
dipipanone, and cocaine for addicts.

Despite marked reduction in the prescribing of
amfetamines, there is concern that abuse of illicit
amfetamine and related compounds is widespread.
Benzodiazepines are commonly misused. However, the
misuse of barbiturates is now uncommon, in line with
d eclining medicinal use and consequent availability.

Cannabis (Indian hemp) has no approved medicinal use and
cannot be prescribed by doctors. Its use is illegal but
widespread. Cannabis is a mild hallucinogen seldom
accompanied by a desire to increase the dose; withdrawal
symptoms are unusual. However, cannabis extract is licensed
as a medicinal product. Lysergide (lysergic acid
diethylamide, LSD) is a much more potent hallucinogen; its
use can lead to severe psychotic states which can be life-
threatening.

There are concerns over increases in the availability and
misuse of other drugs with variously combined
hallucinogenic, anaesthetic, or sedative properties. These
include ketamine p. 1189 and gamma-hydroxybutyrate
(sodium oxybate, GHB).

Supervised consumption
Individuals prescribed opioid substitution therapy can take
their daily dose under the supervision of a doctor, nurse, or
pharmacist during the dose stabilisation phase (usually the
first 3 months of treatment), after a relapse or period of
Controlled drugs and drug dependence

10 Controlled drugs and drug dependence

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instability, or if there is a significant increase in the dose of methadone. Supervised consumption should continue (in accordance with local protocols) until the prescriber is confident that the patient is compliant with their treatment.

Prescribing drugs likely to cause dependence or misuse

The prescriber has three main responsibilities:

- To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other Controlled Drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious.
- To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more likely. This tendency is seen especially with hypnotics and anxiolytics. The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time.
- To avoid being used as an unwitting source of supply for addicts and being vigilant to methods for obtaining medicines. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctor. Doctors should also remember that their own patients may be attempting to collect prescriptions from other prescribers, especially in hospitals. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring. The stealing and misuse of prescription forms could be minimised by the following precautions:

- do not leave unattended if called away from the consulting room or at reception desks; do not leave in a car where they may be visible; when not in use, keep in a locked drawer within the surgery and at home;
- draw a diagonal line across the blank part of the form under the prescription;
- write the quantity in words and figures when prescribing drugs prone to abuse; this is obligatory for controlled drugs;
- alterations are best avoided but if any are made they should be clear and unambiguous; add initials against altered items;
- if prescriptions are left for collection they should be left in a safe place in a sealed envelope.

Travelling abroad

Prescribed drugs listed in Schedule 4 Part II (CD Anab) and Schedule 5 of the Misuse of Drugs Regulations 2001 are not subject to export or import licensing. However, patients intending to travel abroad for more than 3 months carrying any amount of drugs listed in Schedules 2, 3, or 4 Part I (CD Benz) will require a personal export/import licence. Further details can be obtained at www.gov.uk/guidance/controlled-drugs-licences-fees-and-returns or from the Home Office by contacting DFUL.ie@homeoffice.gov.uk. In cases of emergency, telephone (020) 7035 6330.

Applications for licences should be sent to the Home Office, Drugs Licensing & Compliance Unit, Fry Building, 2 Marsham Street, London, SW1P 4DF. Alternatively, completed application forms can be emailed to dlccommsofficer@homeoffice.gsi.gov.uk with a copy of the covering letter from the prescriber as a pdf. A minimum of two weeks should be allowed for processing the application. Patients travelling for less than 3 months do not require a personal export/import licence for carrying Controlled Drugs, but are advised to carry a letter from the prescribing doctor. Those travelling for more than 3 months are advised to make arrangements to have their medication prescribed by a practitioner in the country they are visiting.

Doctors who want to take Controlled Drugs abroad while accompanying patients may similarly be issued with licences. Licences are not normally issued to doctors who want to take Controlled Drugs abroad solely in case a family emergency should arise.

Personal export/import licences do not have any legal status outside the UK and are issued only to comply with the Misuse of Drugs Act and to facilitate passage through UK Customs and Excise control. For clearance in the country to be visited it is necessary to approach that country’s consulate in the UK.

Notification of patients receiving structured drug treatment for substance dependence

In England, doctors should report cases where they are providing structured drug treatment for substance dependence to their local National Drug Treatment Monitoring System (NDTMS) Team. General information about NDTMS can be found at www.nita.nhs.uk/ndtms.aspx. Enquiries about NDTMS, and how to submit data, should initially be directed to:

- EvidenceApplicationTeam@phe.gov.uk

In Scotland, doctors should report cases to the Substance Misuse Programme (SMP).

Tel: (0131) 275 6348

In Northern Ireland, the Misuse of Drugs (Notification of Supply to Addicts) (Northern Ireland) Regulations 1973 require doctors to send particulars of persons whom they consider to be addicted to certain controlled drugs to the Chief Medical Officer of the Department of Health and Social Services. The Northern Ireland contacts are:

Medical contact:
Dr Ian McMaster, C3 Castle Buildings, Belfast, BT4 3FQ
Tel: (028) 9052 2421, Fax: (028) 9052 0718
ian.mcmaster@dhspsni.gov.uk

Administrative contact:
Public Health Information & Research Branch, Department of Health, Anexe 2, Castle Building, Stormont, Belfast BT4 3SQ
Tel: (028) 9052 2504

Public Health Information & Research Branch also maintains the Northern Ireland Drug Misuse Database (NIDMD) which collects detailed information on those presenting for treatment, on drugs misused and injecting behaviour; participation is not a statutory requirement.

In Wales, doctors should report cases where they are providing structured drug treatment for substance dependence on the Welsh National Database for Substance Misuse; enquiries should be directed to: substance.misuse-queries@wales.nhs.uk.
Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts

The Misuse of Drugs (Supply to Addicts) Regulations 1997 require that only medical practitioners who hold a special licence issued by the Home Secretary may prescribe, administer, or supply diamorphine hydrochloride p. 423, dipipanone (Diconal®), or cocaine in the treatment of drug addiction; other practitioners must refer any addict who requires these drugs to a treatment centre. Whenever possible the addict will be introduced by a member of staff from the treatment centre to a pharmacist whose agreement has been obtained and whose pharmacy is conveniently sited for the patient. Prescriptions for weekly supplies will be sent to the pharmacy by post and will be dispensed on a daily basis as indicated by the doctor. If any alterations of the arrangements are requested by the addict, the portion of the prescription affected must be represcribed and not merely altered.

General practitioners and other doctors do not require a special licence for prescribing diamorphine hydrochloride p. 423, dipipanone, and cocaine for patients (including addicts) for relieving pain from organic disease or injury.
Adverse reactions to drugs

Yellow card scheme

Any drug may produce unwanted or unexpected adverse reactions. Rapid detection and recording of adverse drug reactions is of vital importance so that unrecognised hazards are identified promptly and appropriate regulatory action is taken to ensure that medicines are used safely. Healthcare professionals and coroners are urged to report suspected adverse drug reactions directly to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available from the address below and are also found in the inside back cover of the BNF.

Send Yellow Cards to:
FREEPOST YELLOW CARD
(No other address details required).
Tel: 0800 731 6789

Suspected adverse drug reactions to any therapeutic agent should be reported, including drugs (self-medication as well as those prescribed), blood products, vaccines, radiographic contrast media, complementary and herbal products. For biosimilar medicines and vaccines, adverse reaction reports should clearly state the brand name and the batch number of the suspected medicine or vaccine.

Suspected adverse drug reactions should be reported through the Yellow Card Scheme at www.mhra.gov.uk/yellowcard. Yellow Cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, medication errors or from use of unlicensed and off-label medicines. Yellow Cards can also be used to report medical device incidents, defective medicines, and suspected fake medicines.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well recognised, or if other drugs have been given at the same time. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

A freephone service is available to all parts of the UK for advice and information on suspected adverse drug reactions; contact the National Yellow Card Information Service at the MHRA on 0800 731 6789. Outside office hours a telephone-answering machine will take messages.

The following Yellow Card Centres can be contacted for further information:

Yellow Card Centre Northwest
2nd Floor, 70 Pembroke Place, Liverpool, L69 3GF
Tel: (0151) 794 8122

Yellow Card Centre Wales
All Wales Therapeutics and Toxicology Centre, Academic Building, University Hospital Llandough, Penlan Road, Penarth, Vale of Glamorgan, CF64 2XX
Tel: (029) 2074 5831

Yellow Card Centre Northern & Yorkshire
Regional Drug and Therapeutics Centre, 16/17 Framlington Place, Newcastle upon Tyne, NE2 4AB
Tel: (0191) 213 7855

Yellow Card Centre West Midlands
City Hospital, Dudley Road, Birmingham, B18 7QH
Tel: (0121) 507 5672

Yellow Card Centre Scotland
CARDS, Royal Infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh, EH16 4SA
Tel: (0131) 242 2919
YCCScotland@luht.scot.nhs.uk

The MHRA’s database facilitates the monitoring of adverse drug reactions. More detailed information on reporting and a list of products currently under additional monitoring can be found on the MHRA website: www.mhra.gov.uk.

MHRA Drug Safety Update

Drug Safety Update is a monthly newsletter from the MHRA and the Commission on Human Medicines (CHM); it is available at www.gov.uk/drg-safety-update.

Self-reporting

Patients and their carers can also report suspected adverse drug reactions to the MHRA. Reports can be submitted directly to the MHRA through the Yellow Card Scheme using the electronic form at www.mhra.gov.uk/yellowcard, by telephone on 0808 100 3352, or by downloading the Yellow Card form from www.mhra.gov.uk. Alternatively, patient Yellow Cards are available from pharmacies and GP surgeries. Information for patients about the Yellow Card Scheme is available in other languages at www.mhra.gov.uk/yellowcard.

Prescription-event monitoring

In addition to the MHRA’s Yellow Card Scheme, an independent scheme monitors the safety of new medicines using a different approach. The Drug Safety Research Unit identifies patients who have been prescribed selected new medicines and collects data on clinical events in these patients. The data are submitted on a voluntary basis by general practitioners on green forms. More information about the scheme and the Unit’s educational material is available from www.dsru.org.

Newer drugs and vaccines

Only limited information is available from clinical trials on the safety of new medicines. Further understanding about the safety of medicines depends on the availability of information from routine clinical practice. The black triangle symbol identifies newly licensed medicines that require additional monitoring by the European Medicines Agency. Such medicines include new active substances, biosimilar medicines, and medicines that the European Medicines Agency consider require additional monitoring. The black triangle symbol also appears in the Patient Information Leaflets for relevant medicines, with a brief explanation of what it means. Products usually retain a black triangle for 5 years, but this can be extended if required.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. For medicines showing the black triangle symbol, the MHRA asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well recognised, or if other drugs have been given at the same time.

Established drugs and vaccines

Healthcare professionals and coroners are asked to report all suspected reactions to established drugs (including over-the-counter, herbal, and unlicensed medicines and medicines used off-label) and vaccines that are serious, medically significant, or result in harm. Serious reactions include those that are fatal, life-threatening, disabling,
incapacitating, or which result in or prolong hospitalisation, or a congenital abnormality; they should be reported even if the effect is well recognised. Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions. Reports of serious adverse reactions are required to enable comparison with other drugs of a similar class. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

For established drugs there is no need to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants or constipation with opioids.

**Medication errors**

Adverse drug reactions where harm occurs as a result of a medication error are reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

**Adverse reactions to medical devices**

Suspected adverse reactions to medical devices including dental or surgical materials, intra-uterine devices, and contact lens fluids should be reported. Information on reporting these can be found at: [www.mhra.gov.uk](http://www.mhra.gov.uk).

**Side-effects in the BNF**

The BNF includes clinically relevant side-effects for most drugs; an exhaustive list is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Where causality has not been established, side-effects in the manufacturers’ literature may be omitted from the BNF.

Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is not generally listed, unless the drug carries an increased risk of such reactions. The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

Side-effects are generally listed in order of frequency and arranged broadly by body systems. Occasionally a rare side-effect might be listed first if it is considered to be particularly important because of its seriousness. In the product literature the frequency of side-effects is generally described as follows:

<table>
<thead>
<tr>
<th>Description of the frequency of side-effects</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>greater than 1 in 10</td>
</tr>
<tr>
<td>Common</td>
<td>1 in 100 to 1 in 10</td>
</tr>
<tr>
<td>Uncommon [formerly ‘less commonly’ in BNF publications]</td>
<td>1 in 1000 to 1 in 100</td>
</tr>
<tr>
<td>Rare</td>
<td>1 in 10 000 to 1 in 1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>less than 1 in 10 000</td>
</tr>
</tbody>
</table>

**Special problems**

**Delayed drug effects** Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported directly to the MHRA through the Yellow Card Scheme.

**The elderly** Particular vigilance is required to identify adverse reactions in the elderly.

**Congenital abnormalities** When an infant is born with a congenital abnormality or there is a malformed aborted fetus doctors are asked to consider whether this might be an adverse reaction to a drug and to report all drugs (including self-medication) taken during pregnancy.

**Children** Particular vigilance is required to identify and report adverse reactions in children, including those resulting from the unlicensed use of medicines; all suspected reactions should be reported directly to the MHRA through the Yellow Card Scheme (see also Adverse Drug Reactions in Children).

**Prevention of adverse reactions**

Adverse reactions may be prevented as follows:

- never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative;
- allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the patient had previous reactions to the drug or formulation;
- ask if the patient is already taking other drugs including self-medication drugs, health supplements, complementary and alternative therapies; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may be needed. Genetic factors may also be responsible for variations in metabolism, and therefore for the adverse effect of the drug; notably of isoniazid p. 541 and the tricyclic antidepressants;
- prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions;
- whenever possible use a familiar drug; with a new drug, be particularly alert for adverse reactions or unexpected events;
- consider if excipients (e.g. colouring agents) may be contributing to the adverse reaction. If the reaction is minor, a trial of an alternative formulation of the same drug may be considered before abandoning the drug;
- warn the patient if serious adverse reactions are liable to occur.

**Drug allergy (suspected or confirmed)**

Suspected drug allergy is any reaction caused by a drug with clinical features compatible with an immunological mechanism. All drugs have the potential to cause adverse drug reactions, but not all of these are allergic in nature. A reaction is more likely to be caused by drug allergy if:

- The reaction occurred while the patient was being treated with the drug, or
- The drug is known to cause this pattern of reaction, or
- The patient has had a similar reaction to the same drug or drug-class previously.

A suspected reaction is less likely to be caused by a drug allergy if there is a possible non-drug cause or if there are only gastro-intestinal symptoms present. The following signs, allergic patterns and timing of onset can be used to help decide whether to suspect drug allergy: **Immediate, rapidly-evolving reactions** (onset usually less than 1 hour after drug exposure)

- Anaphylaxis, with erythema, urticaria or angioedema, and hypotension and/or bronchospasm. See also Antihistamines, allergen immunotherapy and allergic emergencies p. 259
- Urticaria or angioedema without systemic features
- Exacerbation of asthma e.g. with non-steroidal anti-inflammatory drugs (NSAIDs)

**Non-immediate reactions, without systemic involvement** (onset usually 6–10 days after first drug exposure or 3 days after second exposure)

- Cutaneous reactions, e.g. widespread red macules and/or papules, or, fixed drug eruption (localised inflamed skin)
Adverse reactions to drugs

Non-immediate reactions, with systemic involvement (onset may be variable, usually 3 days to 6 weeks after first drug exposure, depending on features, or 3 days after second exposure)

- Cutaneous reactions with systemic features, e.g. drug reaction with eosinophilia and systemic signs (DRESS) or drug hypersensitivity syndrome (DHS), characterised by widespread red macules, papules or erythrodema, fever, lymphadenopathy, liver dysfunction or eosinophilia
- Toxic epidermal necrolysis or Stevens–Johnson syndrome
- Acute generalised exanthematous pustulosis (AGEP)
- Suspected drug allergy information should be clearly and accurately documented in clinical notes and prescriptions and shared among all healthcare professionals. Patients should be given information about which drugs and drug-classes to avoid and encouraged to share their drug allergy status.

If a drug allergy is suspected, consider stopping the drug. Suspected drug allergy information should be clearly and accurately documented in clinical notes and prescriptions and shared among all healthcare professionals. Patients should be given information about which drugs and drug-classes to avoid and encouraged to share their drug allergy status.

If a drug allergy is suspected, consider stopping the drug and advising the patient or carer to avoid this drug in future. Symptoms of the acute reaction should be treated, in hospital if severe. Patients presenting with a suspected anaphylactic reaction, or a severe or non-immediate cutaneous reaction, should be referred to a specialist drug allergy service. Patients presenting with a suspected drug allergic reaction or anaphylaxis to NSAIDs, and local and general anaesthetics may also need to be referred to a specialist drug allergy service, e.g. in cases of anaphylactic reactions or to determine future treatment options. Patients presenting with a suspected drug allergic reaction or anaphylaxis associated with beta-lactam antibiotics should be referred to a specialist drug allergy service if their disease or condition can only be treated by a beta-lactam antibiotic or they are likely to need beta-lactam antibiotics frequently in the future (e.g. immunodeficient patients).

For further information see Drug allergy: diagnosis and management. NICE Clinical Guideline 183 (September 2014) www.nice.org.uk/guidance/cg183.

Oral side-effects of drugs

Drug-induced disorders of the mouth may be due to a local action on the mouth or to a systemic effect manifested by oral changes. In the latter case urgent referral to the patient’s medical practitioner may be necessary.

Oral mucosa

Medicaments left in contact with or applied directly to the oral mucosa can lead to inpatient, mucosal swelling is not usually prominent. The oral mucosa is particularly vulnerable to ulceration in patients treated with cytotoxic drugs, e.g. methotrexate p. 817. Other drugs capable of causing oral ulceration include ACE inhibitors, gold, nicorandil p. 201, NSAIDs, pancreatic p. 90, penicillamine p. 964, proguanil hydrochloride p. 571, and protease inhibitors.

Erythema multiforme or Stevens–Johnson syndrome may follow the use of a wide range of drugs including anticholinergics, antimuscarinics, sulphonamide derivatives, and anticonvulsants; the oral mucosa may be extensively ulcerated, with characteristic target lesions on the skin. Oral lesions of toxic epidermal necrolysis have been reported with a similar range of drugs.

Lichenoid eruptions are associated with ACE inhibitors, NSAIDs methyl dopa p. 136, chloroquine p. 569, oral antidiabetics, thiazide diuretics, and gold.

Candidiasis can complicate treatment with antibacterials and immunosuppressants and is an occasional side-effect of corticosteroid inhalers.

Teeth and jaw

Brown staining of the teeth frequently follows the use of chlorhexidine mouthwash, spray or gel p. 1064, but can readily be removed by polishing. Iron salts in liquid form can stain the enamel black. Superficial staining has been reported rarely with co-amoxiclav suspension p. 508. Intrinsic staining of the teeth is most commonly caused by tetracyclines. They will affect the teeth if given at any time from about the fourth month in utero until the age of twelve years; they are contra-indicated during pregnancy, in breast-feeding women, and in children under 12 years. All tetracyclines can cause permanent, unsightly staining in children, the colour varying from yellow to grey. Excessive ingestion of fluoride leads to dental fluorosis with mottling of the enamel and areas of hypoplasia or pitting; fluoride supplements occasionally cause mild mottling (white patches) if the dose is too large for the child’s age (taking into account the fluoride content of the local drinking water and of toothpaste).

The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget’s disease. All patients receiving bisphosphonates should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment. Patients with cancer receiving bevacizumab p. 783 or sunitinib p. 876 may also be at risk of osteonecrosis of the jaw.

Periodontium

Gingival overgrowth (gingival hyperplasia) is a side-effect of phenytoin p. 302 and sometimes of cyclosporin p. 766 or of nifedipine p. 153 (and some other calcium-channel blockers). Thrombocytopenia may be drug related and may cause bleeding at the gingival margins, which may be spontaneous or may follow mild trauma (such as toothbrushing).

Salivary glands

The most common effect that drugs have on the salivary glands is to reduce flow (xerostomia). Patients with a persistently dry mouth may have poor oral hygiene; they are at an increased risk of dental caries and oral infections (particularly candidiasis). Many drugs have been implicated in xerostomia, particularly antimuscarinics (anticholinergics), antidepressants (including tricyclic antidepressants, and selective serotonin re-uptake inhibitors), alpha-blockers, antihistamines, antipsychotics, baclofen p. 985, duprobupropion hydrochloride p. 461, clonidine hydrochloride p. 136, 5HT1 agonists, opioids, and tizanidine p. 986. Excessive use of diuretics can also result in xerostomia.

Some drugs (e.g. clozapine p. 371, neostigmine p. 983) can increase saliva production but this is rarely a problem unless the patient has associated difficulty in swallowing. Pain in the salivary glands has been reported with some antihypertensives (e.g. clonidine hydrochloride p. 136, methyl dopa p. 136) and with vinca alkaloids.

Swelling of the salivary glands can occur with iodides, antithyroid drugs, phenothiazines, and sulfonamides.

Taste

There can be decreased taste acuity or alteration in taste sensation. Many drugs are implicated, including amiodarone hydrochloride p. 99, calcitonin, ACE inhibitors, carbimazole p. 706, clarithromycin p. 496, gold, griseofulvin p. 554, lithium salts, metformin hydrochloride p. 631, metronidazole p. 499, penicillamine p. 964, phenindione p. 131, propafenone hydrochloride p. 98, protease inhibitors, terbinafine p. 1089, and zopiclone p. 454.

Defective medicines

During the manufacture or distribution of a medicine an error or accident may occur whereby the finished product does not conform to its specification. While such a defect may impair the therapeutic effect of the product and could
adversely affect the health of a patient, it should **not** be confused with an Adverse Drug Reaction where the product conforms to its specification.

The Defective Medicines Report Centre assists with the investigation of problems arising from licensed medicinal products thought to be defective and co-ordinates any necessary protective action. Reports on suspect defective medicinal products should include the brand or the non-proprietary name, the name of the manufacturer or supplier, the strength and dosage form of the product, the product licence number, the batch number or numbers of the product, the nature of the defect, and an account of any action already taken in consequence. The Centre can be contacted at:

The Defective Medicines Report Centre  
Medicines and Healthcare products Regulatory Agency,  
151 Buckingham Palace Road, London, SW1W 9SZ  
Tel: (020) 3080 6574  
dmrc@mhra.gsi.gov.uk
Guidance on intravenous infusions

Intravenous additives policies
A local policy on the addition of drugs to intravenous fluids should be drawn up by a multi-disciplinary team and issued as a document to the members of staff concerned. Centralised additive services are provided in a number of hospital pharmacy departments and should be used in preference to making additions on wards. The information that follows should be read in conjunction with local policy documents.

Guidelines
- Drugs should only be added to infusion containers when constant plasma concentrations are needed or when the administration of a more concentrated solution would be harmful.
- In general, only one drug should be added to any infusion container and the components should be compatible. Ready-prepared solutions should be used whenever possible. Drugs should not normally be added to blood products, mannitol, or sodium bicarbonate. Only specially formulated additives should be used with fat emulsions or amino-acid solutions.
- Solutions should be thoroughly mixed by shaking and checked for absence of particulate matter before use.
- Strict asepsis should be maintained throughout and in general the giving set should not be used for more than 24 hours (for drug admixtures).
- The infusion container should be labelled with the patient’s name, the name and quantity of additives, and the date and time of addition (and the new expiry date or time). Such additional labelling should not interfere with information on the manufacturer’s label that is still valid. When possible, containers should be retained for a period after use in case they are needed for investigation.
- It is good practice to examine intravenous infusions from time to time while they are running. If cloudiness, crystallisation, change of colour, or any other sign of interaction or contamination is observed the infusion should be discontinued.

Problems

Microbial contamination The accidental entry and subsequent growth of micro-organisms converts the infusion fluid pathway into a potential vehicle for infection with micro-organisms, particularly species of Candida, Enterobacter, and Klebsiella. Ready-prepared infusions containing the additional drugs, or infusions prepared by an additive service (when available) should therefore be used in preference to making extemporaneous additions to infusion containers on wards etc. However, when this is necessary strict aseptic procedure should be followed.

Incompatibility Physical and chemical incompatibilities may occur with loss of potency, increase in toxicity, or other adverse effect. The solutions may become opalescent or turbid. Interaction may take place at any point in the infusion fluid pathway, and the potential for incompatibility is increased when more than one substance is added to the infusion fluid.

Common incompatibilities Precipitation reactions are numerous and varied and may occur as a result of pH, concentration changes, ‘salting-out’ effects, complexation or other chemical changes. Precipitation or other particle formation must be avoided since, apart from lack of control of dosage on administration, it may initiate or exacerbate adverse effects. This is particularly important in the case of drugs which have been implicated in either thrombophlebitis (e.g. diazepam) or in skin sloughing or necrosis caused by extravasation (e.g. sodium bicarbonate and certain cytotoxic drugs). It is also especially important to effect solution of colloidal drugs and to prevent their subsequent precipitation in order to avoid a pyrogenic reaction (e.g. amphotericin). It is considered undesirable to mix beta-lactam antibiotics, such as semi-synthetic penicillins and cephalosporins, with proteinaceous materials on the grounds that immunogenic and allergenic conjugates could be formed.

A number of preparations undergo significant loss of potency when added singly or in combination to large volume infusions. Examples include ampicillin in infusions that contain glucose or lactates. The breakdown products of dacarbazine have been implicated in adverse effects.

Blood Because of the large number of incompatibilities, drugs should not normally be added to blood and blood products for infusion purposes. Examples of incompatibility with blood include hypertonic mannitol solutions (irreversible crenation of red cells), dextrans (rouleaux formation and interference with cross-matching), glucose (clumping of red cells), and oxotocin (inactivated). If the giving set is not changed after the administration of blood, but used for other infusion fluids, a fibrin clot may form which, apart from blocking the set, increases the likelihood of microbial growth.

Intravenous fat emulsions These may break down with coalescence of fat globules and separation of phases when additions such as antibiotics or electrolytes are made, thus increasing the possibility of embolism. Only specially formulated products such as Vitlipid N® may be added to appropriate intravenous fat emulsions.

Other infusions Infusions that frequently give rise to incompatibility include amino acids, mannitol, and sodium bicarbonate.

Bactericides Bactericides such as chlororesol 0.1% or phenylmercuric nitrate 0.001% are present in some injection solutions. The total volume of such solutions added to a container for infusion on one occasion should not exceed 15 mL.

Method
Ready-prepared infusions should be used whenever available. Potassium chloride is usually available in concentrations of 20, 27, and 40 mmol/litre in sodium chloride intravenous infusion (0.9%), glucose intravenous infusion (5%) or sodium chloride and glucose intravenous infusion. Lidocaine hydrochloride is usually available in concentrations of 0.1% or 0.2% in glucose intravenous infusion (5%). When addition is required to be made extemporaneously, any product reconstitution instructions such as those relating to concentration, vehicle, mixing, and handling precautions should be strictly followed using an aseptic technique throughout. Once the product has been reconstituted, addition to the infusion fluid should be made immediately in order to minimise microbial contamination and, with certain products, to prevent degradation or other formulation change which may occur; e.g. reconstituted ampicillin injection degrades rapidly on standing, and also may form polymers which could cause sensitivity reactions. It is also important in certain instances that an infusion fluid of specific pH be used (e.g. furosemide injection requires dilution in infusions of pH greater than 5.5). When drug additions are made it is important to mix thoroughly; additions should not be made to an infusion container that has been connected to a giving set, as mixing is hampered. If the solutions are not thoroughly mixed a concentrated layer of the additive may form owing to
differences in density. **Potassium chloride** is particularly prone to this 'layering' effect when added without adequate mixing to infusions packed in non-rigid infusion containers; if such a mixture is administered it may have a serious effect on the heart.

A time limit between addition and completion of administration must be imposed for certain admixtures to guarantee satisfactory drug potency and compatibility. For admixtures in which degradation occurs without the formation of toxic substances, an acceptable limit is the time taken for 10% decomposition of the drug. When toxic substances are produced stricter limits may be imposed. Because of the risk of microbial contamination a maximum time limit of 24 hours may be appropriate for additions made elsewhere than in hospital pharmacies offering central additive service.

Certain injections must be protected from light during continuous infusion to minimise oxidation, e.g. dacarbazine and sodium nitroprusside.

Dilution with a small volume of an appropriate vehicle and administration using a motorised infusion pump is advocated for preparations such as unfractionated heparin where strict control over administration is required. In this case the appropriate dose may be dissolved in a convenient volume (e.g. 24–48 mL) of sodium chloride intravenous infusion (0.9%).

**Information provided in the BNF**

The BNF gives information about preparations given by three methods:

- continuous infusion;
- intermittent infusion;
- addition via the drip tubing.

**Drugs given by intravenous infusion**

The BNF includes information on addition to **Glucose intravenous infusion** 5 and 10%, and **Sodium chloride intravenous infusion** 0.9%.

Compatibility with glucose 5% and with sodium chloride 0.9% indicates compatibility with **Sodium chloride and glucose intravenous infusion**. Infusion of a large volume of hypotonic solution should be avoided therefore care should be taken if water for injections is used. The information relates to the proprietary preparations indicated; for other preparations suitability should be checked with the manufacturer.

**Information provided in the BNF**

The BNF gives information about preparations given by three methods:

- continuous infusion;
- intermittent infusion;
- addition via the drip tubing.

**Drugs for continuous infusion** must be diluted in a large volume infusion. Penicillins and cephalosporins are not usually given by continuous infusion because of stability problems and because adequate plasma and tissue concentrations are best obtained by intermittent infusion. Where it is necessary to administer them by continuous infusion, detailed literature should be consulted.

Drugs that are both compatible and clinically suitable may be given by **intermittent infusion** in a relatively small volume of infusion over a short period of time, e.g. 100 mL in 30 minutes. The method is used if the product is incompatible or unstable over the period necessary for continuous infusion; the limited stability of ampicillin or amoxicillin in large volume glucose or lactate infusions may be overcome in this way.

Intermittent infusion is also used if adequate plasma and tissue concentrations are not produced by continuous infusion as in the case of drugs such as dacarbazine, gentamicin, and ticarcillin.

An in-line burette may be used for intermittent infusion techniques in order to achieve strict control over the time and rate of administration, especially for infants and children and in intensive care units. Intermittent infusion may also make use of the 'piggy-back' technique provided that no additions are made to the primary infusion. In this method the drug is added to a small secondary container connected to a Y-type injection site on the primary infusion giving set; the secondary solution is usually infused within 30 minutes.

**Addition via the drip tubing** is indicated for a number of cytotoxic drugs in order to minimise extravasation. The preparation is added aseptically via the rubber septum of the injection site of a fast-running infusion. In general, drug preparations intended for a bolus effect should be given directly into a separate vein where possible. Failing this, administration may be made via the drip tubing provided that the preparation is compatible with the infusion fluid when given in this manner.
Prescribing in children

Overview
For detailed advice on medicines used for children, consult BNF for Children.
Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care. At this age, the risk of toxicity is increased by reduced drug clearance and differing target organ sensitivity.
Whenever possible, intramuscular injections should be avoided in children because they are painful.
Where possible, medicines for children should be prescribed within the terms of the marketing authorisation (product licence). However, many children may require medicines not specifically licensed for paediatric use.
Although medicines cannot be promoted outside the limits of the licence, the Human Medicines Regulations 2012 does not prohibit the use of unlicensed medicines. It is recognised that the informed use of unlicensed medicines or of licensed medicines for unlicensed applications (‘off-label’ use) is often necessary in paediatric practice.

Adverse drug reactions in children
Suspected adverse drug reactions in children and young adults under 18 years should be reported through the Yellow Card Scheme. Yellow cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, medication errors or from use of unlicensed and off-label medicines. Yellow Cards can also be used to report medical device incidents, defective products; children and are used either off-label or as unlicensed medicines, and suspected fake medicines.
Report all suspected adverse drug reactions that are:
- serious, medically significant or result in harm.
  Serious events are fatal, life-threatening, a congenital abnormality, disabling or incapacitating, or resulting in hospitalisation;
- associated with newer drugs and vaccines; the most up to date list of black triangle medicines is available at: www.mhra.gov.uk/blacktriangle
If in doubt whether to report a suspected adverse drug reaction, please complete a Yellow Card.
The identification and reporting of adverse reactions to drugs in children and neonates is particularly important because:
- the action of the drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- drugs may not have been extensively tested in children;
- many drugs are not specifically licensed for use in children and are used either ‘off-label’ or as unlicensed products;
- drugs may affect the way a child grows and develops or may cause delayed adverse reactions which do not occur in adults;
- suitable formulations may not be available to allow precise dosing in children or they may contain excipients that should be used with caution in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.
Even if reported through the British Paediatric Surveillance Unit’s Orange Card Scheme, any identified suspected adverse drug reactions should also be submitted to the Yellow Card Scheme.
Adverse drug reactions where harm occurs as a result of a medication error are reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

Prescription writing
Prescriptions should be written according to the guidelines in Prescription Writing. Inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for all prescriptions for children.
It is particularly important to state the strengths of capsules or tablets. Although liquid preparations are particularly suitable for children, they may contain sugar which encourages dental decay. Sugar-free medicines are preferred for long-term treatment.
Many children are able to swallow tablets or capsules and may prefer a solid dose form; involving the child and parents in choosing the formulation is helpful.
When a prescription for a liquid oral preparation is written and the dose ordered is smaller than 5 mL an oral syringe will be supplied. Parents should be advised not to add any medicines to the infant’s feed, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced if the child does not drink all the contents.
Parents must be warned to keep all medicines out of reach of children.

Rare paediatric conditions
Information on substances such as biotin and sodium benzoate used in rare metabolic conditions is included in BNF for Children; further information can be obtained from:
- Alder Hey Children’s Hospital
- Drug Information Centre, Liverpool, L12 2AP
  Tel: (0151) 252 5381
- Great Ormond Street Hospital for Children
  Pharmacy, Great Ormond St, London, WC1N 3JH
  Tel: (020) 7405 9200

Dosage in children
Children’s doses in the BNF are stated in the individual drug entries.
Doses are generally based on body-weight (in kilograms) or specific age ranges. In the BNF and BNF for Children, the term neonate is used to describe a newborn infant aged 0–28 days. The terms child or children are used generally to describe the entire range from infant to adolescent (1 month–17 years). An age range is specified when the dose information applies to a narrower age range than a child from 1 month–17 years.

Dose calculation
Many children’s doses are standardised by weight (and therefore require multiplying by the body-weight in kilograms to determine the child’s dose); occasionally, the doses have been standardised by body surface area (in m²).
These methods should be used rather than attempting to calculate a child’s dose on the basis of doses used in adults. For most drugs the adult maximum dose should not be exceeded. For example if the dose is stated as 8 mg/kg (max. 300 mg), a child weighing 10 kg should receive 80 mg but a child weighing 40 kg should receive 300 mg (rather than 320 mg).
Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases
cases, dose should be calculated from an ideal weight, related to height and age. **Body surface area (BSA) estimates** are sometimes preferable to body-weight for calculation of paediatric doses since many physiological phenomena correlate better with body surface area. Body surface area can be estimated from weight. For more information, refer to *BNF for Children*. Where the dose for children is not stated, prescribers should consult *BNF for Children* or seek advice from a medicines information centre.

**Prescribing in hepatic impairment**

**Overview**
Liver disease may alter the response to drugs in several ways as indicated below, and drug prescribing should be kept to a minimum in all patients with severe liver disease. The main problems occur in patients with jaundice, ascites, or evidence of encephalopathy.

**Impaired drug metabolism**
Metabolism by the liver is the main route of elimination for many drugs, but hepatic reserve is large and liver disease has to be severe before important changes in drug metabolism occur. Routine liver-function tests are a poor guide to the capacity of the liver to metabolise drugs, and in the individual patient it is not possible to predict the extent to which the metabolism of a particular drug may be impaired. A few drugs, e.g. rifampicin p. 535 and fusidic acid p. 527, are excreted in the bile unchanged and can accumulate in patients with intrahepatic or extrahepatic obstructive jaundice.

**Hypoproteinaemia**
The hypoalbuminaemia in severe liver disease is associated with reduced protein binding and increased toxicity of some highly protein-bound drugs such as phenytoin p. 302 and prednisolone p. 622.

**Reduced clotting**
Reduced hepatic synthesis of blood-clotting factors, indicated by a prolonged prothrombin time, increases the sensitivity to oral anticoagulants such as warfarin sodium p. 131 and phenindione p. 131.

**Hepatic encephalopathy**
In severe liver disease many drugs can further impair cerebral function and may precipitate hepatic encephalopathy. These include all sedative drugs, opioid analgesics, those diuretics that produce hypokalaemia, and drugs that cause constipation.

**Fluid overload**
Oedema and ascites in chronic liver disease can be exacerbated by drugs that give rise to fluid retention e.g. NSAIDs and corticosteroids.

**Hepatotoxic drugs**
Hepatotoxicity is either dose-related or unpredictable (idiosyncratic). Drugs that cause dose-related toxicity may do so at lower doses in the presence of hepatic impairment than in individuals with normal liver function, and some drugs that produce reactions of the idiosyncratic kind do so more frequently in patients with liver disease. These drugs should be avoided or used very carefully in patients with liver disease.

Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

**Prescribing in renal impairment**

**Issues encountered in renal impairment**
The use of drugs in patients with reduced renal function can give rise to problems for several reasons:
- reduced renal excretion of a drug or its metabolites may cause toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by patients with renal impairment;
- some drugs are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using alternative drugs.

**Principles of dose adjustment in renal impairment**
The level of renal function below which the dose of a drug must be reduced depends on the proportion of the drug eliminated by renal excretion and its toxicity. For many drugs with only minor or no dose-related side-effects very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient. For more toxic drugs with a small safety margin or patients at extremes of weight, dose regimens based on creatinine clearance should be used. When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be...
Prescribing in renal impairment

Patients at extremes of weight In patients at both extremes of weight (BMI of less than 18.5 kg/m² or greater than 30 kg/m²) the absolute glomerular filtration rate or creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust drug dosages. In the BNF, values for eGFR, creatinine clearance (for toxic drugs), or another measure of renal function are included where possible. However, where such values are not available, the BNF reflects the terms used in the published information.

Degrees of renal impairment defined using estimated glomerular filtration rate (eGFR)

<table>
<thead>
<tr>
<th>Degree of impairment</th>
<th>eGFR mL/minute/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal - Stage 1</td>
<td>More than 90 (with other evidence of kidney damage)</td>
</tr>
<tr>
<td>Mild - Stage 2</td>
<td>60-89 (with other evidence of kidney damage)</td>
</tr>
<tr>
<td>Moderate - Stage 3</td>
<td>30-59</td>
</tr>
<tr>
<td>Severe - Stage 4</td>
<td>15-29</td>
</tr>
<tr>
<td>Established renal failure - Stage 5</td>
<td>Less than 15</td>
</tr>
</tbody>
</table>

1. NICE clinical guideline 73 (September 2008)—Chronic kidney disease: Stage 3A eGFR 45-59, Stage 3B eGFR 30-44

Drug prescribing should be kept to the minimum in all patients with severe renal disease. If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing any drug which requires dose modification.

Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.

Dialysis

For prescribing in patients on continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis, consult specialist literature.

adjusted according to clinical response and plasma-drug concentration.

Renal function declines with age; many elderly patients have renal impairment but, because of reduced muscle mass, this may not be indicated by a raised serum creatinine. It is wise to assume at least mild impairment of renal function when prescribing for the elderly.

The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half-life of the drug to achieve steady-state plasma concentrations. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same size as the initial dose for a patient with normal renal function.

Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced.

Dose recommendations are based on the severity of renal impairment.

Renal function is measured either in terms of estimated glomerular filtration rate (eGFR) calculated from a formula derived from the Modification of Diet in Renal Disease study (‘MDRD formula’ that uses serum creatinine, age, sex, and race (for Afro-Caribbean patients)) or it can be expressed as creatinine clearance (best derived from a 24-hour urine collection but often calculated from the Cockcroft and Gault formula (CG)).

Cockcroft and Gault Formula

Estimated Creatinine Clearance $= \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}}$

Age in years
Weight in kilograms; use ideal body-weight
Serum creatinine in micromol/litre
Constant $= 1.23$ for men; $1.04$ for women

The serum-creatinine concentration is sometimes used instead as a measure of renal function but it is only a rough guide to drug dosing.

Important Renal function in adults is increasingly being reported on the basis of estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73 m² and derived from the Modification of Diet in Renal Disease (MDRD) formula. However, published information on the effects of renal impairment on drug elimination is usually stated in terms of creatinine clearance as a surrogate for glomerular filtration rate (GFR).

The information on dosage adjustment in the BNF is expressed in terms of eGFR, rather than creatinine clearance, for most drugs (exceptions include toxic drugs and patients at extremes of weight). Although the two measures of renal function are not interchangeable, in practice, for most drugs and for most patients (over 18 years) of average build and height, eGFR (MDRD ‘formula’) can be used to determine dosage adjustments in place of creatinine clearance. An individual’s absolute glomerular filtration rate can be calculated from the eGFR as follows: $\text{GFR}_{\text{Absolute}} = \text{eGFR} \times (\text{individual’s body surface area}/1.73)$

Toxic drugs For potentially toxic drugs with a small safety margin, creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust drug dosages in addition to plasma-drug concentration and clinical response.
Prescribing in pregnancy

Overview
Drugs can have harmful effects on the embryo or fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a woman of childbearing age or for men trying to father a child. During the first trimester drugs can produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy. During the second and third trimesters drugs can affect the growth or functional development of the fetus, or they can have toxic effects on fetal tissues. Drugs given shortly before term or during labour can have adverse effects on labour or on the neonate after delivery. Not all the damaging effects of intra-uterine exposure to drugs are obvious at birth, some may only manifest later in life. Such late-onset effects include malignancy, e.g. adenocarcinoma of the vagina after puberty in females exposed to diethylstilbestrol in the womb, and adverse effects on intellectual, social, and functional development. The BNF and BNF for Children identifies drugs which:

- may have harmful effects in pregnancy and indicates the trimester of risk
- are not known to be harmful in pregnancy

The information is based on human data, but information from animal studies has been included for some drugs when its omission might be misleading. Maternal drug doses may require adjustment during pregnancy due to changes in maternal physiology but this is beyond the scope of the BNF and BNF for Children.

Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF and BNF for Children.

Important
Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used. Few drugs have been shown conclusively to be teratogenic in humans, but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available when there is a known risk of certain defects.

Absence of information does not imply safety. It should be noted that the BNF and BNF for Children provide independent advice and may not always agree with the product literature.

Information on drugs and pregnancy is also available from the UK Teratology Information Service. www.uktis.org. Tel: 0344 892 0909 (09.00–17:00 Monday to Friday; urgent enquiries only outside these hours).

Prescribing in breast-feeding

Overview
Breast-feeding is beneficial; the immunological and nutritional value of breast milk to the infant is greater than that of formula feeds. Although there is concern that drugs taken by the mother might affect the infant, there is very little information on this. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from:

- the amount of drug or active metabolite of the drug delivered to the infant (dependent on the pharmacokinetic characteristics of the drug in the mother);
- the efficiency of absorption, distribution, and elimination of the drug by the infant (infant pharmacokinetics);
- the nature of the effect of the drug on the infant (pharmacodynamic properties of the drug in the infant).

The amount of drug transferred in breast milk is rarely sufficient to produce a discernible effect on the infant. This applies particularly to drugs that are poorly absorbed and need to be given parenterally. However, there is a theoretical possibility that a small amount of drug present in breast milk can induce a hypersensitivity reaction. A clinical effect can occur in the infant if a pharmacologically significant quantity of the drug is present in milk. For some drugs (e.g. fluvastatin p. 192), the ratio between the concentration in milk and that in maternal plasma may be high enough to expose the infant to adverse effects. Some infants, such as those born prematurely or who have jaundice, are at a slightly higher risk of toxicity.

Some drugs inhibit the infant’s sucking reflex (e.g. phenobarbital p. 33), while others can affect lactation (e.g. bromocriptine p. 391). The BNF identifies drugs:

- that should be used with caution or are contra-indicated in breast-feeding;
- that can be given to the mother during breastfeeding because they are present in milk in amounts which are too small to be harmful to the infant;
- that might be present in milk in significant amount but are not known to be harmful.

Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.

Important
For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only essential drugs to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast-feeding, absence of information does not imply safety.
Prescribing in palliative care

Overview
Prescribing in palliative care is an approach that improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual. Careful assessment of symptoms and needs of the patient should be undertaken by a multidisciplinary team.

Specialist palliative care is available in most areas as day hospice care, home-care teams (often known as Macmillan teams), in-patient hospice care, and hospital teams. Many acute hospitals and teaching centres now have consultative, hospital-based teams.

Hospice care of terminally ill patients has shown the importance of symptom control and psychosocial support of the patient and family. Families should be included in the care of the patient if they wish.

Many patients wish to remain at home with their families. Although some families may at first be afraid of caring for the patient at home, specialist care provided by community nursing services, social services, voluntary agencies and hospices together with the general practitioner. The family may be reassured by the knowledge that the patient will be admitted to a hospital or hospice if the family cannot cope.

Drug treatment
The number of drugs should be as few as possible, for even the taking of medicine may be an effort.

Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, when parenteral medication may be necessary.

Pain
Pain management in palliative care is focused on achieving control of pain by administering the right drug in the right dose at the right time. Analgesics can be divided into three broad classes: non-opioid (paracetamol p. 414, NSAID), opioid (e.g. codeine phosphate p. 421 ‘weak’, morphine p. 429 ‘strong’) and adjuvant (e.g. antidepressants, antiepileptics). Drugs from the different classes are used alone or in combination according to the type of pain and response to treatment. Analgesics are more effective in preventing pain than in the relief of established pain; it is important that they are given regularly.

Paracetamol p. 414 or a NSAID given regularly will often be sufficient to manage mild pain. If non-opioid analgesics alone are not sufficient, then an opioid analgesic alone or in combination with a non-opioid analgesic at an adequate dosage, may be helpful in the control of moderate pain.

Codeine phosphate p. 421 or tramadol hydrochloride p. 435 can be considered for moderate pain. If these preparations do not control the pain then morphine p. 429 is the most useful opioid analgesic. Alternatives to morphine p. 429, including transdermal buprenorphine p. 417, transdermal fentanyl p. 424, hydromorphone hydrochloride p. 428, methadone hydrochloride p. 464, or oxycodone hydrochloride p. 431, should be initiated by those with experience in palliative care. Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Bone metastases
In addition to the above approach, radiotherapy, bisphosphonates, and radioactive isotopes of strontium ranelate p. 669 (Metastron® available from GE Healthcare) may be useful for pain due to bone metastases.

Neuropathic pain
Patients with neuropathic pain may benefit from a trial of a tricyclic antidepressant. An antiepileptic may be added or substituted if pain persists; gabapentin p. 295 and pregabalin p. 304 are licensed for neuropathic pain. Ketamine p. 1189 is sometimes used under specialist supervision for neuropathic pain that responds poorly to opioid analgesics. Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone p. 618, which reduces oedema around the tumour, thus reducing blemishes, nerve blocks or intrathecal catheters can be considered when pain is localised to a specific area.

Pain management with opioids

Oral route
Treatment with morphine p. 429 is given by mouth as immediate-release or modified-release preparations. During the titration phase the initial dose is based on the previous medication used, the severity of the pain, and other factors such as presence of renal impairment, increasing age, or frailty. The dose is given either as an immediate-release preparation 4-hourly or as a modified-release preparation 12-hourly, in addition to rescue doses. If pain occurs between regular doses of morphine (‘breakthrough pain’), an additional dose (‘rescue dose’) of immediate-release morphine should be given. An additional dose should also be given 30 minutes before an activity that causes pain, such as wound dressing. The standard dose of a strong opioid for breakthrough pain is usually one-twentieth to one-sixth of the regular 24-hour dose, repeated every 2–4 hours as required (up to hourly may be needed if pain is severe or in the last days of life). Review pain management if rescue analgesic is required frequently (twice daily or more). Each patient should be assessed on an individual basis.

Formulations of fentanyl p. 424 that are administered nasally, buccally or sublingually are also licensed for breakthrough pain.

When adjusting the dose of morphine, the number of rescue doses required and the response to them should be taken into account; increments of morphine should not exceed one-third to one-half of the total daily dose every 24 hours.

Thereafter, the dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics should also be considered. Upward titration of the dose of morphine stops when either the pain is relieved or unacceptable adverse effects occur, after which it is necessary to consider alternative measures.

Morphine immediate-release 30mg 4-hourly (or modified-release 100mg 12-hourly) is usually adequate for most patients; some patients require morphine immediate-release up to 200mg 4-hourly (or modified-release 600mg 12-hourly), occasionally more is needed.

Once their pain is controlled, patients started on 4-hourly immediate-release morphine can be transferred to the same total 24-hour dose of morphine given as the modified-release preparation for 12-hourly or 24-hourly administration. The first dose of the modified-release preparation is given with, or within 4 hours of, the last dose of the immediate-release preparation. For preparations suitable for 12-hourly or 24-hourly administration see modified-release preparations under morphine p. 429.

Increments should be made to the dose, not to the frequency of administration. The patient must be monitored closely for efficacy and side-effects, particularly constipation, and nausea and vomiting. A suitable laxative should be prescribed routinely.

Oxycodone hydrochloride p. 431 can be used in patients who require an opioid but cannot tolerate morphine. If the patient is already receiving an opioid, oxycodone hydrochloride should be started at a dose equivalent to the current analgesic (see below). Oxycodone hydrochloride immediate-release preparations can be given for breakthrough pain.
This table is only an approximate guide (doses may not correspond with those given in clinical practice); patients should be carefully monitored after any change in medication and dose titration may be required.

<table>
<thead>
<tr>
<th>Analgesic/Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine: PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Diamorphine: IM, IV, SC</td>
<td>3 mg</td>
</tr>
<tr>
<td>Dihydrocodeine: PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Hydromorphone: PO</td>
<td>2 mg</td>
</tr>
<tr>
<td>Morphine: PO</td>
<td>10 mg</td>
</tr>
<tr>
<td>Morphine: IM, IV, SC</td>
<td>5 mg</td>
</tr>
<tr>
<td>Oxycodone: PO</td>
<td>6.6 mg</td>
</tr>
<tr>
<td>Tramadol: PO</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

PO = by mouth; IM = intramuscular; IV = intravenous; SC = subcutaneous

Parenteral route  The equivalent parenteral dose of morphine p. 429 (subcutaneous, intramuscular, or intravenous) is about half of the oral dose. If the patient becomes unable to swallow, generally morphine is administered as a continuous subcutaneous infusion (for details, see Continuous Subcutaneous Infusions below). Diamorphine hydrochloride p. 423 is sometimes preferred, because being more soluble, it can be given in a smaller volume. The equivalent subcutaneous dose of diamorphine hydrochloride is about one-third of the oral dose of morphine.

If the patient can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous infusion of morphine or diamorphine hydrochloride p. 423, see table above of approximate equivalent doses of morphine and diamorphine hydrochloride. The infusion is discontinued when the first oral dose of morphine is given.

Rectal route Morphine p. 429 is also available for rectal administration as suppositories; alternatively oxycodone hydrochloride p. 431 suppositories can be obtained on special order.

Transdermal route Transdermal preparations of fentanyl p. 424 and buprenorphine p. 417 are available, they are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations, see under buprenorphine p. 417 and fentanyl p. 424 (inappropriate use has caused fatalities). Immediate-release morphine p. 429 can be given for breakthrough pain. The following 24-hour oral doses of morphine are considered to be approximately equivalent to the buprenorphine and fentanyl patches shown, however when switching due to possible opioid-induced hyperalgesia, reduce the calculated equivalent dose of the new opioid by one-quarter to one-half.

#### Buprenorphine patches are approximately equivalent to the following 24-hour doses of oral morphine

- morphine salt 12 mg daily  $\approx$ BuTrans® ‘S’ patch: 7-day patches
- morphine salt 24 mg daily  $\approx$ BuTrans® ‘10’ patch: 7-day patches
- morphine salt 48 mg daily  $\approx$ BuTrans® ‘20’ patch: 7-day patches
- morphine salt 84 mg daily  $\approx$ Transteck® ‘35’ patch: 4-day patches
- morphine salt 126 mg daily  $\approx$ Transteck® ‘52.5’ patch: 4-day patches
- morphine salt 168 mg daily  $\approx$ Transteck® ‘70’ patch: 4-day patches

Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

#### 72-hour Fentanyl patches are approximately equivalent to the following 24-hour doses of oral morphine

- morphine salt 30 mg daily  $\approx$ fentanyl ‘12’ patch
- morphine salt 60 mg daily  $\approx$ fentanyl ‘25’ patch
- morphine salt 120 mg daily  $\approx$ fentanyl ‘50’ patch
- morphine salt 180 mg daily  $\approx$ fentanyl ‘75’ patch
- morphine salt 240 mg daily  $\approx$ fentanyl ‘100’ patch

Fentanyl equivalences in this table are for patients on well-tolerated opioid therapy for long periods; for patients who are opioid naive or who have been stable on oral morphine or other immediate release opioid for only several weeks, see Transdermal Route. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

#### Symptom control

Several recommendations in this section involve unlicensed indications or routes.

**Anorexia** Anorexia may be helped by prednisolone p. 622 or dexamethasone p. 618.

**Bowel colic and excessive respiratory secretions** Bowel colic and excessive respiratory secretions may be reduced by a subcutaneous injection of hyoscine hydrobromide p. 409, hyoscine butylbromide p. 81, or glycopyrronium bromide p. 233. These antimuscarinics are generally given every 4 hours when required, but hourly use is occasionally necessary, particularly in excessive respiratory secretions. If symptoms persist, they can be given regularly via a continuous infusion device. Care is required to avoid the discomfort of dry mouth.

**Capillary bleeding** Capillary bleeding can be treated with tranexamic acid p. 104 by mouth; treatment is usually discontinued one week after the bleeding has stopped, or, if necessary, it can be continued at a reduced dose. Alternatively, gauze soaked in tranexamic acid 100 mg/mL or adrenaline/epinephrine solution 1 mg/mL (1 in 1000) p. 211 can be applied to the affected area. Vitamin K may be useful for the treatment and prevention of bleeding associated with prolonged clotting in liver disease. In severe chronic cholestasis, absorption of vitamin K may be impaired; either parenteral or water-soluble oral vitamin K
(see phytomenadione p. 958 and menadion sodium phosphate p. 957) should be considered.

**Constipation** Constipation is a common cause of distress and is almost invariable after administration of an opioid analgesic. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer p. 58) or lactulose solution p. 52 with a senna preparation p. 59 should be used. Methylbetalactone bromide p. 60 is licensed for the treatment of opioid-induced constipation.

**Convulsions** Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin p. 302 or carbamazepine p. 291 should be considered. When oral medication is no longer possible, diazepam p. 321 given rectally, or phenobarbital p. 313 by injection is continued as prophylaxis. For the use of midazolam p. 318 by subcutaneous infusion using a continuous infusion device see below.

**Dry mouth** Dry mouth may be relieved by good mouth care and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva, dry mouth associated with candidiasis can be treated by oral preparations of nystatin p. 1073 or miconazole p. 760, alternatively, fluconazole p. 548 can be given by mouth. Dry mouth may be caused by certain medications including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antiemetics; if possible, an alternative preparation should be considered.

**Dysphagia** A corticosteroid such as dexamethasone p. 618 may help, temporarily, if there is an obstruction due to tumour. See also **Dry mouth**, above.

**Dyspnoea** Breathlessness at rest may be relieved by regular oral morphine p. 429 in carefully titrated doses. Diazepam p. 321 may be helpful for dyspnoea associated with anxiety. A corticosteroid, such as dexamethasone p. 618, may also be helpful if there is bronchospasm or partial obstruction.

**Fungating tumours** Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole p. 499 is often required to reduce malodour but topical metronidazole p. 1084 is also used.

**Gastro-intestinal pain** The pain of bowel colic may be reduced by loperamide hydrochloride p. 3. Hyoscine hydrobromide p. 409 may also be helpful, given sublingually as Kwells® tablets. Subcutaneous injections of hyoscine butylbromide p. 81, hyoscine hydrobromide, and glycopyrronium bromide p. 233 can also be used to treat bowel colic.

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent and a prokinetic such as domperidone p. 402 before meals.

**Hiccup** Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiflatulent. If this fails, metoclopramide hydrochloride p. 403 by mouth or by subcutaneous or intramuscular injection can be added; if this also fails, baclofen p. 985, or nifedipine p. 153, or chlorpromazine hydrochloride p. 361 can be tried.

**Insomnia** Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam p. 451, may be useful.

**Intractable cough** Intractable cough may be relieved by moist inhalations or by regular administration of oral morphine p. 429. Methadone hydrochloride linctus p. 464 should be avoided because it has a long duration of action and tends to accumulate.

**Muscle spasm** The pain of muscle spasm can be helped by a muscle relaxant such as diazepam p. 321 or baclofen p. 985.

**Nausea and vomiting** Nausea and vomiting are common in patients with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic is started. A prokinetic antiemetic may be a preferred choice for first-line therapy.

Nausea and vomiting may occur with opioid therapy particularly in the initial stages but can be prevented by giving an antiemetic such as haloperidol p. 363 or metoclopramide hydrochloride p. 403. An antiemetic is usually necessary only for the first 4 or 5 days and therefore combined preparations containing an opioid with an antiemetic are not recommended because they lead to unnecessary antiemetic therapy (and associated side-effects when used long-term).

Metoclopramide hydrochloride has a prokinetic action and is used by mouth for nausea and vomiting associated with gastritis, gastric stasis, and functional bowel obstruction. Drugs with antimuscarinic effects antagonise prokinetic drugs and, if possible, should not be used concurrently. Haloperidol is used by mouth for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure). Cyclizine p. 401 is given by mouth. It is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness. Levomepromazine p. 411 is used as an antiemetic; it is given by mouth or by subcutaneous injection at bedtime. For the dose by subcutaneous infusion see below. Dexamethasone p. 618 by mouth can be used as an adjunct.

Antiemetic therapy should be reviewed every 24 hours; it may be necessary to substitute the antiemetic or to add another one.

For the administration of antiemetics by subcutaneous infusion using a continuous infusion device, see below. For the treatment of nausea and vomiting associated with cancer chemotherapy see Cytotoxic drugs p. 797.

**Pruritus** Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients. In the case of obstructive jaundice, further measures include administration of colestyramine p. 186.

**Raised intracranial pressure** Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone p. 618 and should be given before 6 p.m. to reduce the risk of insomnia.

**Restlessness and confusion** Restlessness and confusion may require treatment with an antipsychotic, e.g. haloperidol p. 363 or levomepromazine p. 411, by mouth or by subcutaneous injection, both repeated every 2 hours if required. The dose and frequency is adjusted according to the level of patient distress and the response. A regular maintenance dose should also be considered, given twice daily either by mouth or by subcutaneous injection; alternatively use a continuous infusion device. Levomepromazine is licensed to treat pain in palliative care—this use is reserved for distressed patients with severe pain unresponsive to other measures (seek specialist advice).

**Continuous subcutaneous infusions** Although drugs can usually be administered by mouth to control the symptoms of advanced cancer, the parental route may sometimes be necessary. Repeated administration of **intramuscular injections** can be difficult in a cachectic patient. This has led to the use of portable continuous infusion devices, such as syringe drivers, to give a continuous **subcutaneous infusion**, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Indications for the **parenteral route** are:
Mixing and compatibility

Pain control

Convulsions

If a patient has previously been receiving an antiepileptic drug or medication, antiepileptic should not be stopped. Midazolam absorption and inhibits water secretion in the small bowel, continuous subcutaneous infusion is particularly likely to precipitate if mixed with midazolam.

Syringe driver rate settings

Staff using syringe drivers should be adequately trained and different rate settings should be clearly identified and differentiated; incorrect use of syringe drivers is a common cause of medication errors.

Bowel colic and excessive respiratory secretions

Hyoscine hydrobromide p. 409 effectively reduces respiratory secretions and bowel colic and is sedative (but occasionally causes paradoxical agitation). Hyoscine butylbromide p. 81 is used for bowel colic and for excessive respiratory secretions, and is less sedative than hyoscine hydrobromide. Glycopyrronium bromide p. 233 may also be used to treat bowel colic or excessive respiratory secretions.

Confusion and restlessness

Haloperidol p. 363 has little sedative effect. Levomepromazine p. 411 has a sedative effect. Midazolam p. 318 is a sedative and an antiepileptic that may be used in addition to an antipsychotic drug in a very restless patient. Midazolam is also used for myoclonus.

Convulsions

If a patient has previously been receiving an antiepileptic drug or has a primary or secondary cerebral tumour or is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam p. 318 is the benzodiazepine antiepileptic of choice for continuous subcutaneous infusion.

Nausea and vomiting

Haloperidol p. 363 and levomepromazine p. 411 can both be given as a subcutaneous infusion but sedation can limit the dose of levomepromazine. Cyclizine is particularly likely to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below). Metoclopramide hydrochloride p. 403 can cause skin reactions.

Octracetide p. 846, which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, can be used by subcutaneous infusion to reduce intestinal secretions and to reduce vomiting due to bowel obstruction.

Pain control

Diamorphine hydrochloride p. 423 is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table shows approximate equivalent doses of morphine and diamorphine hydrochloride.

Mixing and compatibility

The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, chlorpromazine hydrochloride p. 361, prochlorperazine p. 365, and diazepam p. 321 are contra-indicated as they cause skin reactions at the injection site; to a lesser extent cyclizine p. 401 and levomepromazine p. 411 also sometimes cause local irritation.

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to their hypotonicity). The use of physiological saline (sodium chloride 0.9% p. 914) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

Compatibility with diamorphine

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL either water for injections or physiological saline (sodium chloride 0.9%) is a suitable diluent—above that strength only water for injections is used (to avoid precipitation).

The following can be mixed with diamorphine:

- **Cyclizine**, may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9% or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.
- **Dexamethasone**, special care is needed to avoid precipitation of dexamethasone when preparing it.
- **Haloperidol**, mixtures of haloperidol and diamorphine are likely to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
- **Hyoscine butylbromide**
- **Hyoscine hydrobromide**
- **Levomepromazine**
- **Metoclopramide**, under some conditions infusions containing metoclopramide become discoloured; such solutions should be discarded.
- **Midazolam**

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discolouration) and to ensure that the infusion is running at the correct rate.

Problems encountered with syringe drivers

The following are problems that may be encountered with syringe drivers and the action that should be taken:

- If the subcutaneous infusion runs too quickly check the rate setting and the calculation;
- If the subcutaneous infusion runs too slowly check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- If there is an injection site reaction make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.
Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours

These equivalences are *approximate only* and should be adjusted according to response

<table>
<thead>
<tr>
<th>ORAL MORPHINE</th>
<th>PARENTERAL MORPHINE</th>
<th>PARENTERAL DIAMORPHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine sulfate over 24 hours</td>
<td>Subcutaneous infusion of morphine sulfate over 24 hours</td>
<td>Subcutaneous infusion of diamorphine hydrochloride over 24 hours</td>
</tr>
<tr>
<td>30 mg</td>
<td>15 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>60 mg</td>
<td>30 mg</td>
<td>20 mg</td>
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<td>90 mg</td>
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<td>260 mg</td>
</tr>
<tr>
<td>960 mg</td>
<td>480 mg</td>
<td>320 mg</td>
</tr>
<tr>
<td>1200 mg</td>
<td>600 mg</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle). To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
Prescribing in the elderly

Overview
Old people, especially the very old, require special care and consideration from prescribers. *Medicines for Older People*, a component document of the National Service Framework for Older People (Department of Health. National Service Framework for Older People. London: Department of Health, March 2001), describes how to maximise the benefits of medicines and how to avoid excessive, inappropriate, or inadequate consumption of medicines by older people.

Appropriate prescribing
Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance. The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients' medicines should be reviewed regularly and medicines which are not of benefit should be stopped. Non-pharmacological measures may be more appropriate for symptoms such as headache, sleeplessness, and light-headedness when associated with social stress as in widowhood, loneliness, and family dispersal.

In some cases prophylactic drugs are inappropriate if they are likely to complicate existing treatment or introduce unnecessary side-effects, especially in elderly patients with poor prognosis or with poor overall health. However, elderly patients should not be denied medicines which may help them, such as anticoagulants or antiplatelet drugs for atrial fibrillation.

Form of medicine
Frail elderly patients may have difficulty swallowing tablets; if left in the mouth, ulceration may develop. They should always be encouraged to take their tablets or capsules with enough fluid, and whilst in an upright position to avoid the possibility of oesophageal ulceration. It can be helpful to discuss with the patient the possibility of taking the drug as a liquid if available.

Manifestations of ageing
In the very old, manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing. In addition, age-related muscle weakness and difficulty in maintaining balance should not be confused with neurological disease. Disorders such as light-headedness not associated with postural or postprandial hypotension are unlikely to be helped by drugs.

Sensitivity
The nervous system of elderly patients is more sensitive to many commonly used drugs, such as opioid analgesics, benzodiazepines, antipsychotics, and antiparkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as anti-hypertensives and NSAIDs.

Pharmacokinetics
Pharmacokinetic changes can markedly increase the tissue concentration of a drug in the elderly, especially in debilitated patients. The most important effect of age is reduced renal clearance. Many aged patients thus *excrete drugs slowly*, and are highly susceptible to nephrotoxic drugs. Acute illness can lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Hence, a patient stabilised on a drug with a narrow margin between the therapeutic and the toxic dose (e.g. digoxin p. 103) can rapidly develop adverse effects in the aftermath of a myocardial infarction or a respiratory-tract infection. The hepatic metabolism of lipid soluble drugs is reduced in elderly patients because there is a reduction in liver volume. This is important for drugs with a narrow therapeutic window.

Adverse reactions
Adverse reactions often present in the elderly in a vague and non-specific fashion. Confusion is often the presenting symptom (caused by almost any of the commonly used drugs). Other common manifestations are constipation (with antimuscarnics and many tranquilisers) and postural hypotension and falls (with diuretics and many psychotropics).

Hypnotics
Many hypnotics with long half-lives have serious hangover effects, including drowsiness, unsteady gait, slurred speech, and confusion. Hypnotics with short half-lives should be used but they too can present problems. Short courses of hypnotics are occasionally useful for helping a patient through an acute illness or some other crisis but every effort must be made to avoid dependence. Benzodiazepines impair balance, which can result in falls.

Diuretics
Diuretics are overprescribed in old age and should not be used on a long-term basis to treat simple gravitational oedema which will usually respond to increased movement, raising the legs, and support stockings. A few days of diuretic treatment may speed the clearing of the oedema but it should rarely need continued drug therapy.

NSAIDs
Bleeding associated with aspirin and other NSAIDs is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place older patients at particular risk.

Owing to the increased susceptibility of the elderly to the side-effects of NSAIDs the following recommendations are made:

- for osteoarthritis, soft-tissue lesions, and back pain, first try measures such as weight reduction (if obese), warmth, exercise, and use of a walking stick;
- for osteoarthritis, soft-tissue lesions, back pain, and pain in rheumatoid arthritis, paracetamol p. 414 should be used first and can often provide adequate pain relief;
- alternatively, a low-dose NSAID (e.g. ibuprofen p. 999 up to 1.2 g daily) may be given;
- for pain relief when either drug is inadequate, paracetamol in a full dose plus a low-dose NSAID may be given;
- if necessary, the NSAID dose can be increased or an opioid analgesic given with paracetamol;
- do not give two NSAIDs at the same time.

Prophylaxis of NSAID-induced peptic ulcers may be required if continued NSAID treatment is necessary see, NSAID-associated ulcers under Peptic ulceration p. 68.

Other drugs
Other drugs which commonly cause adverse reactions are antiparkinsonian drugs, anti-hypertensives, psychotropics, and digoxin p. 103. The usual maintenance dose of digoxin in very old patients is 125 micrograms daily (62.5 micrograms in those with renal disease); lower doses are often inadequate but toxicity is common in those given 250 micrograms daily. Drug-induced blood disorders are much more common in the elderly. Therefore drugs with a tendency to cause bone marrow depression (e.g. co-trimoxazole p. 518, mianserin
hydrochloride p. 348) should be avoided unless there is no acceptable alternative. The elderly generally require a lower maintenance dose of warfarin sodium p. 131 than younger adults; once again, the outcome of bleeding tends to be more serious.

**Guidelines**

Always consider whether a drug is indicated at all.

**Limit range** It is a sensible policy to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.

**Reduce dose** Dosage should generally be substantially lower than for younger patients and it is common to start with about 50% of the adult dose. Some drugs (e.g. long-acting antidiabetic drugs such as glibenclamide p. 645) should be avoided altogether.

**Review regularly** Review repeat prescriptions regularly. In many patients it may be possible to stop some drugs, provided that clinical progress is monitored. It may be necessary to reduce the dose of some drugs as renal function declines.

**Simplify regimens** Elderly patients benefit from simple treatment regimens. Only drugs with a clear indication should be prescribed and whenever possible given once or twice daily. In particular, regimens which call for a confusing array of dosage intervals should be avoided.

**Explain clearly** Write full instructions on every prescription (including repeat prescriptions) so that containers can be properly labelled with full directions. Avoid imprecisions like ‘as directed’. Child-resistant containers may be unsuitable.

**Repeats and disposal** Instruct patients what to do when drugs run out, and also how to dispose of any that are no longer necessary. Try to prescribe matching quantities. If these guidelines are followed most elderly people will cope adequately with their own medicines. If not then it is essential to enrol the help of a third party, usually a relative or a friend.

**Drugs and sport**

**Anti-doping**

UK Anti-Doping, the national body responsible for the UK’s anti-doping policy, advises that athletes are personally responsible should a prohibited substance be detected in their body. Information regarding the use of medicines in sport is available from:

- UK Anti-doping
  Fleetbank House
  2-6 Salisbury Square
  London
  EC4Y 8AE
  (020) 7842 3450
  ukad@ukad.org.uk
  www.ukad.org.uk

Information about the prohibited status of specific medications based on the current World Anti-Doping Agency Prohibited List is available from Global Drug Reference Online: www.globaldro.com/UK/search

**General Medical Council’s advice**

Doctors who prescribe or collude in the provision of drugs or treatment with the intention of improperly enhancing an individual’s performance in sport contravene the GMC’s guidance, and such actions would usually raise a question of a doctor’s continued registration. This does not preclude the provision of any care or treatment where the doctor’s intention is to protect or improve the patient’s health.
Prescribing in dental practice

General guidance
Advice on the drug management of dental and oral conditions has been integrated into the main text. For ease of access, guidance on such conditions is usually identified by means of a relevant heading (e.g. Dental and Orofacial Pain) in the appropriate sections of the BNF. The following is a list of topics of particular relevance to dentists.

Prescribing by dentists, see Prescription writing p. 5
Oral side-effects of drugs, see Adverse reactions to drugs p. 12
Medical emergencies in dental practice, see below
Medical problems in dental practice, see below

Drug management of dental and oral conditions

Dental and Orofacial Pain

Neuropathic pain p. 446
Non-opioid analgesics and compound analgesic preparations, see Analgesics p. 412
Opioid analgesics, see Analgesics p. 412
Non-steroidal anti-inflammatory drugs p. 987

Oral infections
Bacterial infections, see Antibacterials, principles of therapy p. 467
Phenoxymethylpenicillin p. 505
Broad-spectrum penicillins (amoxicillin p. 506 and ampicillin p. 507)
Cephalosporins (cefalexin p. 485 and cefradine p. 485)
Tetracyclines p. 520
Macrolides (clarithromycin p. 496, erythromycin p. 497 and azithromycin p. 495)
Clindamycin p. 493
Metronidazole p. 499
Fusidic acid p. 527

Fungal infections
Local treatment, see Oropharyngeal fungal infections p. 1071
Systemic treatment, see Antifungals, systemic use p. 544

Viral infections
Herpetic gingivostomatitis, local treatment, see Oropharyngeal viral infections p. 1073
Herpetic gingivostomatitis, systemic treatment, see Oropharyngeal viral infections p. 1073 and Herpesvirus infections p. 584
Herpes labialis, see Skin infections p. 1082

Adhaesthetics, anxiolitics and hypnotics
Sedation, anaesthesia, and resuscitation in dental practice p. 1174
Hypnotics, see Hypnotics and anxiolitics p. 447
Sedation for dental procedures, see Hypnotics and anxiolitics p. 447
Local anaesthesia p. 1191

Minerals
Fluorides p. 942

Oral ulceration and inflammation p. 1067
Mouthwashes, gargles and dentifrices, see Mouthwashes and other preparations for oropharyngeal use p. 1064
Dry mouth, see Treatment of dry mouth p. 1062
Aromatic inhalations, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 277
Nasal decongestants, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 277

Dental Practitioners’ Formulary p. 1411

Medical emergencies in dental practice
This section provides guidelines on the management of the more common medical emergencies which may arise in dental practice. Dentists and their staff should be familiar with standard resuscitation procedures, but in all circumstances it is advisable to summon medical assistance as soon as possible. See also algorithm of the procedure for Cardiopulmonary resuscitation p. 1465.

The drugs referred to in this section include:
Adrenaline/epinephrine Injection p. 211, adrenaline 1 in 1000, (adrenaline 1 mg/mL as acid tartrate), 1 mL amp.
Aspirin Dispersible Tablets 300 mg p. 114
Glucagon Injection p. 660, glucagon (as hydrochloride), 1- unit vial (with solvent) p. 660
Glucose (for administration by mouth) p. 915
Glycerol trinitrate Spray p. 207
Midazolam Oromucosal Solution p. 318, midazolam 5 mg/mL
Oxytocin
Salbutamol Aerosol Inhalation p. 239, salbutamol 100 micrograms/metered inhalation p. 239

Adrenal insufficiency
Adrenal insufficiency may follow prolonged therapy with corticosteroids and can persist for years after stopping. A patient with adrenal insufficiency may become hypotensive under the stress of a dental visit (important: see individual monographs for details of corticosteroid cover before dental surgical procedures under general anaesthesia).

Management
● Lay the patient flat
● Give oxygen
● Transfer patient urgently to hospital

Anaphylaxis
A severe allergic reaction may follow oral or parenteral administration of a drug. Anaphylactic reactions in dentistry may follow the administration of a drug or contact with substances such as latex in surgical gloves. In general, the more rapid the onset of the reaction the more profound it tends to be. Symptoms may develop within minutes and rapid treatment is essential. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens (including those for topical application, particularly if they are intended for use in the mouth or for application to the nasal mucosa).

Symptoms and signs
● Paraesthesia, flushing, and swelling of face
● Generalised itching, especially of hands and feet
● Bronchospasm and laryngospasm (with wheezing and difficulty in breathing)
● Rapid weak pulse together with fall in blood pressure and pallor; finally cardiac arrest

Management
First-line treatment includes securing the airway, restoration of blood pressure (laying the patient flat and raising the feet, or in the recovery position if unconscious or nauseous and at risk of vomiting), and administration of adrenaline/epinephrine injection p. 211. This is given intramuscularly in a dose of 500 micrograms (0.5 mL adrenaline injection 1 in 1000); a dose of 300 micrograms (0.3 mL adrenaline injection 1 in 1000) may be appropriate for immediate self-administration. The dose is repeated if
necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. **Oxygen** administration is also of primary importance. Arrangements should be made to transfer the patient to hospital urgently.

### Asthma
Patients with asthma may have an attack while at the dental surgery. Most attacks will respond to 2 puffs of the patient’s short-acting beta-agonist inhaler such as salbutamol 100 micrograms/puff. Further puffs are required if the patient does not respond rapidly. If the patient is unable to use the inhaler effectively, further puffs should be given through a large-volume spacer device (or, if not available, through a plastic or paper cup with a hole in the bottom for the inhaler mouthpiece). If the response remains unsatisfactory, or if further deterioration occurs, then the patient should be transferred urgently to hospital. Whilst awaiting transfer, **oxygen** should be given with salbutamol 5 mg or terbutaline sulfate 10 mg p. 241 by nebuliser; if a nebuliser is unavailable, then 2–10 puffs of salbutamol 100 micrograms-metered inhalation should be given (preferably by a large-volume spacer), and repeated every 10–20 minutes if necessary. If asthma is part of a more generalised anaphylactic reaction, an intramuscular injection of adrenaline/epinephrine p. 211 (as detailed under Anaphylaxis) should be given. Patients with severe chronic asthma or whose asthma has deteriorated previously during a dental procedure may require an increase in their prophylactic medication before a dental procedure. This should be discussed with the patient’s medical practitioner and may include increasing the dose of inhaled or oral corticosteroid.

### Cardiac emergencies
If there is a history of angina the patient will probably carry glyceryl trinitrate spray or tablets p. 207 (or isosorbide dinitrate tablets p. 208) and should be allowed to use them. Hospital admission is not necessary if symptoms are mild and resolve rapidly with the patient’s own medication. See also Coronary Artery Disease below. **Arrhythmias** may lead to a sudden reduction in cardiac output with loss of consciousness. Medical assistance should be summoned. For advice on pacemaker interference, see also Pacemakers below. The pain of myocardial infarction is similar to that of angina but generally more severe and more prolonged. For general advice see also Coronary Artery Disease below.

#### Symptoms and signs of myocardial infarction:
- Progressive onset of severe, crushing pain across front of chest; pain may radiate towards the shoulder and down arm, or into neck and jaw
- Skin becomes pale and clammy
- Nausea and vomiting are common
- Pulse may be weak and blood pressure may fall
- Breathlessness

#### Initial management of myocardial infarction:
Call immediately for medical assistance and an ambulance, as appropriate.
Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. **Oxygen** may be administered.
Sublingual glyceryl trinitrate p. 207 may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug. Reassure the patient as much as possible to relieve further anxiety. If available, aspirin p. 114 in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see Management of ST-Segment Elevation Myocardial Infarction. If the patient collapses and loses consciousness attempt standard resuscitation measures. See also algorithm of the procedure for Cardiopulmonary resuscitation p. 1465.

### Epileptic seizures
Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

#### Symptoms and signs
- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while

#### Management
During a convulsion try to ensure that the patient is not at risk from injury but make no attempt to put anything in the mouth or between the teeth (in mistaken belief that this will protect the tongue). Give **oxygen** to support respiration if necessary.
Do not attempt to restrain convulsive movements. After convulsive movements have subsided place the patient in the coma (recovery) position and check the airway. After the convulsion the patient may be confused (post-ictal confusion) and may need reassurance and sympathy. The patient should not be sent home until fully recovered. Seek medical attention or transfer the patient to hospital if it was the first episode of epilepsy, or if the convulsion was atypical, prolonged (or repeated), or if injury occurred.
Medication should only be given if convulsive seizures are prolonged (convulsive movements lasting 5 minutes or longer) or repeated rapidly.
Midazolam oromucosal solution p. 318 can be given by the buccal route in adults as a single dose of 10 mg [unlicensed]. For further details on the management of status epilepticus, including details of paediatric doses of midazolam, see Drugs used in status epilepticus (Epilepsy p. 286).
Focal seizures similarly need very little active management (in an automatism only a minimum amount of restraint should be applied to prevent injury). Again, the patient should be observed until post-ictal confusion has completely resolved.

### Hypoglycaemia
Insulin-treated diabetic patients attending for dental treatment under local anaesthesia should inject insulin and eat meals as normal. If food is omitted the blood glucose will fall to an abnormally low level (hypoglycaemia). Patients can often recognise the symptoms themselves and this state responds to sugar in water or a few lumps of sugar. Children may not have such prominent changes but may appear unduly lethargic.

#### Symptoms and signs
- Shaking and trembling
Management
Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of Lucozade®, Energy Original 55 mL, Coca-Cola® 100 mL, Ribena® Blackcurrant 19 mL (to be diluted), 2 teaspoons sugar, and also from 3 sugar lumps. (Proprietary products of quick-acting carbohydrate (e.g. GlucoGel®, DextroGel®, GSF-Syrup®, Rapilose® gel) are available on prescription for the patient to keep to hand in case of hypoglycaemia). If necessary this may be repeated in 10–15 minutes.
If glucose cannot be given by mouth, if it is ineffective, or if the hypoglycaemia causes unconsciousness, glucagon 1 mg (1 unit) should be given by intramuscular (or subcutaneous) injection; a child under 8 years or of body-weight under 25 kg should be given 500 micrograms. Once the patient regains consciousness oral glucose should be administered as above. If glucagon is ineffective or contra-indicated, the patient should be transferred urgently to hospital. The patient must also be admitted to hospital if hypoglycaemia is caused by an oral antidiabetic drug.

Syncope
Insufficient blood supply to the brain results in loss of consciousness. The commonest cause is a vasovagal attack or simple faint (syncope) due to emotional stress.

Symptoms and signs
- Patient feels faint
- Low blood pressure
- Pallor and sweating
- Yawning and slow pulse
- Nausea and vomiting
- Dilated pupils
- Muscular twitching

Management
- Lay the patient as flat as is reasonably comfortable and, in the absence of associated breathlessness, raise the legs to improve cerebral circulation
- Loosen any tight clothing around the neck
- Once consciousness is regained, give sugar in water or a cup of sweet tea

Other possible causes Postural hypotension can be a consequence of rising abruptly or of standing upright for too long; antihypertensive drugs predispose to this. When rising, susceptible patients should take their time. Management is as for a vasovagal attack. Under stressful circumstances, some patients hyperventilate. This gives rise to feelings of faintness but does not usually result in syncope. In most cases reassurance is all that is necessary; rebreathing from cupped hands or a bag may be helpful but calls for careful supervision. Adrenal insufficiency or arrhythmias are other possible causes of syncope.

Medical problems in dental practice
Individuals presenting at the dental surgery may also suffer from an unrelated medical condition; this may require modification to the management of their dental condition. If the patient has systemic disease or is taking other medication, the matter may need to be discussed with the patient’s general practitioner or hospital consultant.

Allergy
Patients should be asked about any history of allergy; those with a history of atopic allergy (asthma, eczema, hay fever, etc.) are at special risk. Those with a history of a severe allergy or of anaphylactic reactions are at high risk—it is essential to confirm that they are not allergic to any medication, or to any dental materials or equipment (including latex gloves). See also Anaphylaxis above.

Arrhythmias
Patients, especially those who suffer from heart failure or who have sustained a myocardial infarction, may have irregular cardiac rhythm. Atrial fibrillation is a common arrhythmia even in patients with normal hearts and is of little concern except that dentists should be aware that such patients may be receiving anticoagulant therapy. The patient’s medical practitioner should be asked whether any special precautions are necessary. Premedication (e.g. with temazepam p. 451) may be useful in some instances for very anxious patients. See also Cardiac emergencies above, and Dental Anaesthesia (Local anaesthesia p. 1191).

Cardiac prostheses
For an account of the risk of infective endocarditis in patients with prosthetic heart valves, see Infective Endocarditis below. For advice on patients receiving anticoagulants, see Thromboembolic disease below.

Coronary artery disease
Patients are vulnerable for at least 4 weeks following a myocardial infarction or following any sudden increase in the symptoms of angina. It would be advisable to check with the patient’s medical practitioner before commencing treatment. See also Cardiac Emergencies above.
Treatment with low-dose aspirin (75 mg daily), clopidogrel p. 115, or dipyridamole p. 116 should not be stopped routinely nor should the dose be altered before dental procedures.
A Working Party of the British Society for Antimicrobial Chemotherapy has not recommended antibiotic prophylaxis for patients following coronary artery bypass surgery.

Cyanotic heart disease
Patients with cyanotic heart disease are at risk in the dental chair, particularly if they have pulmonary hypertension. In such patients a syncopal reaction increases the shunt away from the lungs, causing more hypoxia which worsens the syncopal reaction—a vicious circle that may prove fatal. The advice of the cardiologist should be sought on any patient with congenital cyanotic heart disease. Treatment in hospital is more appropriate for some patients with this condition.

Hypertension
Patients with hypertension are likely to be receiving antihypertensive drugs. Their blood pressure may fall dangerously low under general anaesthesia, see also under Dental Anaesthesia (Local anaesthesia p. 1191).

Immunosuppression and indwelling intraperitoneal catheters
Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis.
The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraventricular catheters.

**Infective endocarditis**

While almost any dental procedure can cause bacteraemia, there is no clear association with the development of infective endocarditis. Routine daily activities such as tooth brushing also produce a bacteraemia and may present a greater risk of infective endocarditis than a single dental procedure.

Antibacterial prophylaxis and chlorhexidine mouthwash p. 1064 are not recommended for the prevention of endocarditis in patients undergoing dental procedures. Such prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

**Reduction of oral bacteraemia**

Patients at risk of endocarditis including those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endotheialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis, should be advised to maintain the highest possible standards of oral hygiene in order to reduce the:

- need for dental extractions or other surgery;
- chances of severe bacteraemia if dental surgery is needed;
- possibility of ‘spontaneous’ bacteraemia.

**Postoperative care**

Patients at risk of endocarditis including those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endotheialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis, should be warned to report to the doctor or dentist any unexplained illness that develops after dental treatment.

Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

**Patients on anticoagulant therapy**

For general advice on dental surgery in patients receiving oral anticoagulant therapy see Thromboembolic Disease below.

**Joint prostheses**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive.

The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

**Pacemakers**

Pacemakers prevent asystole or severe bradycardia. Some ultrasonic scalers, electronic apex locators, electro-analgesic devices, and electrocautery devices interfere with the normal function of pacemakers (including shielded pacemakers) and should not be used. The manufacturer’s literature should be consulted whenever possible. If severe bradycardia occurs in a patient fitted with a pacemaker, electrical equipment should be switched off and the patient placed supine with the legs elevated. If the patient loses consciousness and the pulse remains slow or is absent, cardiopulmonary resuscitation may be needed. Call immediately for medical assistance and an ambulance, as appropriate.


**Thromboembolic disease**

Patients receiving a heparin or an oral anticoagulant such as warfarin sodium p. 131, acenocoumarol (nicoumalone) p. 131, phenindione p. 131, apixaban p. 117, dabigatran etexilate p. 128 or rivaroxaban p. 120 may be liable to excessive bleeding after extraction of teeth or other dental surgery. Often dental surgery can be delayed until the anticoagulant therapy has been completed.

For a patient requiring long-term therapy with warfarin sodium p. 131, the patient’s medical practitioner should be consulted and the International Normalised Ratio (INR) should be assessed 72 hours before the dental procedure.

This allows sufficient time for dose modification if necessary. In those with an unstable INR (including those who require weekly monitoring of their INR, or those who have had some INR measurements greater than 4.0 in the last 2 months), the INR should be assessed within 24 hours of the dental procedure. Patients requiring minor dental procedures (including extractions) who have an INR below 4.0 may continue warfarin sodium without dose adjustment. There is no need to check the INR for a patient requiring a non-invasive dental procedure.

If it is necessary to remove several teeth, a single extraction should be done first; if this goes well further teeth may be extracted at subsequent visits (two or three at a time). Measures should be taken to minimise bleeding during and after the procedure. This includes the use of sutures and a haemostatic such as oxidised cellulose, collagen sponge or resorbable gelatin sponge. Scaling and root planing should initially be restricted to a limited area to assess the potential for bleeding.

For a patient on long-term warfarin sodium, the advice of the clinician responsible for the patient’s anticoagulation should be sought if:

- the INR is unstable, or if the INR is greater than 4.0;
- the patient has thrombocytopenia, haemophilia, or other disorders of haemostasis, or suffers from liver impairment, alcoholism, or renal failure;
- the patient is receiving antiplatelet drugs, cytotoxic drugs or radiotherapy.

Intramuscular injections are contra-indicated in patients taking anticoagulants with an INR above the therapeutic range, and in those with any disorder of haemostasis. In patients taking anticoagulants who have a stable INR within the therapeutic range, intramuscular injections should be avoided if possible; if an intramuscular injection is necessary, the patient should be informed of the increased risk of localised bleeding and monitored carefully.

A local anaesthetic containing a vasoconstrictor should be given by infiltration, or by intraligamentary or mental nerve injection if possible. If regional nerve blocks cannot be avoided the local anaesthetic should be given cautiously using an aspirating syringe.

Drugs which have potentially serious interactions with anticoagulants include aspirin and other NSAIDs,
carbamazepine, imidazole and triazole antifungals (including miconazole), erythromycin, clarithromycin, and metronidazole; for details of these and other interactions with anticoagulants, see Appendix 1 (dabigatran etexilate, heparins, phenindione, rivaroxaban, and coumarins).

Although studies have failed to demonstrate an interaction, common experience in anticoagulant clinics is that the INR can be altered following a course of an oral broad-spectrum antibiotic, such as ampicillin or amoxicillin.

Information on the treatment of patients who take anticoagulants is available at www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant.

Liver disease
Liver disease may alter the response to drugs and drug prescribing should be kept to a minimum in patients with severe liver disease. Problems are likely mainly in patients with jaundice, ascites, or evidence of encephalopathy.

For guidance on prescribing for patients with hepatic impairment, see Prescribing in hepatic impairment p. 19. Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

Renal impairment
The use of drugs in patients with reduced renal function can give rise to many problems. Many of these problems can be avoided by reducing the dose or by using alternative drugs. Special care is required in renal transplantation and immunosuppressed patients; if necessary such patients should be referred to specialists.

For guidance on prescribing in patients with renal impairment, see Prescribing in renal impairment p. 19. Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.

Pregnancy
Drugs taken during pregnancy can be harmful to the fetus and should be prescribed only if the expected benefit to the mother is thought to be greater than the risk to the fetus; all drugs should be avoided if possible during the first trimester.

For guidance on prescribing in pregnancy, see Prescribing in pregnancy p. 21. Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF.

Breast-feeding
Some drugs taken by the mother whilst breast-feeding can be transferred to the breast milk, and may affect the infant.

For guidance on prescribing in breast-feeding, see Prescribing in breast-feeding p. 21. Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.
Chapter 1
Gastro-intestinal system

1 Chronic bowel disorders

1.1 Coeliac disease

Description of condition
Coeliac disease is an autoimmune condition which is associated with chronic inflammation of the small intestine. Dietary proteins known as gluten, which are present in wheat, barley and rye, activate an abnormal immune response in the intestinal mucosa, which can lead to malabsorption of nutrients.

Aims of treatment
The management of coeliac disease is aimed at eliminating symptoms (such as diarrhoea, bloating and abdominal pain) and reducing the risk of complications, including those resulting from malabsorption.

Non-drug treatment
The only effective treatment for coeliac disease is a strict, life-long, gluten-free diet. A range of gluten-free products is available for prescription (see Borderline substances).

Drug treatment
Patients who have coeliac disease are at an increased risk of malabsorption of key nutrients (such as calcium and vitamin D). Their risk of osteoporosis and the need for active treatment of bone disease should form part of the ongoing management of coeliac disease. Supplementation of key nutrients may be required if dietary intake is insufficient.

Patients who have coeliac disease should be advised not to self-medicate with over-the-counter vitamins or mineral supplements. Initiation of supplementation should involve a discussion with a member of the patient’s healthcare team in order to identify the individual needs of the patient and to allow for appropriate ongoing monitoring.

Confirmed cases of refractory coeliac disease should be referred to a specialist centre. Treatment with prednisolone can be considered for initial management while awaiting specialist advice.

Useful Resources

1.2 Diverticular disease and diverticulitis

Diverticular disease and diverticulitis

Description of condition
Diverticular disease is a condition where diverticula (sac-like protrusions of mucosa through the muscular colonic...
A high-fibre diet is recommended for the treatment of symptomatic diverticular disease, although evidence supporting this is inconsistent and of low quality. Bulk-forming drugs have also been used, but evidence of their effectiveness is lacking.

Treatment of uncomplicated diverticulitis includes a low residue diet and bowel rest. Antibacterials are recommended only when the patient presents with signs of infection or is immunocompromised, as there is no evidence to support routine administration.

Patients with complicated diverticulitis or with severe presentation, require hospital admission, treatment with intravenous antibacterials (covering Gram-negative organisms and anaerobes), and bowel rest.

There is insufficient evidence to justify the role of fibre, rifaximin p. 531, antispasmodics, mesalazine p. 37, and probiotics in the prevention or treatment of diverticulitis.

Elective surgery to provide symptomatic relief or prevent recurrence, should be considered for patients following recovery from an episode of complicated diverticulitis. This includes episodes associated with free perforation, abscess, fistula, obstruction, or stricture. Urgent sigmoid colectomy is required for patients with diffuse peritonitis or for those in whom non-operative management of acute diverticulitis fails.

### 1.3 Inflammatory bowel disease

#### Inflammatory bowel disease

Management of acute ulcerative colitis and Crohn’s disease

Chronic inflammatory bowel diseases include ulcerative colitis and Crohn’s disease. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

**Aminosalicylates** (balsalazide sodium p. 36, mesalazine p. 37, olsalazine sodium p. 39, and sulfasalazine p. 39), **corticosteroids** (hydrocortisone p. 620, beclometasone dipropionate p. 40, budesonide p. 41, and prednisolone p. 622), and **drugs that affect the immune response** are used in the treatment of inflammatory bowel disease.

**Treatment of acute ulcerative colitis and Crohn’s disease**

Acute mild to moderate disease affecting the rectum (proctitis) or the recto–sigmoid is treated initially with local application of an aminosalicylate; alternatively, a local corticosteroid can be used but it is less effective. A combination of a local aminosalicylate and a local corticosteroid can be used for proctitis that does not respond to a local aminosalicylate alone. Foam preparations and suppositories are especially useful when patients have difficulty retaining liquid enemas.

Diffuse inflammatory bowel disease or disease that does not respond to local therapy requires oral treatment. Mild disease affecting the proximal colon can be treated with an oral aminosalicylate alone; a combination of a local and an oral aminosalicylate can be used in proctitis or distal colitis. Refractory or moderate inflammatory bowel disease usually requires adjunctive use of an oral corticosteroid such as prednisolone for 4–8 weeks. Modified-release budesonide is licensed for Crohn’s disease affecting the ileum and the ascending colon; it causes fewer systemic side-effects than oral prednisolone but may be less effective. Beclometasone dipropionate by mouth is licensed as an adjunct to mesalazine for mild to moderate ulcerative colitis, but it is not known whether it is as effective as other corticosteroids.

Severe inflammatory bowel disease or disease that is not responding to an oral corticosteroid requires hospital admission and treatment with an intravenous corticosteroid (such as hydrocortisone or methylprednisolone p. 621); other therapy may include intravenous fluid and electrolyte replacement, and parenteral nutrition. Specialist supervision is required for patients who fail to respond adequately to these measures. Patients with severe ulcerative colitis that has not responded to intravenous corticosteroids, may benefit from a short course of intravenous ciclosporin p. 766 [unlicensed indication]. Patients with unresponsive or chronically active Crohn’s disease may benefit from azathioprine p. 765, mercaptopurine p. 816 [unlicensed indication], or once-weekly methotrexate p. 817 [unlicensed indication]; these drugs have a slower onset of action.

Infliximab p. 976 is licensed for the management of severe active Crohn’s disease and severe ulcerative colitis in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional drug that affects the immune response, or who are intolerant of them.

Adalimumab p. 969 is licensed for the treatment of severe active Crohn’s disease and severe ulcerative colitis in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional drug that affects the immune response, or who are intolerant of them.

For inducing remission, adalimumab can be used in combination with a corticosteroid, but it may be given alone if a corticosteroid is inappropriate or is not tolerated. Adalimumab may also be used for Crohn’s disease in patients who have relapsed while taking infliximab or who cannot tolerate infliximab because of hypersensitivity reactions.

Golimumab p. 974 is licensed for the treatment of severe ulcerative colitis in patients whose condition has not responded adequately to conventional therapy, or who are intolerant of it.

 Vedolizumab p. 41 is licensed for the treatment of moderate to severe active Crohn’s disease and ulcerative colitis in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor.

**Maintenance of remission of acute ulcerative colitis and Crohn’s disease**

Smoking cessation reduces the risk of relapse in Crohn’s disease and should be encouraged. **Aminosalicylates** are efficacious in the maintenance of remission of ulcerative colitis, but there is no evidence of efficacy in the maintenance of remission of Crohn’s disease. Corticosteroids are not suitable for maintenance treatment because of their side-effects. In resistant or frequently relapsing cases either azathioprine or mercaptopurine [unlicensed indication], given under close supervision may be helpful. Methotrexate is tried in Crohn’s disease if azathioprine or mercaptopurine cannot be used [unlicensed indication].
Aminosalicylates

Aminosalicylates

**SIDE-EFFECTS**
- **Rare** Acute pancreatitis, agranulocytosis, alopecia, aplastic anaemia, arthralgia, blood disorders, eosinophilia, fibrosing alveolitis, hepatitis, interstitial nephritis, leucopenia, lung disorders, lupus erythematosus, lymphoma, myalgia, myasthenia, nephrotic syndrome, neuropathy, peripheral neuropathy, renal dysfunction, skin reactions, Stevens-Johnson syndrome, thrombocytopenia.
- **Frequency not known** Abdominal pain, diarrhoea, exacerbation of symptoms of colitis, headache, hypersensitivity reactions, nausea, rash, urticaria, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- **Blood Disorders** A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.
- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in salicylate hypersensitivity.
- **RENAL IMPAIRMENT** Renal function should be monitored more frequently in renal impairment.
- **MONITORING REQUIREMENTS** Renal function should be monitored before starting an oral aminosalicylate, at 3 months of treatment, and then annually during treatment.
- **PATIENT AND CARER ADVICE**
  - Blood disorders: Patients receiving aminosalicylates, and their carers, should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

**Balsalazide sodium**

**INDICATIONS AND DOSE**

- **Treatment of mild to moderate ulcerative colitis, acute attack**
  - **BY MOUTH**
  - **Adult:** 2.25 g 3 times a day until remission occurs or for up to maximum of 12 weeks

- **Maintenance of remission of ulcerative colitis**
  - **BY MOUTH**
  - **Adult:** 1.5 g twice daily (max. per dose 3 g), adjusted according to response; maximum 6 g per day

**CAUTIONS** History of asthma

**SIDE-EFFECTS** Cholelithiasis

**PREGNANCY** Manufacturer advises avoid.

**BREAST FEEDING** Diarrhoea may develop in the infant.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.

**RENAL IMPAIRMENT** Manufacturer advises avoid in moderate to severe impairment.

**MEDIICAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS 21, 25**
- **Colazide** (Almirall Ltd)
  - **Balsalazide disodium 750 mg** Colazide 750mg capsules | 130 capsule (Pm) £30.42 DT price = £30.42

**Drugs used in chronic bowel disorders**

**Aminosalicylates**

- Sulfasalazine is a combination of 5-aminosalicylic acid (5-ASA) and sulfapyridine; sulfapyridine acts only as a carrier to the colonic site of action but still causes side-effects. In the newer aminosalicylates, mesalazine (5-aminosalicylic acid), balsalazide sodium (a pro-drug of 5-aminosalicylic acid) and olsalazine sodium (a dimer of 5-aminosalicylic acid which cleaves in the lower bowel), the sulfonamide-related side-effects of sulfasalazine are avoided, but 5-aminosalicylic acid alone can still cause side-effects including blood disorders and lupus-like syndrome also seen with sulfasalazine p. 39.

**Drugs affecting the immune response**

- Azathioprine p. 765, ciclosporin p. 766, mercaptopurine p. 816, and methotrexate p. 817 have a role in the treatment of inflammatory bowel disease.
- Folic acid p. 898 should be given to reduce the possibility of methotrexate toxicity [unlicensed indication]. Folic acid is usually given once weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

**Cytokine modulators**

- Infliximab p. 976, adalimumab p. 969, and golimumab p. 974 are monoclonal antibodies which inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha. They should be used under specialist supervision. Adequate resuscitation facilities must be available when infliximab is used.
Mesalazine

- **INDICATIONS AND DOSE**

**ASACOL® MR 400MG TABLETS**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Child 12-17 years: 800 mg 3 times a day
  - Adult: 2.4–4.8 g daily in divided doses
- Maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis
  - BY MOUTH
  - Child 12-17 years: 400–800 mg 2–3 times a day
  - Adult: 1.2–2.4 g daily in divided doses

**ASACOL® MR 800MG TABLETS**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Adult: 2.4–4.8 g daily in divided doses
- Maintenance of remission of ulcerative colitis
  - BY MOUTH
  - Adult: Up to 2.4 g once daily, alternatively up to 2.4 g daily in divided doses

**MEZAVANT®**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Adult: 2.4 g daily in divided doses
- Maintenance of remission of ulcerative colitis
  - BY MOUTH
  - Adult: 1.2–2.4 g daily in divided doses

**IPOCOL®**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Adult: 2.4 g once daily
- Maintenance of remission of ulcerative colitis
  - BY MOUTH
  - Adult: 2.4 g once daily

**PENTASA®**
- Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region
  - BY RECTUM
  - Adult: 1 g daily for 4–6 weeks, to be administered into the rectum
- Treatment of acute attack of mild to moderate ulcerative colitis, affecting the descending colon
  - BY RECTUM
  - Adult: 2 g once daily for 4–6 weeks, to be administered into the rectum

**ASACOL® FOAM ENEMA**
- Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region
  - BY RECTUM
  - Adult: 1 g daily for 4–6 weeks, to be administered into the rectum

**IPOCOL®**
- Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region
  - BY RECTUM
  - Adult: 0.75–1.5 g daily in divided doses, last dose to be administered at bedtime

**OCTASA®**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Adult: 2.4–4.8 g once daily, alternatively 2.4–4.8 g daily in divided doses, dose over 2.4 g daily in divided doses only
- Maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis
  - BY MOUTH
  - Adult: 1.2–2.4 g once daily, alternatively daily in divided doses

**PENTASA® GRANULES**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Child 5–17 years (body-weight up to 40 kg): 10–20 mg/kg 3 times a day
  - Child 5–17 years (body-weight 40 kg and above): 1–2 g twice daily, total daily dose may alternatively be given in 3–4 divided doses
  - Adult: Up to 4 g once daily, alternatively up to 4 g daily in 2–4 divided doses

**PENTASA® RETENTION ENEMA**
- Treatment of acute attack of mild to moderate ulcerative colitis or maintenance of remission
  - BY RECTUM
  - Adult: 1 g once daily, dose to be administered at bedtime
- Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region
  - BY RECTUM
  - Child 12–17 years: 1 g once daily, dose to be administered at bedtime

**PENTASA® SUPPOSITORIES**
- Treatment of acute attack, ulcerative proctitis
  - BY RECTUM
  - Child 15–17 years: 1 g daily for 2–4 weeks
  - Adult: 1 g daily for 2–4 weeks
- Maintenance, ulcerative proctitis
  - BY RECTUM
  - Child 15–17 years: 1 g daily
  - Adult: 1 g daily

**PENTASA® TABLETS**
- Treatment of mild to moderate ulcerative colitis, acute attack
  - BY MOUTH
  - Adult: Up to 4 g once daily, alternatively up to 4 g daily in 2–3 divided doses
- Maintenance of remission of ulcerative colitis
  - BY MOUTH
  - Adult: 2 g once daily

**SALOFALK® ENEMA**
- Treatment of acute attack of mild to moderate ulcerative colitis or maintenance of remission
  - BY RECTUM
  - Adult: 2 g once daily, dose to be administered at bedtime

continued →
SALOFALK® GRANULES
Treatment of mild to moderate ulcerative colitis, acute attack
▶ BY MOUTH
▶ Child 5–17 years (body-weight up to 40 kg): 30–50 mg/kg once daily, dose preferably given in the morning, alternatively 10–20 mg/kg 3 times a day
▶ Child 5–17 years (body-weight 40 kg and above): 1.5–3 g once daily, dose preferably given in the morning, alternatively 0.5–1.5 g 3 times a day
▶ Adult: 1.5–3 g once daily, dose preferably taken in the morning, alternatively 0.5–1 g 3 times a day

Maintenance of remission of ulcerative colitis
▶ BY MOUTH
▶ Child 5–17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
▶ Child 5–17 years (body-weight 40 kg and above): 500 mg 3 times a day
▶ Adult: 500 mg 3 times a day

SALOFALK® RECTAL FOAM
Treatment of mild ulcerative colitis affecting sigmoid colon and rectum
▶ BY RECTUM
▶ Child 12–17 years: 2 g once daily, dose to be administered into the rectum at bedtime, alternatively 2 g daily in 2 divided doses
▶ Adult: 2 g once daily, dose to be administered into the rectum at bedtime, alternatively 2 g daily in 2 divided doses

SALOFALK® SUPPOSITORY
Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectum, sigmoid colon and descending colon
▶ BY RECTUM
▶ Adult: 0.5–1 g 2–3 times a day, adjusted according to response, dose to be given using 500 mg suppositories

Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectum
▶ BY RECTUM
▶ Adult: 1 g daily, preferably at bedtime, dose to be given using 1 g suppositories

SALOFALK® TABLETS
Treatment of mild to moderate ulcerative colitis, acute attack
▶ BY MOUTH
▶ Child 5–17 years (body-weight up to 40 kg): 10–20 mg/kg 3 times a day
▶ Child 5–17 years (body-weight 40 kg and above): 0.5–1 g 3 times a day
▶ Adult: 0.5–1 g 3 times a day

Maintenance of remission of ulcerative colitis
▶ BY MOUTH
▶ Child 5–17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
▶ Child 5–17 years (body-weight 40 kg and above): 500 mg 3 times a day
▶ Adult: 500 mg 3 times a day

DOSE EQUIVALENT AND CONVERSION
▶ There is no evidence to show that any one oral preparation of mesalazine is more effective than another; however, the delivery characteristics of oral mesalazine preparations may vary.


CONTRA-INDICATIONS
Blood clotting abnormalities (in children)

CAUTIONS
Elderly · pulmonary disease

INTERACTIONS
The manufacturers of some mesalazine gastro-resistant and modified-release medicines (Asacol®, MR tablets, Ipocol®, Salofalk® granules) suggest that preparations that lower stool pH (e.g. lactulose) may prevent the release of mesalazine.

SIDE-EFFECTS
Rare Dizziness
Very rare Oligospermia (reversible)

PREGNANCY
Negligible quantities cross placenta.

BREAST FEEDING
Diarrhoea reported in breast-fed infants, but negligible amounts of mesalazine detected in breast milk.
Monitor breast-fed infant for diarrhoea.

HEPATIC IMPAIRMENT
Avoid in severe impairment.

RENAL IMPAIRMENT
In adults Use with caution. Avoid if eGFR less than 20 mL/minute/1.73 m².
In children Use with caution. Avoid if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
PENTASA® TABLETS
Tables may be halved, quartered, or dispersed in water, but should not be chewed.

SALOFALK® GRANULES
Granules should be placed on tongue and washed down with water without chewing.

PENTASA® GRANULES
Granules should be placed on tongue and washed down with water or orange juice without chewing.

In children Contents of one sachet should be weighed and divided immediately before use; discard any remaining granules.

PRESCRIBING AND DISPENSING INFORMATION
There is no evidence to show that any one oral preparation of mesalazine is more effective than another; however, the delivery characteristics of oral mesalazine preparations may vary.

Flavours of granule formulations of Salofalk® may include vanilla.

PATIENT AND CARER ADVICE
If it is necessary to switch a patient to a different brand of mesalazine, the patient should be advised to report any changes in symptoms.

Some products may require special administration advice; patients and carers should be informed.

Medicines for Children leaflet: Mesalazine (oral) for inflammatory bowel disease www.medicinesforchildren.org.uk/mesalazine-oral-for-inflammatory-bowel-disease
Medicines for Children leaflet: Mesalazine foam enema for inflammatory bowel disease www.medicinesforchildren.org.uk/mesalazine-foam-enema-for-inflammatory-bowel-disease
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Modified-release tablet

**CAUTIONARY AND ADVISORY LABELS** 21 (does not apply to Pentasa® tablets), 25 (does not apply to Pentasa® tablets)

- **Mezavant XL** (Shire Pharmaceuticals Ltd)
  - Mesalazine 1.2 gram Mezavant XL 1200mg tablets | 60 tablet [POM] £42.95 DT price = £42.95
- **Pentasa** (Ferring Pharmaceuticals Ltd)
  - Mesalazine 1 gram Pentasa 1g modified-release tablets | 60 tablet [POM] £36.89 DT price = £36.89
  - Mesalazine 500 mg Pentasa 500mg modified-release tablets | 100 tablet [POM] £30.74 DT price = £30.74

### Gastro-resistant tablet

**CAUTIONARY AND ADVISORY LABELS** 25 (does not apply to Octasa®)

- **Asacol MR** (Allergan Ltd)
  - Mesalazine 400 mg Asacol 400mg MR gastro-resistant tablets | 84 tablet [POM] £27.45 DT price = £27.45 | 168 tablet [POM] £54.90
  - Mesalazine 800 mg Asacol 800mg MR gastro-resistant tablets | 84 tablet [POM] £54.90 DT price = £54.90
- **Ipocol** (Sandoz Ltd)
  - Mesalazine 400 mg Ipocol 400mg gastro-resistant tablets | 120 tablet [POM] £17.68
- **Octasa MR** (Tillotts Pharma Ltd)
  - Mesalazine 400 mg Octasa 400mg MR gastro-resistant tablets | 90 tablet [POM] £19.50 DT price = £19.50 | 120 tablet [POM] £26.00
  - Mesalazine 800 mg Octasa 800mg MR gastro-resistant tablets | 90 tablet [POM] £47.50 | 180 tablet [POM] £95.00 DT price = £95.00
- **Salofalk** (Dr. Falk Pharma UK Ltd)
  - Mesalazine 250 mg Salofalk 250mg gastro-resistant tablets | 100 tablet [POM] £16.19
  - Mesalazine 500 mg Salofalk 500mg gastro-resistant tablets | 100 tablet [POM] £32.38

### Modified-release granules

**CAUTIONARY AND ADVISORY LABELS** 25 (does not apply to Pentasa® granules)

EXCIPIENTS: May contain Aspartame

- **Pentasa** (Ferring Pharmaceuticals Ltd)
  - Mesalazine 1 gram Pentasa 1g modified-release granules sachets sugar-free | 50 sachet [POM] £30.74 DT price = £30.74
  - Mesalazine 2 gram Pentasa 2g modified-release granules sachets sugar-free | 60 sachet [POM] £73.78 DT price = £73.78
  - Mesalazine 4 gram Pentasa 4g modified-release granules sachets sugar-free | 30 sachet [POM] £73.78
- **Salofalk** (Dr. Falk Pharma UK Ltd)
  - Mesalazine 1 gram Salofalk 1g gastro-resistant modified-release granules sachets sugar-free | 50 sachet [POM] £28.74 DT price = £28.74
  - Mesalazine 1.5 gram Salofalk 1.5g gastro-resistant modified-release granules sugar-free | 60 sachet [POM] £48.85 DT price = £48.85
  - Mesalazine 3 gram Salofalk 3g gastro-resistant modified-release granules sachets sugar-free | 60 sachet [POM] £97.70 DT price = £97.70
  - Mesalazine 500 mg Salofalk 500mg gastro-resistant modified-release granules sachets sugar-free | 100 sachet [POM] £28.74

### Foam

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol, sodium metabisulfite

- **Asacol** (Allergan Ltd)
  - Mesalazine 1 gram per 1 application Asacol 1g/application foam enema | 14 dose [POM] £26.72
- **Salofalk** (Dr. Falk Pharma UK Ltd)
  - Mesalazine 1 gram per 1 application Salofalk 1g/application foam enema | 14 dose [POM] £30.17

### Suppository

- **Asacol** (Allergan Ltd)
  - Mesalazine 250 mg Asacol 250mg suppositories | 20 suppository [POM] £4.82 DT price = £4.82
  - Mesalazine 500 mg Asacol 500mg suppositories | 10 suppository [POM] £4.82 DT price = £4.82
- **Pentasa** (Ferring Pharmaceuticals Ltd)
  - Mesalazine 1 gram Pentasa 1g suppositories | 28 suppository [POM] £40.01 DT price = £40.01

### Enema

- **Pentasa** (Ferring Pharmaceuticals Ltd)
  - Mesalazine 10 mg per 1 ml Pentasa Mesalazine 1g/100ml enema | 7 enema [POM] £17.73 DT price = £17.73
- **Salofalk** (Dr. Falk Pharma UK Ltd)
  - Mesalazine 33.9 mg per 1 ml Salofalk 2g/59ml enema | 7 enema [POM] £29.92 DT price = £29.92

### CAUTIONARY AND ADVISORY LABELS

21 (does not apply to Pentasa® tablets).

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21

- **Olsalazine sodium (Non-proprietary)**
  - Olsalazine sodium 500 mg Olsalazine 500mg tablets | 60 tablet [POM] £85.00-£161.00 DT price = £161.00

**Capsule**

**CAUTIONARY AND ADVISORY LABELS** 21

- **Olsalazine sodium (Non-proprietary)**
  - Olsalazine sodium 250 mg Olsalazine 250mg capsules | 112 capsule [POM] £75.00-£144.00 DT price = £144.00

## Olsalazine sodium

### INDICATIONS AND DOSE

**Treatment of acute attack of mild ulcerative colitis**

- **BY MOUTH**
  - Adult: 1 g daily in divided doses, doses to be taken after meals, then increased if necessary up to 3 g daily in divided doses (max. per dose 1 g), dose to be increased over 1 week

**Maintenance of remission of mild ulcerative colitis**

- **BY MOUTH**
  - Adult: Maintenance 500 mg twice daily, dose to be taken after food

### SIDE-EFFECTS

- Common or very common: Watery diarrhoea
- Frequency not known: Blurred vision · palpitation · photosensitivity · pyrexia · tachycardia

### PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk.

### BREAST FEEDING

Monitor breast-fed infants for diarrhoea.

### RECAL IMPAIRMENT

Use with caution; manufacturer advises avoid in significant impairment.

### DIRECTIONS FOR ADMINISTRATION

Capsules can be opened and contents sprinkled on food.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21

- **Olsalazine sodium (Non-proprietary)**
  - Olsalazine sodium 500 mg Olsalazine 500mg tablets | 60 tablet [POM] £85.00-£161.00 DT price = £161.00

**Capsule**

**CAUTIONARY AND ADVISORY LABELS** 21

- **Olsalazine sodium (Non-proprietary)**
  - Olsalazine sodium 250 mg Olsalazine 250mg capsules | 112 capsule [POM] £75.00-£144.00 DT price = £144.00

## Sulfasalazine

*( Sulphasalazine)*

### INDICATIONS AND DOSE

**Treatment of acute attack of mild to moderate and severe ulcerative colitis** | Active Crohn's disease

- **BY MOUTH**
  - Adult: 1–2 g 4 times a day until remission occurs, corticosteroids may also be given, if necessary
  - **BY RECTUM**
    - Adult: 0.5–1 g twice daily, administered alone or in conjunction with oral therapy, morning and night after a bowel movement

## Notes

- Active Crohn, S. Salm. Monocytogenes.
- Olsalazine sodium (Non-proprietary)
- Active Crohn, S. Salm. Monocytogenes.
- Olsalazine sodium (Non-proprietary)
- Active Crohn, S. Salm. Monocytogenes.
Maintenance of remission of mild to moderate and severe ulcerative colitis

- **BY MOUTH**
- Adult: 500 mg 4 times a day
- **BY RECTUM**
- Adult: 0.5–1 g twice daily, administered alone or in conjunction with oral therapy, morning and night after a bowel movement

Active rheumatoid arthritis (administered on expert advice)

- **BY MOUTH**
- Adult: Initially 500 mg daily, increased in steps of 500 mg every week, increased to 2–3 g daily in divided doses, enteric coated tablets to be administered

- **CAUTIONS** Acute porphyrias p. 930 • G6PD deficiency • history of allergy • history of asthma • maintain adequate fluid intake • risk of haematological toxicity • risk of hepatic toxicity • slow acetylator status

- **INTERACTIONS** → Appendix 1 (aminosalicylates).

- **SIDE-EFFECTS**
  - Common or very common Blood disorders • cough • dizziness • fever • Heinz body anaemia • insomnna • megaloblastic anaemia • proteinuria • pruritus • stomatitis • taste disturbances • tinnitus
  - Uncommon Alopecia • convulsions • depression • dyspnoea • vasculitis
  - Frequency not known Anaphylaxis • aseptic meningitis • ataxia • crystalluria • disturbances of smell • epidermal necrolysis • exfoliative dermatitis • gastro-intestinal intolerance • hallucinations • hypersensitivity reactions • leucopenia (especially in patients with rheumatoid arthritis) • loss of appetite • neutropenia (especially in patients with rheumatoid arthritis) • oligospermia • parotitis • photosensitivity • rashes • serum sickness • some soft contact lenses may be stained • thrombocytopenia (especially in patients with rheumatoid arthritis) • yellow-orange discoloration of other body fluids • yellow-orange discoloration of skin • yellow-orange discoloration of urine

**SIDE-EFFECTS, FURTHER INFORMATION**
- Gastro-intestinal side effects Upper gastro-intestinal side-effects common over 4 g daily.
- Blood disorders Haematological abnormalities occur usually in the first 3 to 6 months of treatment and are reversible on cessation of treatment.
- **PREGNANCY** Theoretical risk of neonatal haemolysis in third trimester; adequate folate supplements should be given to mother.
- **BREAST FEEDING** Small amounts in milk (1 report of bloody diarrhoea); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants.
- **HEPATIC IMPAIRMENT** Use with caution.
- **RENAL IMPAIRMENT** Risk of toxicity, including crystalluria, in moderate impairment—ensure high fluid intake. Avoid in severe impairment.
- **MONITORING REQUIREMENTS**
  - Blood disorders Close monitoring of full blood counts (including differential white cell count and platelet count) is necessary initially, and at monthly intervals during the first 3 months.
  - Renal function Although the manufacturer recommends renal function tests in rheumatic diseases, evidence of practical value is unsatisfactory.
  - Liver function Liver function tests should be performed at monthly intervals for first 3 months.

- **PATIENT AND CARER ADVICE**
  Contact lenses Some soft contact lenses may be stained.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 14 |
| Sulfasalazine (Non-proprietary) |
| Sulfasalazine 500 mg Sulfasalazine 500mg tablets | 112 tablet | £9.00 DT price = £6.86 |
| Salazopyrin (Pfizer Ltd) |
| Sulfasalazine 500 mg Salazopyrin 500mg tablets | 112 tablet | £6.97 DT price = £6.86 |

**Gastro-resistant tablet**

| CAUTIONARY AND ADVISORY LABELS 5, 14, 25 |
| Sulfasalazine (Non-proprietary) |
| Sulfasalazine 500 mg Sulfasalazine 500mg gastro-resistant tablets | 100 tablet | no price available |
| 112 tablet | £11.08 DT price = £11.08 |
| Salazopyrin EN (Pfizer Ltd) |
| Sulfasalazine 500 mg Salazopyrin EN-Tabs 500mg | 112 tablet | £8.43 DT price = £11.08 |
| Sulazine EC (Genesis Pharmaceuticals Ltd) |
| Sulfasalazine 500 mg Sulazine EC 500mg tablets | 112 tablet | £11.08 DT price = £11.08 |

**Oral suspension**

| CAUTIONARY AND ADVISORY LABELS 14 |
| EXCIPIENTS: May contain Alcohol |
| Sulfasalazine 50 mg per 1 ml Sulfasalazine 250mg/5ml oral suspension sugar free sugar-free | 500 ml | £44.09 DT price = £43.42 |

**Suppository**

| CAUTIONARY AND ADVISORY LABELS 14 |
| Salazopyrin (Pfizer Ltd) |
| Sulfasalazine 500 mg Salazopyrin 500mg suppositories | 10 suppository | £3.30 |

**CORTICOSTEROIDS**

**Beclometasone dipropionate**

(*Beclometasone dipropionate*)

- **INDICATIONS AND DOSE**
  Adjunct to aminosalicylates in acute mild to moderate ulcerative colitis
  - **BY MOUTH**
  - Adult: 5 mg daily maximum duration of treatment of 4 weeks, dose to be taken in the morning

- **SIDE-EFFECTS** Constipation • drowsiness

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

| CAUTIONARY AND ADVISORY LABELS 25 |
| Clipper (Chiesi Ltd) |
| Beclometasone dipropionate 5 mg Clipper 5mg gastro-resistant modified-release tablets | 30 tablet | £56.56 |
Budesonide

**INDICATIONS AND DOSE**

**BUDENOFALK® CAPSULES**

Mild to moderate Crohn's disease affecting the ileum or ascending colon | Chronic diarrhoea due to collagenous colitis

- **BY MOUTH**
- Adult: 3 mg 3 times a day for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment

Autoimmune hepatitis, induction of remission

- **BY MOUTH**
- Adult: 3 mg 3 times a day

Autoimmune hepatitis, maintenance

- **BY MOUTH**
- Adult: 3 mg twice daily

**BUDENOFALK® GRANULES**

Mild to moderate Crohn's disease affecting the ileum or ascending colon | Collagenous colitis

- **BY MOUTH**
- Adult: 9 mg daily for up to 8 weeks, to be taken in the morning, dose to be reduced for the last two weeks of treatment

**BUDENOFALK® RECTAL FOAM**

Ulcerative colitis affecting sigmoid colon and rectum

- **BY RECTUM**
- Adult: 1 metered application once daily for up to 8 weeks

**DOSE EQUIVALENT AND CONVERSION**

- For Budenofalk® rectal foam: 1 metered application is equivalent to budesonide 2 mg.

**ENTOCORT® CAPSULES**

Mild to moderate Crohn's disease affecting the ileum or ascending colon

- **BY MOUTH**
- Adult: 9 mg once daily for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment, to be taken in the morning

**ENTOCORT® ENEMA**

Ulcerative colitis involving rectal and recto-sigmoid disease

- **BY RECTUM**
- Adult: 1 enema daily for 4 weeks, to be administered at bedtime

**CAUTIONS**

- Autoimmune hepatitis

**HEPATIC IMPAIRMENT**

- With systemic use: When used in autoimmune hepatitis liver function tests should be monitored every 2 weeks for 1 month, then at least every 3 months.

**DIRECTIONS FOR ADMINISTRATION**

-Granules should be placed on tongue and washed down with water without chewing.

**PRESCRIBING AND DISPENSING INFORMATION**

- Flavours of granule formulations may include lemon.

**ENTOCORT® CAPSULES**

Dispense modified-release capsules in original container (contains desiccant).

**PATIENT AND CARER ADVICE**

- Patients or carers should be given advice on how to administer budesonide granules.

**NATIONAL FUNDING/ACCESS DECISIONS**

**BUDENOFALK® CAPSULES**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (April 2015) that Budenofalk® gastro-resistant capsules are accepted for restricted use within NHS Scotland for the treatment of autoimmune hepatitis in non-cirrhotic patients who are intolerant of conventional oral corticosteroids (prednisolone) with severe corticosteroid-related side effects (actual or anticipated) such as psychosis, poorly controlled diabetes or osteoporosis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>5, 10, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entocort CR (Tillotts Pharma Ltd)</td>
<td>Budesonide 3 mg</td>
</tr>
</tbody>
</table>

**Gastro-resistant capsule**

<table>
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<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>5, 10, 22, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budenofalk (Dr. Falk Pharma UK Ltd)</td>
<td>Budesonide 3 mg</td>
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**Gastro-resistant granules**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Budenofalk (Dr. Falk Pharma UK Ltd)</td>
<td>Budesonide 9 mg gastro-resistant granules sachets 60 sachet £135.00</td>
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**Foam**

<table>
<thead>
<tr>
<th>EXCIPIENTS:</th>
<th>May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, propylene glycol, sorbic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budenofalk (Dr. Falk Pharma UK Ltd)</td>
<td>Budesonide 2 mg per 1 actuation Foam enema £5.11</td>
</tr>
</tbody>
</table>

**Enema**

<table>
<thead>
<tr>
<th>Entocort (Tillotts Pharma Ltd)</th>
<th>Budesonide 20 microgram per 1 ml Foam enema 14 dose</th>
<th>£39.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enema</td>
<td>Entocort 2mg/100ml enema 7 enema</td>
<td>£99.00</td>
</tr>
</tbody>
</table>

**IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES, ANTI-LYMPHOCYTE**

Vedolizumab

**DRUG ACTION**

Vedolizumab is a monoclonal antibody that binds specifically to the α4β7 integrin, which is expressed on gut homing T helper lymphocytes and causes a reduction in gastrointestinal inflammation.

**INDICATIONS AND DOSE**

Moderate to severe active ulcerative colitis in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor (under expert supervision)

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 300 mg, then 300 mg after 2 weeks, followed by 300 mg after 4 weeks, followed by 300 mg every 8 weeks, dose to be given over 30 minutes, if treatment is interrupted or response decreases, dosing frequency may be increased—consult product literature; review treatment if no response within 10 weeks of initial dose

Moderate to severe active Crohn's disease in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor (under expert supervision)

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 300 mg, then 300 mg after 2 weeks, followed by 300 mg after 4 weeks, followed by 300 mg every 8 weeks, dose to be given over 30 minutes, if no response is observed, an additional dose of 300 mg may be given 10 weeks after initial dose; if treatment is interrupted or response decreases, dosing frequency may be increased—consult product literature; review treatment if no response within 14 weeks of initial dose
Gastro-intestinal system

1

1.4 Irritable bowel syndrome

Irritable bowel syndrome 24-Feb-2016

Description of condition
Irritable bowel syndrome (IBS) is a common, chronic, relapsing, and often life-long condition, mainly affecting people aged between 20 and 30 years. It is more common in women. Symptoms include abdominal pain or discomfort, disordered defaecation (either diarrhoea, or constipation with straining, urgency, and incomplete evacuation), passage of mucus, and bloating. Symptoms are usually relieved by defaecation. Obtaining an accurate clinical diagnosis of IBS prior to treatment is crucial.

Aims of treatment
The treatment of IBS is focused on symptom control, in order to improve quality of life.
Non-drug treatment

Diet and lifestyle changes are important for effective self-management of IBS. Patients should be encouraged to increase physical activity, and advised to eat regularly, without missing meals or leaving long gaps between meals. Dietary advice should also include, limiting fresh fruit consumption to no more than 3 portions per day. The fibre intake of patients with IBS should be reviewed. If an increase in dietary fibre is required, soluble fibre such as ispaghula husk p. 50, or foods high in soluble fibre such as oats, are recommended. Intake of insoluble fibre (e.g. bran) and ‘resistant starch’ should be reduced or discouraged as they may exacerbate symptoms. Fluid intake (mostly water) should be increased to at least 8 cups each day and the intake of caffeine, alcohol and fizzy drinks reduced. The artificial sweetener sorbitol should be avoided in patients with diarrhoea. Where probiotics are being used, continue for at least 4 weeks while monitoring the effect.

If a patient’s symptoms persist following lifestyle and dietary advice, single food avoidance and exclusion diets may be an option under the supervision of a dietitian or medical specialist.

Drug treatment

The choice of drug treatment depends on the nature and severity of the symptoms. Many drug treatment options for IBS are available over-the-counter.

Antispasmodics (such as alverine citrate p. 82, mebeverine hydrochloride p. 82 and peppermint oil below) can be taken in addition to dietary and lifestyle changes. A laxative (excluding lactulose p. 52 as it may cause bloating) can be used to treat constipation. Patients who have not responded to laxatives from the different classes and who have had constipation for at least 12 months, can be treated with linaclotide p. 44. Loperamide hydrochloride p. 63 is the first-line choice of anti-motiility drug for relief of diarrhoea. Patients with IBS should be advised how on to adjust their dose of laxative or anti-motiility drug according to stool consistency, with the aim of achieving a soft, well-formed stool. See Constipation p. 48, for information on other drugs used for chronic constipation.

A low-dose tricyclic antidepressant, such as amitriptyline hydrochloride p. 349 [unlicensed indication], can be used for abdominal pain or discomfort as a second-line option in patients who have not responded to antispasmodics, anti-motiility drugs, or laxatives. A selective serotonin reuptake inhibitor may be considered in those who do not respond to a tricyclic antidepressant [unlicensed indication].

Psychological intervention can be offered to patients who have no relief of IBS symptoms after 12 months of drug treatment.

Useful Resources


ANTISpasmodics

Mebeverine with ispaghula husk

04-Feb-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, mebeverine hydrochloride p. 82, ispaghula husk p. 50.

- **INDICATIONS AND DOSE**
  - **Irritable bowel syndrome**
    - **BY MOUTH**
      - **Child 12-17 years:** 1 sachet twice daily, in water, morning and evening, 30 minutes before food and 1 sachet daily if required, taken 30 minutes before midday meal
      - **Adult:** 1 sachet twice daily, in water, morning and evening, 30 minutes before food and 1 sachet daily if required, taken 30 minutes before midday meal

- **DIRECTIONS FOR ADMINISTRATION** Contents of one sachet should be stirred into a glass (approx. 150 mL) of cold water and drunk immediately.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer ispaghula husk with mebeverine granules.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Effervescent granules**

- **CAUTIONARY AND ADVISORY LABELS**
  - **13, 22**
  - **EXCIPIENTS:** May contain Aspartame
  - **ELECTROLYTES:** May contain Potassium

**Fybogel Mebeverine** (Reckitt Benckiser Healthcare (UK) Ltd)

- **Ispaghula husk 3.5 gram, Mebeverine hydrochloride 135 mg**
- **Fybogel Mebeverine effervescent granules sachets orange sugar-free**
  - **10 sachet**
  - **£4.64 DT price = £4.22**

Peppermint oil

- **INDICATIONS AND DOSE**

**COLPERMIN®**

Relief of abdominal colic and distension, particularly in irritable bowel syndrome

- **BY MOUTH**

  - **Child 15-17 years:** 1–2 capsules 3 times a day for up to 3 months if necessary, capsule to be swallowed whole with water
  - **Adult:** 1–2 capsules 3 times a day for up to 3 months if necessary, capsule to be swallowed whole with water

**MINTEC®**

Relief of abdominal colic and distension, particularly in irritable bowel syndrome

- **BY MOUTH**

  - **Adult:** 1–2 capsules 3 times a day for up to 2–3 months if necessary, dose to be taken before meals, swallowed whole with water

- **CAUTIONS** Sensitivity to menthol

- **SIDE-EFFECTS**
  - **Rare** Allergic reactions • ataxia • bradycardia • headache • muscle tremor • rash
  - **Frequency not known** Heartburn • perianal irritation

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Significant levels of menthol in breast milk unlikely.

- **DIRECTIONS FOR ADMINISTRATION** Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus.
1.5 Short bowel syndrome

Description of condition

Patients with a shortened bowel due to large surgical resection (with or without stoma formation) may require medical management to ensure adequate absorption of nutrients and fluid. Absorption of oral medication is also often impaired.

Aims of treatment

The management of short bowel syndrome focuses on ensuring adequate nutrition and drug absorption, thereby reducing the risk of complications resulting from these effects.

Drug treatment

Nutritional deficiencies

Patients with a short bowel may require replacement of vitamins and minerals depending on the extent and position of the bowel resection. Deficiencies in vitamins A, B12, D, E, and K, essential fatty acids, zinc, and selenium can occur.

Hypomagnesaemia is common and is treated with oral or intravenous magnesium supplementation (see under Magnesium, in Minerals p. 923), though administration of oral magnesium may cause diarrhoea. Occasionally the use of oral alfalcaldipol p. 952 and correction of sodium depletion may be useful. Nutritional support can range from oral supplements to parenteral nutrition, depending on the severity of intestinal failure.

Diarrhoea and high output stomas

Diarrhoea is common in short bowel syndrome and can be due to multiple factors. The use of oral rehydration salts can be considered in order to promote adequate hydration. Oral intake influences the volume of stool passed, so reducing food intake will lessen diarrhoea, but will also exacerbate the problems of undernutrition. A patient may require parenteral nutrition to allow them to eat less, if the extent of diarrhoea is unacceptable.

Pharmacological treatment may be necessary, with the choice of drug depending on the potential for side-effects and the degree of resection.

Antimotility drugs

Loperamide hydrochloride p. 63 and codeine phosphate p. 421 reduce intestinal motility and thus exert antidiarhoeal actions. Loperamide hydrochloride is preferred as it is not sedative and does not cause dependence or fat malabsorption. High doses of loperamide hydrochloride [unlicensed] may be required in patients with a short bowel due to disrupted enterohepatic circulation and rapid gastrointestinal transit time. If the desired response is not obtained with loperamide hydrochloride, codeine phosphate may be added to therapy.

Co-phenotrope p. 62 has traditionally been used alone or in combination with other medications to help decrease faecal output. Co-phenotrope crosses the blood–brain barrier and can produce central nervous system side-effects, which may limit its use; the potential for dependence and anticholinergic effects may also restrict its use.

Colestyramine

In patients with an intact colon and less than 100 cm of ileum resected, colestyramine p. 186 can be used to bind the unabsorbed bile salts and reduce diarrhoea. When colestyramine is given to these patients, it is important to monitor for evidence of fat malabsorption (steatorrhoea) or fat-soluble vitamin deficiencies.
Antisecretory drugs

Drugs that reduce gastric acid secretion reduce jejunostomy output. Omeprazole p. 76 is readily absorbed in the duodenum and upper small bowel, but if less than 50 cm of jejunum remains, it may need to be given intravenously. Use of a proton pump inhibitor alone does not eliminate the need for further intervention for fluid control (such as antimitoty agents, intravenous fluids, or oral rehydration salts).

Octreotide [unlicensed indication] reduces ileostomy diarrhoea and large volume jejunostomy output by inhibiting multiple pro-secretory substances. There is insufficient evidence to establish its role in the management of short bowel syndrome. ☑

Growth factors

Growth factors can be used to facilitate intestinal adaptation after surgery in patients with short bowel syndrome, thus enhancing fluid, electrolyte, and micronutrient absorption.

Teduglutide below is an analogue of endogenous human glucagon-like peptide-2 (GLP-2), which is licensed for use in the management of short bowel syndrome. It may be considered after a period of stabilisation following surgery, during which intravenous fluids and nutritional support should have been optimised.

Drug absorption

For Prescribing in patients with stoma, see Stoma care p. 91. ☛ Many drugs are incompletely absorbed by patients with a short bowel and may need to be prescribed in much higher doses than usual (such as levothyroxine, warfarin, oral contraceptives, and digoxin) or may need to be given intravenously. ☑

Several factors can alter the absorption of drugs taken by mouth in patients with a compromised gastrointestinal system. The most important factors are the length of intestine available for drug absorption, and which section has been removed. The small intestine, with its large surface area and high blood flow, is the most important site of drug absorption. The larger the amount of the small intestine that has been removed, the higher the possibility that drug absorption will be affected. Other factors, such as gastric emptying and gastric transit time, also affect drug handling. ☛

Dosage forms with quick dissolution (soluble tablets) should be used. Uncoated tablets and liquid formulations may also be suitable. ☛ Before prescribing liquid formulations, prescribers should consider the osmolarity, excipient content and volume required. Hyperosmolar liquids and some excipients (such as sorbitol) can result in fluid loss. The calorie density of oral supplements should also be considered, as it will influence the volume to be taken. ☛

Other drugs used for Short bowel syndrome Cimetidine, p. 71

AMINO ACIDS AND DERIVATIVES

Teduglutide

01-Sep-2016

Drug action

Teduglutide is an analogue of human glucagon-like peptide-2 (GLP-2), which preserves mucosal integrity by promoting growth and repair of the intestine.

Indications and dose

Short bowel syndrome (initiated under specialist supervision)

By subcutaneous injection

- Adult: 0.05 mg/kg once daily, dose to be administered to alternating quadrants of the abdomen; alternatively the thigh can be used, for optimal injection volume per body weight, consult product literature. Review treatment after 6 months

Contra-indications

Active or suspected malignancy - history of gastro-intestinal malignancy (in previous 5 years)

Cautions

Abrupt withdrawal of parenteral support (reduce gradually with concomitant monitoring of fluid status) - cardiac insufficiency - cardiovascular disease - colo-rectal polyps - hypertension

Side-effects

Common or very common Abdominal distension - abdominal pain - allergic dermatitis - anxiety - arthralgia - chest pain - cholecystitis - cholestasis - congestive heart failure - cough - decreased appetite - dyspnoea - flushing - headache - intestinal obstruction - nausea - night sweats - pancreatitis - paraesthesia - peripheral oedema - rash - renal colic - sleep disorder - vomiting

Uncommon Syncope

Frequency not known Gastro-intestinal neoplasia - pancreatic duct stenosis - pancreatic infection

Allergy and cross-sensitivity

Manufacturer advises caution in patients with tetracycline hypersensitivity.

Pregnancy

Specialist sources indicate use if necessary — no human data available.

Breast feeding

Manufacturer advises avoid—toxicity in animal studies.

Renal impairment

Manufacturer advises use half the daily dose in moderate or severe impairment and end-stage renal disease.

Monitoring requirements

Manufacturer advises monitoring of small bowel function, gall bladder, bile ducts and pancreas during treatment.

Treatment cessation

Caution when discontinuing treatment — risk of dehydration.

Patient and carer advice

Patients with cardiovascular disease should seek medical attention if they notice sudden weight gain, swollen ankles or dyspnoea — may indicate increased fluid absorption.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

- Teduglutide 5 mg [Revestive (Shire Pharmaceuticals Ltd)]
- Teduglutide 28 vial [no price available]
2 Constipation and bowel cleansing

2.1 Bowel cleansing

Other drugs used for Bowel cleansing Bисакодил, p. 57 • Docusate sodium, p. 56 • Magnesium sulfate, p. 924

LAXATIVES > OSMOTIC LAXATIVES

<table>
<thead>
<tr>
<th>Citric acid with magnesium carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Formulated as a bowel cleansing preparation)</td>
</tr>
</tbody>
</table>

**INDICATIONS AND DOSE**

Bowel evacuation for surgery, colonoscopy or radiological examination

- **BY MOUTH**
  - Child 5–9 years: One-third of a sachet to be given at 8 a.m. the day before the procedure and, one-third of a sachet to be given between 2 and 4 p.m. the day before the procedure
  - Child 10–17 years: 0.5–1 sachet, given at 8 a.m. the day before the procedure and 0.5–1 sachet, given between 2 and 4 p.m. the day before the procedure
  - Adult: 1 sachet, given 8 a.m. the day before the procedure and 1 sachet, given between 2 and 4 p.m. the day before the procedure, use half the dose in frail elderly patients

**CONTRA-INDICATIONS**

Acute severe colitis • gastric retention • gastro-intestinal obstruction • gastro-intestinal perforation • toxic megacolon

**CAUTIONS**

Children • colitis (avoid if acute severe colitis) • debilitated • elderly (in adults) • hypovolaemia (should be corrected before administration of bowel cleansing preparations) • impaired gag reflex or possibility of regurgitation or aspiration • patients with fluid and electrolyte disturbances

**CAUTIONS, FURTHER INFORMATION**

Adequate hydration should be maintained during treatment.

**INTERACTIONS**

Other oral drugs should not be taken one hour before or after administration of bowel cleansing preparations because absorption may be impaired.

In adults Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and for up to 72 hours after the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**

- **Common or very common** Abdominal distention • abdominal pain • nausea • vomiting
- **Uncommon** Dehydration • dizziness • electrolyte disturbances • headache

**SIDE-EFFECTS, FURTHER INFORMATION**

Abdominal pain is usually transient and can be reduced by taking preparation more slowly.

**PREGNANCY**

Use with caution.

**BREAST FEEDING**

Use with caution.

**HEPATIC IMPAIRMENT**

Avoid in hepatic coma if risk of renal failure.

**RENAL IMPAIRMENT**

In adults Avoid if eGFR less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia.

In children Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia.

**MONITORING REQUIREMENTS**

Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances.

**DIRECTIONS FOR ADMINISTRATION**

One sachet should be reconstituted with 200 mL of hot water; the solution should be allowed to cool for approx. 30 minutes before drinking.

**PRESCRIBING AND DISPENSING INFORMATION**

Reconstitution of one sachet containing 11.57 g magnesium carbonate and 17.79 g anhydrous citric acid produces a solution containing magnesium citrate with 118 mmol Mg²⁺.

Flavours of oral powders may include lemon and lime.

**PATIENT AND CARER ADVICE**

Low residue or fluid only diet (e.g. water, fruit squash, clear soup, black tea or coffee) recommended before procedure (according to prescriber’s advice) and copious intake of clear fluids recommended until procedure. Patient or carers should be given advice on how to administer oral powder.

**MEDIUM FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Effervescent powder**

CAUTIONARY AND ADVISORY LABELS 13, 10

**ELECTROLYTES**: May contain Magnesium

- Citramag (Sanochemia Diagnostics UK Ltd)
  
  Magnesium carbonate heavy 11.57 gram, Citric acid anhydrous 17.79 gram
  
  Citramag effervescent powder sachets sugar-free 10 sachet £18.92

**Macrogol 3350 with anhydrous sodium sulfate, ascorbic acid, potassium chloride, sodium ascorbate and sodium chloride**

(Polyethylene glycols)

**INDICATIONS AND DOSE**

MOVIPREP®

Bowel evacuation for surgery, colonoscopy or radiological examination

- **BY MOUTH**
  - Adult: 1 litre daily for 2 doses: first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure, alternatively 2 litres daily for 1 dose; reconstituted solution to be taken on the evening before the procedure, treatment should be completed at least 1 hour before colonoscopy

**CONTRA-INDICATIONS**

Acute severe colitis • G6PD deficiency • gastric retention • gastro-intestinal obstruction • gastro-intestinal perforation • toxic megacolon

**CAUTIONS**

Colitis (avoid if acute severe colitis) • debilitated patients • elderly • fluid and electrolyte disturbances • heart failure • hypovolaemia (should be corrected before administration of bowel cleansing preparations) • impaired gag reflex or possibility of regurgitation or aspiration

**INTERACTIONS**

Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and for up to 72 hours after the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**

- **Common or very common** Abdominal distention • abdominal pain • nausea • vomiting
- **Uncommon** Dehydration • dizziness • electrolyte disturbances • headache
Indications and dose

Bowel cleansing before radiological examination, colonoscopy, or surgery

- Initially by mouth
- Adult: Initially 2 litres daily for 2 doses: first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure, alternatively (by mouth) initially 250 mL every 10–15 minutes, reconstituted solution to be administered, alternatively (by nasogastric tube) initially 20–30 mL/minute, starting on the day before procedure until 4 litres have been consumed

Contraindications

Acute severe colitis, gastric retention, gastro-intestinal obstruction, gastro-intestinal perforation, toxic megacolon

Caution

Colitis (avoid if acute severe colitis), debilitated patients, elderly, fluid and electrolyte disturbances, heart failure, hypovolaemia (should be corrected before administration of bowel cleansing preparations), impaired gag reflex or possibility of regurgitation or aspiration

LAXATIVES > STIMULANT LAXATIVES

Magnesium citrate with sodium picosulfate

(Formulated as a bowel cleansing preparation)
**CONTRA-INDICATIONS** Acute severe colitis • ascites • congestive cardiac failure • gastric retention • gastro-intestinal obstruction • gastro-intestinal perforation • gastro-intestinal ulceration • toxic megacolon

**CAUTIONS** Cardiac disease (avoid in congestive cardiac failure) • children • colitis (avoid if acute severe colitis) • debilitated patients • elderly • fluid and electrolyte disturbances • hypovolaemia (should be corrected before administration) • impaired gag reflex or possibility of regurgitation or aspiration • recent gastro-intestinal surgery

**SIDE-EFFECTS**
- **Common or very common** Abdominal distention • abdominal pain (usually transient—reduced by taking more slowly) • nausea • vomiting
- **Uncommon** Dehydration • dizziness • electrolyte disturbances • headache
- **Frequency not known** Anal discomfort • fatigue • rash • sleep disturbances

**PREGNANCY** Caution.

**BREAST FEEDING** Caution.

**HEPATIC IMPAIRMENT** Avoid in hepatic coma if risk of renal failure.

**RENAL IMPAIRMENT**
- in adults Avoid if eGFR less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia.
- in children Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia.

**DIRECTIONS FOR ADMINISTRATION** One sachet of sodium picosulfate with magnesium citrate powder should be reconstituted with 150 mL (approx. half a glass) of cold water; patients should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking.

**PICOLAX® SACHETS AND CITRAFLEET® SACHETS** One sachet should be reconstituted with 150 mL (approx. half a glass) of cold water.

**PRESCRIBING AND DISPENSING INFORMATION**
- **Flavours of oral powder formulations may include lemon.**
- **PICOLAX® SACHETS** One reconstituted sachet contains K⁺ 5 mmol and Mg²⁺ 87 mmol.
- **CITRAFLEET® SACHETS** One reconstituted sachet contains K⁺ 5 mmol and Mg²⁺ 86 mmol.

**PATIENT AND CARER ADVICE** Low residue diet recommended on the day before procedure and copious intake of water or other clear fluids recommended during treatment.

Patients and carers should be given advice on how to administer oral powder; they should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder**

**CAUTIONARY AND ADVISORY LABELS** 10, 13

**ELECTROLYTES:** May contain Magnesium, potassium

- **CitraFleet (Casen Recordati S.L.)**
  - Magnesium oxide light 3.5 gram, Citric acid anhydrous 10.97 gram, Sodium picosulfate 10 mg

- **CitraFleet oral powder 15.08g sachets sugar-free | 2 sachet tube £3.25**

- **Picolax (Ferring Pharmaceuticals Ltd)**
  - Magnesium oxide 3.5 gram, Citric acid anhydrous 12 gram, Sodium picosulfate 10 mg

  Picolax oral powder 16.1g sachets sugar-free | 20 sachet pack no price available

### 2.2 Constipation

**Overview**
Before prescribing laxatives it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint.

It is also important for those who complain of constipation to understand that bowel habit can vary considerably in frequency without doing harm. Some people tend to consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient’s own normal pattern and this can be explained to the patient.

Misconceptions about bowel habits have led to excessive laxative use. Abuse may lead to hypokalaemia.

Thus, laxatives should generally be avoided except where straining will exacerbate a condition (such as angiography) or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are also of value in drug-induced constipation, for the expulsion of parasites after anthelmintic treatment, and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is sometimes necessary.

Laxatives also have a role in the treatment of irritable bowel syndrome.

Also see the prevention of opioid-induced constipation in palliative care.

The laxatives that follow have been divided into 5 main groups. This simple classification disguises the fact that some laxatives have a complex action.

**Bulk-forming laxatives**
Bulk-forming laxatives are of value if the diet is deficient in fibre. Bulk-forming laxatives are of particular value in those with small hard stools, but should not be required unless fibre cannot be increased in the diet. A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation.

Bulk-forming laxatives can be used in the management of patients with colostomy, ileostomy, haemorrhoids, anal fissure, chronic diarrhea associated with diverticular disease, irritable bowel syndrome, and as adjuncts in ulcerative colitis.

Adequate fluid intake must be maintained to avoid intestinal obstruction. Unprocessed wheat bran, taken with food or fruit juice, is a most effective bulk-forming preparation. Finely ground bran, though more palatable, has poorer water-retaining properties, but can be taken as bran bread or...
biscuits in appropriately increased quantities. Oat bran is also used.
Methylcellulose p. 50, ispaghula husk p. 50, and sterculia p. 51 are useful in patients who cannot tolerate bran.
Methylcellulose also acts as a faecal softener.

**Stimulant laxatives**
Stimulant laxatives include bisacodyl p. 57, sodium picosulfate p. 60, and members of the *anthraquinone* group, senna p. 59, co-danthramer p. 58 and co-danthrusate p. 58. The indications for co-danthramer and co-danthrusate are limited by its potential carcinogenicity (based on rodent carcinogenicity studies) and evidence of genotoxicity.
Powerful stimulants such as *cascara* (an anthraquine) and castor oil are obsolete. Docusate sodium p. 56 probably acts both as a stimulant and as a softening agent. Stimulant laxatives increase intestinal motility and often cause abdominal cramp; they should be avoided in intestinal obstruction. Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia; however, prolonged use may be justifiable in some circumstances.
Glycerol suppositories p. 59 act as a lubricant and as a rectal stimulant by virtue of the mildly irritant action of glycerol.
Unstandardised preparations of cascara, frangula, rhubarb, and senna should be avoided as their laxative action is unpredictable. Aloes, colocynth, and jalap should be avoided as they have a drastic purgative action.
The *parasympathomimetics* bethanecol chloride p. 720, neostigmine p. 983, and pyridostigmine bromide p. 984 enhance parasympathetic activity in the gut and increase intestinal motility.
They are rarely used for their gastro-intestinal effects. Organic obstruction of the gut must first be excluded and they should not be used shortly after bowel anastomosis.

**Other stimulant laxatives**
Unstandardised preparations of cascara, frangula, rhubarb, and senna should be avoided as their laxative action is unpredictable. Aloes, colocynth, and jalap should be avoided as they have a drastic purgative action.

**Faecal softeners**
Liquid paraffin p. 57, the traditional lubricant, has disadvantages. Bulk laxatives and non-ionic surfactant ‘wetting’ agents e.g. docusate sodium also have softening properties. Such drugs are useful for oral administration in the management of haemorrhoids; glycerol is useful for rectal use.
Enemas containing arachis oil p. 56 (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement.

**Osmotic laxatives**
Osmotic laxatives increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid they were administered with.
Lactulose p. 52 is a semi-synthetic disaccharide which is not absorbed from the gastro-intestinal tract. It produces an osmotic diarrhoea of low faecal pH, and discourages the proliferation of ammonia-producing organisms. It is therefore useful in the treatment of *hepatic encephalopathy*.

**Macrogols** are inert polymers of ethylene glycol which sequester fluid in the bowel; giving fluid with macrogols may reduce the dehydrating effect sometimes seen with osmotic laxatives.
Saline purgatives such as magnesium hydroxide p. 54 are commonly abused but are satisfactory for occasional use; adequate fluid intake should be maintained. Magnesium salts, such as magnesium sulfate p. 924 are useful where rapid bowel evacuation is required. Sodium salts should be avoided as they may give rise to sodium and water retention in susceptible individuals. *Phosphate enemas* are useful in bowel clearance before radiology, endoscopy, and surgery.

**Other drugs used in constipation**
Linaclotide p. 44 is a guanylate cyclase-C receptor agonist that is licensed for the treatment of moderate to severe irritable bowel syndrome associated with constipation. It increases intestinal fluid secretion and transit, and decreases visceral pain. It is metabolised within the gastro-intestinal tract and is virtually undetectable in the plasma after therapeutic doses.
Lubiprostone p. 51 is a chloride-channel activator that is licensed for the treatment of chronic idiopathic constipation in adults whose condition has not responded adequately to lifestyle changes (including dietary changes).
Prucalopride p. 55 is a selective serotonin 5HT4-receptor agonist with prokinetic properties. It is licensed for the treatment of chronic constipation in women, when other laxatives have failed to provide an adequate response.

**Bowel cleansing preparations**
Bowel cleansing preparations are used before colonic surgery, colonoscopy, or radiological examination to ensure the bowel is free of solid contents. They are not treatments for constipation.

**Pregnancy**
If dietary and lifestyle changes fail to control constipation in pregnancy, moderate doses of poorly absorbed laxatives may be used. A bulk-forming laxative should be tried first. An osmotic laxative, such as lactulose, can also be used. Bisacodyl or senna may be suitable, if a stimulant effect is necessary.

**Constipation in children**
Laxatives should be prescribed by a healthcare professional experienced in the management of constipation in children. Delays of greater than 3 days between stools may increase the likelihood of pain on passing hard stools leading to anal fissure, anal spasm and eventually to a learned response to avoid defaecation.
In *infants*, increased intake of fluids, particularly fruit juice containing sorbitol (e.g. prune, pear, or apple), may be sufficient to soften the stool. In infants under 1 year of age with mild constipation, lactulose p. 52 can be used to soften the stool; either an oral preparation containing macrogols or, rarely, glycerol p. 59 suppositories can be used to clear faecal impaction. The infant should be referred to a hospital paediatrician if these measures fail.
The diet of *children* over 1 year of age should be reviewed to ensure that it includes an adequate intake of fibre and fluid.
An osmotic laxative containing macrogols can also be used, particularly in children with chronic constipation; lactulose is an alternative in children who cannot tolerate a macrogol. If there is an inadequate response to the osmotic laxative, a stimulant laxative can be added.
Treatment of faecal impaction may initially increase symptoms of soiling and abdominal pain. In children over 1 year of age with faecal impaction, an oral preparation containing macrogols is used to clear faecal mass and to establish and maintain soft well-formed stools. If disimpaction does not occur after 2 weeks, a stimulant laxative can be added. If the impacted mass is not expelled following treatment with macrogols and a stimulant laxative, a sodium citrate enema can be administered. Although rectal administration of laxatives may be effective, this route is frequently distressing for the child and may lead to persistence of withholding. A phosphate enema may be administered under specialist supervision if disimpaction does not occur after a sodium citrate enema; a bowel cleansing preparation is an alternative. Manual evacuation
under anaesthetic may be necessary if disimpaction does not occur after oral and rectal treatment, or if the child is afraid.

Long-term regular use of laxatives is essential to maintain well-formed stools and prevent recurrence of faecal impaction; intermittent use may provoke relapses. In children with chronic constipation, laxatives should be continued for several weeks after a regular pattern of bowel movements or toilet training is established. The dose of laxatives should then be tapered gradually, over a period of months, according to response. Some children may require laxative therapy for several years.

**Chronic constipation**

For children with chronic constipation, it may be necessary to exceed the licensed doses of some laxatives. Parents and carers of children should be advised to adjust the dose of laxative in order to establish a regular pattern of bowel movements in which stools are soft, well-formed, and passed without discomfort. Laxatives should be administered at a time that produces an effect that is likely to fit in with the child’s toilet routine.

**Other drugs used for Constipation** Sodium citrate, p. 721

### LAXATIVES  BULK-FORMING LAXATIVES

**Ispaghula husk**

**Drug action**  Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis.

**Indications and dose**

**Constipation**

- **By mouth**
  - Child 1 month–5 years: 2.5–5 mL twice daily, dose to be taken only when prescribed by a doctor, as half or whole level spoonful in water, preferably after meals, morning and evening
  - Child 6–11 years: 2.5–5 mL twice daily, dose to be given as a half or whole level spoonful in water, preferably after meals, morning and evening
  - Child 12–17 years: 1 sachet twice daily, dose to be given in water preferably after meals, morning and evening
  - Adult: 1 sachet twice daily, dose to be given in water preferably taken after food, morning and evening

**Dose equivalence and conversion**

- 1 sachet equivalent to 2 level 5 mL spoonful.

**Contra-indications**  Colonic atony · faecal impaction · intestinal obstruction · reduced gut motility

**Caution**  Adequate fluid intake should be maintained to avoid intestinal obstruction

**Side-effects**  Abdominal distension · flatulence · gastro-intestinal impaction · gastro-intestinal obstruction · hypersensitivity

**Directions for administration**  Dose to be taken with at least 150 mL liquid.

**Prescribing and dispensing information**  Flavours of soluble granules formulations may include plain, lemon, or orange.

**Handling and storage**  Ispaghula husk contains potent allergens. Individuals exposed to the product (including those handling the product) can develop hypersensitivity reactions such as rhinitis, conjunctivitis, bronchospasm and in some cases, anaphylaxis.

**Patient and carer advice**  Manufacturer advises that preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed. Patients and their carers should be advised that the full effect may take some days to develop and should be given advice on how to administer ispaghula husk.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Granules**

**Cautionary and advisory labels**  13

**Excipients:**  May contain Aspartame

- **Ispaghula husk (Non-proprietary)**
  - Ispaghula husk 3.5 gram: Ispaghula husk 3.5g sachets gluten free | 30 sachet GSS £2.48

**Effervescent granules**

**Cautionary and advisory labels**  13

**Excipients:**  May contain Aspartame

- **Ispaghula husk (Non-proprietary)**
  - Ispaghula husk 3.5 gram: Ispaghula husk 3.5g effervescent granules sachets gluten free sugar free sugar-free | 30 sachet GSS £2.48
  - Fybogel (Reckitt Benckiser Healthcare (UK) Ltd)
    - Fybogel 3.5g effervescent granules sachets plain SF sugar-free | 30 sachet GSS £2.26
    - Fybogel Orange 3.5g effervescent granules sachets SF sugar-free | 30 sachet GSS £2.26
    - Fybogel Lemon 3.5g effervescent granules sachets SF sugar-free | 30 sachet GSS £2.26

**Fybogel Hi-Fibre (Reckitt Benckiser Healthcare (UK) Ltd)**

- Ispaghula husk 3.5 gram: Ispaghula husk 3.5g effervescent granules sachets sugar-free | 10 sachet GSS £2.26
  - Fybogel Hi-Fibre Orange 3.5g effervescent granules sachets sugar-free | 10 sachet GSS £2.26
  - Ispagel (Bristol Laboratories Ltd)
    - Ispaghula husk 3.5 gram: Ispaghula husk 3.5g effervescent granules sachets sugar-free | 10 sachet GSS £2.26
  - Ispaghula husk 3.5 gram: Ispaghula husk 3.5g effervescent granules sachets sugar-free | 10 sachet GSS £2.26

**Combinations available:**  Senna with Ispaghula husk, p. 59

### Methylcellulose

**Drug action**  Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis.

**Indications and dose**

**Constipation**  |  **Diarrhoea**

- **By mouth using tablets**
  - Adult: 3–6 tablets twice daily

**Contra-indications**  Colonic atony · difficulty in swallowing · faecal impaction · infective bowel disease · intestinal obstruction

**Caution**  Adequate fluid intake should be maintained to avoid intestinal obstruction

**Caution, further information**  It may be necessary to supervise elderly or debilitated patients or those with intestinal narrowing or decreased motility to ensure adequate fluid intake.

**Side-effects**  Abdominal distension (especially during the first few days of treatment) · flatulence (especially during the first few days of treatment) · gastro-intestinal impaction · gastro-intestinal obstruction · hypersensitivity

**Directions for administration**  In constipation the dose should be taken with at least 300 mL liquid. In diarrhoea, ileostomy, and colostomy control, avoid liquid intake for 30 minutes before and after dose.

**Patient and carer advice**  Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.
**Sterculia with frangula**

The properties listed below are those particular to the combination only. For the properties of the components please consider, sterculia above.

**INDICATIONS AND DOSE**

**After haemorrhoidectomy**
- **BY MOUTH**
  - Adult: 1–2 sachets 1–2 times a day, alternatively, 1–2 heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals

**Constipation**
- **BY MOUTH**
  - Adult: 1–2 sachets 1–2 times a day, alternatively, 1–2 heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals

**PREGNANCY** Manufacturer advises avoid.

**BREAST FEEDING** Manufacturer advises avoid.

**PATIENT AND CARER ADVICE** Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with liquid and should not be taken immediately before going to bed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Granules**
- **Normacol Plus** (Norgine Pharmaceuticals Ltd)
  - Frangula 80 mg per 1 gram, Sterculia 620 mg per
  - 1 gram Normacol Plus granules 7g sachets | 60 sachet GSL £6.78
  - DT price = £6.78 Normacol Plus granules | 500 gram GSL £8.05 DT price = £8.05

**LAXATIVES**

**Lubiprostone**

**DRUG ACTION** Lubiprostone is a chloride-channel activator that acts locally in the gut to increase intestinal fluid secretion and intestinal motility, resulting in a laxative effect.

**INDICATIONS AND DOSE**

**Chronic idiopathic constipation when response to lifestyle changes (including diet) inadequate**
- **BY MOUTH**
  - Adult: 24 micrograms twice daily for 2–4 weeks, discontinue if no response after initial 2 weeks

**CONTRA-INDICATIONS** Gastro-intestinal obstruction

**SIDE-EFFECTS**
- **Common or very common** Abdominal discomfort • abdominal distension • abdominal pain • diarrhoea • dizziness • dyspepsia • dysphagia • flatulence • headache • hot flush • hyperhidrosis • nausea • oedema • palpitation
- **Uncommon** Chest pain • muscle spasm • syncope • vomiting
- **Frequency not known** Influenza-like symptoms • rash • tachycardia

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Unknown if excreted in milk. If benefits of use outweigh the risk, monitor infant for side effects (e.g. diarrhoea).

**HEPATIC IMPAIRMENT** In moderate to severe impairment initially 24 micrograms once daily; if tolerated, and if necessary, increased to 24 micrograms twice daily.

**PRESCRIBING AND DISPENSING INFORMATION** Dispense capsules in original container; discard any capsules remaining 4 weeks after opening.
Lubiprostone for treating chronic idiopathic constipation (July 2014) NICE TA318
Lubiprostone is recommended as an option for treating chronic idiopathic constipation for adults in whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and for whom invasive treatment for constipation is being considered. If treatment with lubiprostone is not effective after 2 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered.
Lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, after careful review of the patient’s previous courses of laxative treatments.

www.nice.org.uk/TA318
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2014) that lubiprostone (Amitiza) is not recommended for use within NHS Scotland.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
CAUTIONARY AND ADVISORY LABELS 21
Amitiza (Sucampo Pharma Europe Ltd) ▼
Lubiprostone 24 microgram Amitiza 24microgram capsules | 28 capsule pack £29.68 | 56 capsule pack £53.48

LAXATIVES ∨ OSMOTIC LAXATIVES

Lactulose

● INDICATIONS AND DOSE
Constipation
BY MOUTH
- Child 1–11 months: 2.5 mL twice daily, adjusted according to response
- Child 1–4 years: 2.5–10 mL twice daily, adjusted according to response
- Child 5–17 years: 5–20 mL twice daily, adjusted according to response
- Adult: Initially 15 mL twice daily, adjusted according to response

Hepatic encephalopathy (portal systemic encephalopathy)
BY MOUTH
- Adult: Adjusted according to response to 30–50 mL 3 times a day, subsequently adjusted to produce 2–3 soft stools per day

PHARMACOKINETICS
Lactulose may take up to 48 hours to act.

● UNLICENSED USE
In adults Lactulose doses in the BNF may differ from those in product literature.

● CONTRA-INDICATIONS
Galactosaemia · intestinal obstruction

● CAUTIONS
Lactose intolerance

● INTERACTIONS → Appendix 1 (lactulose).

● SIDE-EFFECTS
Common or very common Abdominal discomfort · cramps · flatulence · nausea · vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Nausea. Nausea can be reduced by administration with water, fruit juice or meals.

● PREGNANCY
Not known to be harmful.

Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride

● INDICATIONS AND DOSE
Chronic constipation (dose for non-proprietary 'full-strength' sachets)
BY MOUTH
- Child 12–17 years: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily
- Adult: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily

Faecal impaction (dose for non-proprietary 'full-strength' sachets)
BY MOUTH
- Child 12–17 years: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day
- Adult: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day

MOVICOL-HALF®
Chronic constipation
BY MOUTH
- Child 12–17 years: 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance 2–4 sachets daily
- Adult: 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance 2–4 sachets daily

Faecal impaction
BY MOUTH
- Child 12–17 years: Initially 8 sachets daily on first day, then increased in steps of 4 sachets daily, total daily dose to be drunk within 6 hours, after disimpaction, switch to maintenance laxative therapy; maximum 16 sachets per day
- Adult: Initially 8 sachets daily on first day, then increased in steps of 4 sachets daily, total daily dose to be drunk within 6 hours, after disimpaction, switch to maintenance laxative therapy; maximum 16 sachets per day

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Lactulose for constipation
www.medicinesforchildren.org.uk/lactulose-for-constipation

● NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Lubiprostone for treating chronic idiopathic constipation (July 2014) NICE TA318

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral solution
- Lactulose (Non-proprietary)
  Lactulose 666.67 mg per 1 ml Lactulose 10g/15ml oral solution 15ml sachets sugar free sugar-free | 10 sachet pack £2.50 DT price = £2.50
  Lactulose 680 mg per 1 ml Lactulose 3.1:3.7g/5ml oral solution 300 mL pack | 500 mL pack £4.55 DT price = £2.47
- Duphalac (BGP Products Ltd)
  Lactulose 680 mg per 1 ml Duphalac 3.35g/5ml syrup | 200 mL pack £1.92
- Lactugal (Intrapharm Laboratories Ltd)
  Lactulose 680 mg per 1 ml Lactugal 3.1:3.7g/5ml oral solution | 500 mL pack | 2000 mL pack £16.42

www.nice.org.uk/TA318
www.medicinesforchildren.org.uk/lactulose-for-constipation
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2014) that lubiprostone (Amitiza) is not recommended for use within NHS Scotland.
**MOVICOL-PAEDIATRIC®**

**Chronic constipation | Prevention of faecal impaction**

- **BY MOUTH**
  - Child 2-5 years: 1 sachet daily, adjust dose to produce regular soft stools; maximum 4 sachets per day
  - Child 6-11 years: 2 sachets daily, adjust dose to produce regular soft stools; maximum 4 sachets per day

**Faecal impaction**

- **BY MOUTH**
  - Child 5-11 years: Initially 4 sachets daily on first day, then increased in steps of 2 sachets daily, total daily dose to be taken over a 12-hour period, after disimpaction, switch to maintenance laxative therapy; maximum 12 sachets per day

**MOVICOL® LIQUID**

**Chronic constipation**

- **BY MOUTH**
  - Child 12-17 years: 25 mL 1–3 times a day usually for up to 2 weeks; maintenance 25 mL 1–2 times a day
  - Adult: 25 mL 1–3 times a day usually for up to 2 weeks; maintenance 25 mL 1–2 times a day

**MOVICOL® ORAL POWDER**

**Chronic constipation**

- **BY MOUTH**
  - Child 12-17 years: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily
  - Adult: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily

**Faecal impaction**

- **BY MOUTH**
  - Child 12-17 years: Initially 4 sachets daily on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day
  - Adult: Initially 4 sachets daily on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day

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### UNLICENSED USE

**MOVICOL-PAEDIATRIC®** *Movicol® Paediatric* not licensed for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years.

### CONTRA-INDICATIONS

- Crohn’s disease
- Intestinal obstruction
- Intestinal perforation
- Paralytic ileus
- Severe inflammatory conditions of the intestinal tract
- Toxic megacolon
- Ulcerative colitis

**MOVICOL-PAEDIATRIC®** Cardiovascular impairment - renal impairment

### CAUTIONS

Cardiovascular impairment (should not take more than 2 ‘full-strength’ sachets or 4 ‘half-strength’ sachets in any one hour) - discontinue if symptoms of fluid and electrolyte disturbance

**MOVICOL-PAEDIATRIC®** Impaired consciousness (with high doses) - impaired gag reflex (with high doses) - reflux oesophagitis (with high doses)

### INTERACTIONS

- Appendix 1 (macrogols).

### SIDE-EFFECTS

- Abdominal distention - abdominal pain - flatulence - nausea

### PREGNANCY

Limited data, but manufacturer advises that it can be used.

### BREAST FEEDING

Manufacturer advises that it can be used.

### RENAL IMPAIRMENT

**MOVICOL-PAEDIATRIC®** Contra-indicated in renal impairment.

### DIRECTIONS FOR ADMINISTRATION

Contents of each ‘full strength’ sachet of oral powder to be dissolved in half a glass (approx. 125 mL) of water; after reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours.

**MOVICOL® LIQUID** 25 mL of oral concentrate to be diluted with half a glass (approx. 100 mL) of water. After dilution the solution should be discarded if unused after 24 hours.

**MOVICOL-PAEDIATRIC®** Contents of each sachet to be dissolved in quarter of a glass (approx. 60–65 mL) of water; after reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours.

**MOVICOL® ORAL POWDER** Contents of each sachet to be dissolved in half a glass (approx. 125 mL) of water; after reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours.

### PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include orange.

Flavours of oral powder formulations may include chocolate, lime and lemon, or plain.

**MOVICOL® LIQUID** 25 mL of oral concentrate when diluted with 100 mL water provides K⁺ 5.4 mmol/litre.

**MOVICOL® ORAL POWDER** Amount of potassium chloride varies according to flavour of Movicol® as follows:

- Plain-flavour (sugar-free) = 50.2 mg/sachet; lime and lemon flavour = 46.6 mg/sachet; chocolate flavour = 31.7 mg/sachet. 1 sachet when reconstituted with 125 mL water provides K⁺ 5.4 mmol/litre.

### PATIENT AND CARER ADVICE

Patients or carers should be counselled on how to take the oral powder and oral solution.

Medicines for Children leaflet: Movicol for constipation [www.medicinesforchildren.org.uk/movicol-for-constipation](http://www.medicinesforchildren.org.uk/movicol-for-constipation)

**MOVICOL® LIQUID** Patients or carers should be counselled on how to take Movicol® oral solution.

**MOVICOL® ORAL POWDER** Patients or carers should be counselled on how to take Movicol® oral powder.

**MOVICOL-HALF®** Patients or carers should be given advice on how to administer Movicol-Half® oral powder.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 13**

**ELECTROLYTES** May contain Bicarbonate, chloride, potassium, sodium

- **Bicarbonate** 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Macrogol ‘3350’ 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Sodium 65 mmol per 1 litre Movicol Liquid sugar-free | 500 ml | £5.15 DT price = £5.15

**Powder**

**CAUTIONARY AND ADVISORY LABELS 13**

**ELECTROLYTES** May contain Bicarbonate, chloride, potassium, sodium

- **Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride (Non-proprietary)**

  - **Bicarbonate** 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Macrogol ‘3350’ 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Sodium 65 mmol per 1 litre

  **Movicol compound oral powder sachets sugar free sugar-free**

  - 20 sachet | £4.45 sugar-free | 30 sachet | £6.68 DT price = £4.27

  **Macrogol compound oral powder sachets sugar free plain sugar-free**

  - 20 sachet | £3.42 sugar-free | 30 sachet | £4.27 DT price = £4.27

  **Movicol compound oral powder sachets sugar free half strength**

  - 20 sachet | £2.85 sugar-free | 30 sachet | £4.27 DT price = £4.27

  **Movicol compound oral powder sachets sugar free citrus sugar-free**

  - 20 sachet | £2.85 sugar-free | 30 sachet | £4.27 DT price = £4.27

  **Movicol compound oral powder sachets sugar free half strength**

  - 20 sachet | £2.85 sugar-free | 30 sachet | £4.27 DT price = £4.27

  **Movicol compound oral powder sachets sugar free citrus sugar-free**

  - 20 sachet | £2.85 sugar-free | 30 sachet | £4.27 DT price = £4.27

  **Movicol compound oral powder sachets sugar free half strength**

  - 20 sachet | £2.85 sugar-free | 30 sachet | £4.27 DT price = £4.27
### Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Magnesium hydroxide 83 mg per 1 ml

**Indications and Dose**
- **Constipation** (using Phosphates Enema BP Formula B)
  - Adult: 30–45 mL as required, dose to be given mixed with water at bedtime

**Contra-Indications**
- Acute gastro-intestinal conditions

**Precautions**
- Debilitated patients · elderly

**Interactions**
- Appendix 1 (antacids).

**Side-Effects**
- Colic

**Hepatic Impairment**
- Avoid in hepatic coma if risk of renal failure.

**Renal Impairment**
- Avoid or reduce dose. Increased risk of toxicity in renal impairment.

**Prescribing and Dispensing Information**
- When prepared extemporaneously, the BP states Magnesium Hydroxide Mixtute, BP consists of an aqueous suspension containing about 8% hydrated magnesium oxide.

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug.

### Sodium acid phosphate with sodium phosphate

**Indications and Dose**
- **Constipation (using Phosphates Enema BP Formula B)**
- **Bowel evacuation before abdominal radiological procedures, endoscopy, and surgery (using Phosphates Enema BP Formula B)**

**Contra-Indications**
- Acute gastro-intestinal conditions

**Precautions**
- Debilitated patients · elderly

**Interactions**
- Appendix 1 (antacids).

**Side-Effects**
- Colic

**Hepatic Impairment**
- Avoid in hepatic coma if risk of renal failure.

**Renal Impairment**
- Avoid or reduce dose. Increased risk of toxicity in renal impairment.

**Prescribing and Dispensing Information**
- When prepared extemporaneously, the BP states Magnesium Hydroxide Mixtute, BP consists of an aqueous suspension containing about 8% hydrated magnesium oxide.

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug.

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**Magnesium hydroxide**

- **Constitution**
  - **By Mouth**
    - Adult: 30-45 mL as required, dose to be given mixed with water at bedtime

- **Contra-Indications**
  - Acute gastro-intestinal conditions

- **Precautions**
  - Debilitated patients · elderly

- **Interactions**
  - Appendix 1 (antacids).

- **Side-Effects**
  - Colic

- **Hepatic Impairment**
  - Avoid in hepatic coma if risk of renal failure.

- **Renal Impairment**
  - Avoid or reduce dose. Increased risk of toxicity in renal impairment.

- **Prescribing and Dispensing Information**
  - When prepared extemporaneously, the BP states Magnesium Hydroxide Mixtute, BP consists of an aqueous suspension containing about 8% hydrated magnesium oxide.

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug.

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**Sodium acid phosphate with sodium phosphate**

- **Indications and Dose**
  - **Constipation (using Phosphates Enema BP Formula B)**
  - **Bowel evacuation before abdominal radiological procedures, endoscopy, and surgery (using Phosphates Enema BP Formula B)**

- **Contra-Indications**
  - Acute gastro-intestinal conditions

- **Precautions**
  - Debilitated patients · elderly

- **Interactions**
  - Appendix 1 (antacids).

- **Side-Effects**
  - Colic

- **Hepatic Impairment**
  - Avoid in hepatic coma if risk of renal failure.

- **Renal Impairment**
  - Avoid or reduce dose. Increased risk of toxicity in renal impairment.

- **Prescribing and Dispensing Information**
  - When prepared extemporaneously, the BP states Magnesium Hydroxide Mixtute, BP consists of an aqueous suspension containing about 8% hydrated magnesium oxide.

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug.
**CONTRA-INDICATIONS**
- With oral use: Acute severe colitis (in adults) - ascites (in adults) - congestive cardiac failure (in adults) - gastric retention (in adults) - gastro-intestinal obstruction - gastro-intestinal perforation (in adults) - toxic megacolon (in adults)
- With rectal use: conditions associated with increased colonic absorption - gastro-intestinal obstruction - inflammatory bowel disease

**CAUTIONS**
- With oral use: cardiac disease (avoiding congestive cardiac failure) (in adults) - colitis (avoiding acute severe colitis)(in adults) - elderly and debilitated patients (in adults) - fluid and electrolyte disturbances (in adults) - hypovolaemia (should be corrected before administration) (in adults) - impaired gag reflex or possibility of regurgitation or aspiration (in adults)
- With rectal use: Ascites - congestive heart failure - elderly and debilitated patients (in adults) - electrolyte disturbances - uncontrolled hypertension

**INTERACTIONS**
- With oral use: Other oral drugs should not be taken one hour before or after administration of bowel cleansing preparations be taken as absorption may be impaired. Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and are usually transient. After the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**
- Common or very common
  - With oral use: Abdominal distention (in adults) - abdominal pain (usually transient — reduced by taking more slowly) (in adults) - nausea (in adults) - vomiting (in adults)
  - Uncommon
    - With oral use: Dehydration (in adults) - dizziness (in adults) - headache (in adults)
  - Frequency not known
    - With oral use: Arrhythmias (in adults) - asthenia (in adults) - chest pain (in adults) - electrolyte disturbances - renal failure (in adults)
    - With rectal use: Electrolyte disturbances - local irritation

**PREGNANCY**
- With oral use: Caution.

**BREAST FEEDING**
- With oral use: Caution.

**HEPATIC IMPAIRMENT**
- Use with caution in cirrhosis.

**RENAL IMPAIRMENT**
- With oral use: Avoid if eGFR less than 60 mL/minute/1.73 m².
- With rectal use: Use with caution.

**MONITORING REQUIREMENTS**
- With oral use: Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances.

**DIRECTIONS FOR ADMINISTRATION**
**FLEET® PHOSPHO-SODA**
- Copy intact of water or other clear fluids (e.g. clear soup, strained fruit juice without pulp, black tea or coffee) recommended until midnight before morning procedure and until 8 a.m. before afternoon procedure. At least one glass (approx 240 mL) of water or other clear fluid should also be taken immediately before each dose.

**PRESCRIBING AND DISPENSING INFORMATION**
- When prepared extemporaneously, the BP states Phosphates Enema BP Formula B consists of sodium dihydrogen phosphate dihydrate 181 mg per 1 ml, sodium dihydrogen phosphate dodecahydrate 100 mg per 1 ml, sodium dihydrogen phosphate dihydrate 542 mg per 1 ml, sodium dihydrogen phosphate dihydrate 240 mg per 1 ml.

**PATIENT AND CARER ADVICE**
**FLEET® PHOSPHO-SODA**
- Intake of solid food should be stopped for at least 6 hours before starting treatment and until procedure completed.
- Patients or carers should be advised that adequate hydration should be maintained during treatment.
- Patients or carers should be given advice on administration of Fleet Phospho-soda® oral solution.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**
**CAUTIONARY AND ADVISORY LABELS 10**
**ELECTROLYTES: May contain Phosphate, sodium**
- **Fleet Phospho-soda** (Casen Recordati S.L.)
  - Disodium hydrogen phosphate dodecahydrate 240 mg per 1 ml, Sodium dihydrogen phosphate dihydrate 542 mg per 1 ml

**Enema**
- Sodium acid phosphate with sodium phosphate (Non proprietary)
  - Disodium hydrogen phosphate dodecahydrate 80 mg per 1 ml, Sodium dihydrogen phosphate dihydrate 100 mg per 1 ml
  - Phosphates enema (Formula B) 128ml standard tube | 1 enema £27.93 DT price = £27.93
  - Phosphates enema (Formula B) 27 ml standard tube | 1 enema £3.98 DT price = £3.98
- **Fleet Ready-to-use** (Casen Recordati S.L.)
  - Disodium hydrogen phosphate dodecahydrate 80 mg per 1 ml, Sodium dihydrogen phosphate dihydrate 181 mg per 1 ml

**LAXATIVES > SELECTIVE 5-HT₄ RECEPTOR AGONISTS**

**Prucalopride**
- **DRUG ACTION** A selective serotonin 5HT₄ receptor agonist with prokinetic properties.

**INDICATIONS AND DOSE**
- **Chronic constipation when other laxatives fail to provide an adequate response**
  - **BY MOUTH**
  - Adult: 2 mg once daily, review treatment if no response after 4 weeks
  - Elderly: Initially 1 mg once daily, increased if necessary to 2 mg once daily, review treatment if no response after 4 weeks

**CONTRA-INDICATIONS**
- Crohn’s disease - intestinal obstruction - intestinal perforation - toxic megacolon - ulcerative colitis

**CAUTIONS**
- History of arrhythmias - history of ischaemic heart disease

**SIDE-EFFECTS**
- **Common or very common**
  - Abdominal pain - decreased appetite - diarrhoea - dizziness - dyspepsia - fatigue - flatulence - headache - nausea - polyuria - rectal bleeding - vomiting
  - **Uncommon**
  - Fever - malaise - palpitation - tremor

**SIDE-EFFECTS, FURTHER INFORMATION**
- Manufacturer advises that side-effects generally occur at the start of treatment and are usually transient.

**CONCEPTION AND CONTRACEPTION**
- Manufacturer recommends effective contraception during treatment.

**PREGNANCY**
- Manufacturer advises avoid—limited data available.

**BREAST FEEDING**
- Manufacturer advises avoid—present in milk.
**Indications and dose**

**Docusate sodium (Diocytol sodium sulphoscuccinate)**

**INDICATIONS AND DOSE**

**Chronic constipation**

- **BY MOUTH**
  - Child 6 months-1 year: 12.5 mg 3 times a day, adjusted according to response, use paediatric oral solution
  - Child 2-11 years: 12.5–25 mg 3 times a day, adjusted according to response, use paediatric oral solution
  - Child 12-17 years: Up to 500 mg daily in divided doses, adjusted according to response
  - Adult: Up to 500 mg daily in divided doses, adjusted according to response
- **BY RECTUM**
  - Adult: 120 mg for 1 dose

**Adjuent in abdominal radiological procedures**

- **BY MOUTH**
  - Adult: 400 mg, to be administered with barium meal
- **BY RECTUM**
  - Adult: 120 mg for 1 dose

**PHARMACOKINETICS**

Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.

**UNLICENSED USE**

*Adult oral solution and capsules not licensed for use in children under 12 years.*

**CONTRA-INDICATIONS**

Avoid in intestinal obstruction

**CAUTIONS**

Do not give with liquid paraffin - excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - rectal preparations not indicated if haemorrhoids or anal fissure

**SIDE-EFFECTS**

Abdominal cramp - diarrhoea (excessive use) - hypokalaemia - rash

**PREGNANCY**

Not known to be harmful — manufacturer advises caution.

**BREAST FEEDING**

Present in milk following oral administration — manufacturer advises caution.

**WITH RECTAL USE**

Rectal administration not known to be harmful.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use in children For administration by mouth, solution may be mixed with milk or squash.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **Diocytol (UCB Pharma Ltd)**
  - Docusate sodium 100 mg Diocytol 100mg capsules | 30 capsule £2.09 DT price = £2.09 | 100 capsule £6.98

**Oral solution**

- **Docusate sodium (Non-proprietary)**
  - Docusate sodium 2.5 mg per 1 ml Docusate 2.5mg/5ml oral solution sugar free sugar-free | 300 ml £7.79 DT price = £5.29
  - Docusate sodium 5 mg per 1 ml Docusate 5mg/5ml oral solution sugar free sugar-free | 300 ml £7.99 DT price = £5.49
  - **Docusol (Typharm Ltd)**
    - Docusate sodium 2.5 mg per 1 ml Docusol Paediatric 2.5mg/5ml oral solution sugar-free | 300 ml £5.29 DT price = £5.29

**Enema**

- **Norgalax (Essential Pharma Ltd)**
  - Docusate sodium 12 mg per 1 gram Norgalax 120mg/10g enema | 6 enema £28.00

**Arachis oil (Non-proprietary)**

- Arachis oil 1 ml per 1 ml Arachis oil 130ml enema | 1 enema £37.50 DT price = £37.50

**CAUTIONS**

Hypersensitivity to soya - intestinal obstruction

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated if history of hypersensitivity to arachis oil or peanuts.

**DIRECTIONS FOR ADMINISTRATION**

Warm enema in warm water before use.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Arachis oil (Non-proprietary)**
  - Arachis oil 1 ml per 1 ml Arachis oil 130ml enema | 1 enema
  - Arachis oil 5 ml per 5 ml Arachis oil 650ml enema | 10 enema
  - Arachis oil 10 ml per 10 ml Arachis oil 1300ml enema | 10 enema

**LAXATIVES**

**SOFTENING LAXATIVES**

**DIRECTIONS FOR ADMINISTRATION**

**With oral use in children**

- By mouth
  - Adult: 130 mL as required

**With rectal use**

- Adult: 120 mg for 1 dose

**PHARMACOKINETICS**

Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.

**UNLICENSED USE**

*Adult oral solution and capsules not licensed for use in children under 12 years.*

**CONTRA-INDICATIONS**

Avoid in intestinal obstruction

**CAUTIONS**

Do not give with liquid paraffin - excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - rectal preparations not indicated if haemorrhoids or anal fissure

**SIDE-EFFECTS**

Abdominal cramp - diarrhoea (excessive use) - hypokalaemia - rash

**PREGNANCY**

Not known to be harmful — manufacturer advises caution.

**BREAST FEEDING**

Present in milk following oral administration — manufacturer advises caution.

**WITH RECTAL USE**

Rectal administration not known to be harmful.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use in children For administration by mouth, solution may be mixed with milk or squash.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **Diocytol (UCB Pharma Ltd)**
  - Docusate sodium 100 mg Diocytol 100mg capsules | 30 capsule £2.09 DT price = £2.09 | 100 capsule £6.98

**Oral solution**

- **Docusate sodium (Non-proprietary)**
  - Docusate sodium 2.5 mg per 1 ml Docusate 2.5mg/5ml oral solution sugar free sugar-free | 300 ml £7.79 DT price = £5.29
  - Docusate sodium 5 mg per 1 ml Docusate 5mg/5ml oral solution sugar free sugar-free | 300 ml £7.99 DT price = £5.49
  - **Docusol (Typharm Ltd)**
    - Docusate sodium 2.5 mg per 1 ml Docusol Paediatric 2.5mg/5ml oral solution sugar-free | 300 ml £5.29 DT price = £5.29

**Enema**

- **Norgalax (Essential Pharma Ltd)**
  - Docusate sodium 12 mg per 1 gram Norgalax 120mg/10g enema | 6 enema £28.00

**CAUTIONS**

Hypersensitivity to soya - intestinal obstruction

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated if history of hypersensitivity to arachis oil or peanuts.

**DIRECTIONS FOR ADMINISTRATION**

Warm enema in warm water before use.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Arachis oil (Non-proprietary)**
  - Arachis oil 1 ml per 1 ml Arachis oil 130ml enema | 1 enema £37.50 DT price = £37.50

**LAXATIVES**

**SOFTENING LAXATIVES**

**DIRECTIONS FOR ADMINISTRATION**

**With oral use in children**

- By mouth
  - Adult: 130 mL as required

**With rectal use**

- Adult: 120 mg for 1 dose

**PHARMACOKINETICS**

Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.

**UNLICENSED USE**

*Adult oral solution and capsules not licensed for use in children under 12 years.*

**CONTRA-INDICATIONS**

Avoid in intestinal obstruction

**CAUTIONS**

Do not give with liquid paraffin - excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - rectal preparations not indicated if haemorrhoids or anal fissure

**SIDE-EFFECTS**

Abdominal cramp - diarrhoea (excessive use) - hypokalaemia - rash

**PREGNANCY**

Not known to be harmful — manufacturer advises caution.

**BREAST FEEDING**

Present in milk following oral administration — manufacturer advises caution.

**WITH RECTAL USE**

Rectal administration not known to be harmful.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use in children For administration by mouth, solution may be mixed with milk or squash.
Liquid paraffin

**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Adult: 10–30 mL daily if required, to be administered at night

**CAUTIONS** Avoid prolonged use

**SIDE-EFFECTS** Anal irritation after prolonged use - anal seepage of paraffin after prolonged use - granulomatous reactions caused by absorption of small quantities of liquid paraffin (especially from the emulsion) - interference with the absorption of fat-soluble vitamins - lipoid pneumonia

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Liquid Paraffin Oral Emulsion, BP consists of liquid paraffin 5 mL, vanillin 5 mg, chloroform 0.025 mL, benzoic acid solution 0.2 mL, methylcellulose-20 200 mg, saccharin sodium 500 micrograms, water to 10 mL.

**PATIENT AND CARER ADVICE** Oral emulsion should not be taken immediately before going to bed.

**LESS SUITABLE FOR PRESCRIBING** Liquid Paraffin Oral Emulsion BP is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Liquid**
  - **Liquid paraffin (Non-proprietary)**
    - Liquid paraffin 1 ml per 1 ml Liquid paraffin liquid 150 ml £1.32–£1.45 | 500 ml £2.52

  Combinations available: **Liquid paraffin with magnesium hydroxide**, below

Liquid paraffin with magnesium hydroxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, liquid paraffin above, magnesium hydroxide p. 54.

**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Adult: 5–20 mL as required

**PRESCRIBING AND DISPENSING INFORMATION**

Liquid paraffin and magnesium hydroxide preparations are on sale to the public.

When prepared extemporaneously, the BP states Liquid Paraffin and Magnesium Hydroxide Oral Emulsion, BP consists of 25% liquid paraffin in aqueous suspension containing 6% hydrated magnesium oxide.

**LESS SUITABLE FOR PRESCRIBING** Liquid paraffin with magnesium hydroxide is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, suppository, enema

- **Gastro-resistant tablet**

- **Dulco-Lax (bisacodyl)** (Boehringer Ingelheim Self-Medication Division)

- **Bisacodyl 5 mg** Dulcolax 5 mg gastro-resistant tablets | 40 tablet £2.44 | 100 tablet £3.60

- **Enema**

  - **Bisacodyl (Non-proprietary)**
    - Bisacodyl 333.333 microgram per 1 mL Fleet Bisacodyl 10mg/30ml enema 1 enema £0.45 no price available

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**LAXATIVES > STIMULANT LAXATIVES**

**Bisacodyl**

**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Child 4–17 years: 5–20 mg once daily, adjusted according to response, dose to be taken at night
  - Adult: 5–10 mg once daily increased if necessary up to 20 mg once daily, dose to be taken at night

- **BY RECTUM**
  - Child 2–17 years: 5–10 mg once daily, adjusted according to response
  - Adult: 10 mg once daily, dose to be taken in the morning

**Bowel clearance before radiological procedures and surgery**

- **INITIALLY BY MOUTH**
  - Adult: 10 mg twice daily, does to be taken in the morning and evening on the day before procedure and (by rectum) 10 mg, to be administered 1–2 hours before the procedure the following day

**PHARMACOKINETICS**

Tablets act in 10–12 hours; suppositories act in 20–60 minutes.

**CONTRA-INDICATIONS** Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

**CAUTIONS** Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - risk of electrolyte imbalance with prolonged use (in children)

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

Abdominal cramp, colitis, nausea, vomiting

**SPECIFIC SIDE-EFFECTS**

- With rectal use Local irritation

**PREGNANCY** May be suitable for constipation in pregnancy, if a stimulant effect is necessary.
Co-danthramer

**INDICATIONS AND DOSE**

Constitution in terminally ill patients (standard strength capsules)

- **BY MOUTH USING CAPSULES**
  - Child 6–11 years: 1 capsule once daily, dose should be taken at night
  - Child 12–17 years: 1–2 capsules once daily, dose should be taken at night
  - Adult: 1–2 capsules once daily, dose should be taken at night

Constitution in terminally ill patients (strong capsules)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 6–11 years: 1 capsule once daily, dose should be taken at night
  - Child 12–17 years: 1–2 capsules once daily, dose should be taken at night
  - Adult: 1–2 capsules once daily, dose should be taken at night

Constitution in terminally ill patients (standard strength suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 2–11 years: 2.5–5 mL once daily, dose should be taken at night
  - Child 12–17 years: 5–10 mL once daily, dose should be taken at night
  - Adult: 5–10 mL once daily, dose should be taken at night

**DOSE EQUIVALENCE AND CONVERSION**

- Co-danthramer (standard strength) capsules contain dantron 25 mg with poloxamer ‘188’ 200 mg per capsule.
- Co-danthramer (standard strength) oral suspension contains dantron 25 mg with poloxamer ‘188’ 200 mg per 5 mL.
- Co-danthramer strong capsules contain dantron 37.5 mg with poloxamer ‘188’ 500 mg.
- Co-danthramer strong oral suspension contains dantron 75 mg with poloxamer ‘188’ 1 g per 5 mL.
- Co-danthramer suspension 5 mL = one co-danthramer capsule, but strong co-danthramer suspension 5 mL = two strong co-danthramer capsules.

**CONTRA-INDICATIONS**

Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

**CAUTIONS**

Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - may cause local irritation - rodent studies indicate potential carcinogenic risk

**CAUTIONS, FURTHER INFORMATION**

- Local irritation - Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies—risk of irritation and excoriation).
- **SIDE-EFFECTS** Abdominal cramp - urine may be coloured red
- **PREGNANCY** Manufacturers advise avoid—limited information available.
- **BREAST FEEDING** Manufacturers advise avoid—no information available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

- **Co-danthrusate (Non-proprietary)**
  - Dantron 5 mg per 1 ml, Poloxamer 188 40 mg per 1 ml Co-danthrusate 25mg/200mg/5ml oral suspension sugar free sugar-free | 300 ml Pod | £146.39 DT price = £146.39
  - Dantron 15 mg per 1 ml, Poloxamer 188 200 mg per 1 ml Co-danthrusate 75mg/1000mg/5ml oral suspension sugar free sugar-free | 300 ml Pod | £293.63 DT price = £293.63

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**Co-danthrusate**

**INDICATIONS AND DOSE**

Constitution in terminally ill patients

- **BY MOUTH USING CAPSULES**
  - Child 6–11 years: 1 capsule once daily, to be taken at night
  - Child 12–17 years: 1–3 capsules once daily, to be taken at night
  - Adult: 1–3 capsules once daily, to be taken at night

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 6–11 years: 5 mL once daily, to be taken at night
  - Child 12–17 years: 5–15 mL once daily, to be taken at night
  - Adult: 5–15 mL once daily, to be taken at night

**DOSE EQUIVALENCE AND CONVERSION**

- Co-danthrusate suspension contains dantron 50 mg and docusate 60 mg per 5 mL.
- Co-danthrusate capsules contain dantron 50 mg and docusate 60 mg per capsule.

**CONTRA-INDICATIONS**

Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

**CAUTIONS**

Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - may cause local irritation - rodent studies indicate potential carcinogenic risk

**CAUTIONS, FURTHER INFORMATION**

- Local irritation - Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies—risk of irritation and excoriation).
- **SIDE-EFFECTS** Abdominal cramp - urine may be coloured red
- **PREGNANCY** Manufacturers advise avoid—limited information available.
- **BREAST FEEDING** Manufacturers advise avoid—no information available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **Co-danthrusate (Non-proprietary)**
  - Dantron 50 mg, Docusate sodium 60 mg Co-danthrusate 50mg/60mg capsules | 63 capsule Pod | £55.20 DT price = £52.50

**Oral suspension**

- **Co-danthrusate (Non-proprietary)**
  - Dantron 10 mg per 1 ml, Docusate sodium 12 mg per 1 ml Co-danthrusate 50mg/60mg/5ml oral suspension sugar free sugar-free | 200 ml Pod | £89.92 DT price = £89.92
Glycerol
(Glycerin)

- **INDICATIONS AND DOSE**
  - **Constipation**
    - By Rectum
      - Child 1-11 months: 1 g as required
      - Child 1-11 years: 2 g as required
      - Child 12-17 years: 4 g as required
      - Adult: 4 g as required
  - **Prescribing and Dispensing Information**
    - When prepared extemporaneously, the BP consists of gelatin 140 mg, glycerol 700 mg, purified water to 1 g.
  - **Patient and Carer Advice**
    - Medicines for Children leaflet: Glycerol suppositories for constipation www.medicinesforchildren.org.uk/glycerin-suppositorys-for-constipation
  - **Medicinal Forms**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository
      - **Glycerol (Non-proprietary)**
        - Gelatin 140 mg per 1 gram, Glycerol 700 mg per 1 gram Glycerol 2g suppositories | 12 suppository GSL £1.73 DT price = £1.67
        - Glycerol 1g suppositories | 12 suppository GSL £1.69 DT price = £1.04
        - Glycerol 4g suppositories | 12 suppository GSL £1.39 DT price = £1.15
  - **DIRECTIONS FOR ADMINISTRATION**
    - Moisten suppositories with water before insertion.
  - **Pharmacokinetics**
    - Onset of action 8–12 hours.

Senna

- **Drug Action**
  - Senna is a stimulant laxative. After metabolism of sennosides in the gut the anthrone component stimulates peristalsis thereby increasing the motility of the large intestine.

- **Indications and Dose**
  - **Constipation**
    - By Mouth Using Tablets
      - Child 6–17 years: 7.5–30 mg once daily, adjusted according to response
      - Adult: 7.5–15 mg daily (max. per dose 30 mg daily), dose usually taken at bedtime; initial dose should be low then gradually increased, higher doses may be prescribed under medical supervision
        - By Mouth Using Syrup
          - Child 1 month–3 years: 3.75–15 mg once daily, adjusted according to response
          - Child 4–17 years: 3.75–30 mg once daily, adjusted according to response
          - Adult: 7.5–15 mg once daily (max. per dose 30 mg daily), dose usually taken at bedtime, higher doses may be prescribed under medical supervision
  - **Pharmacokinetics**
    - Onset of action 8–12 hours.

- **Unlicensed Use**
  - Tablets not licensed for use in children under 6 years. Syrup not licensed for use in children under 2 years.
  - Doses in BNF adhere to national guidelines and may differ from those in product literature.
- **Contra-Indications**
  - Intestinal obstruction · undiagnosed abdominal pain
- **Side-Effects**
  - Abdominal spasm · discoloration of urine · pruritus

Senna with ispaghula husk

- **Indications and Dose**
  - **Constipation**
    - By Mouth
      - Child 12–17 years: 5–10 g once daily, to be taken at night, 5 g equivalent to one level spoonful of granules
      - Adult: 5–10 g once daily, to be taken at night, 5 g equivalent to one level spoonful of granules
  - **Side-Effects**
    - Urine coloured yellow or red-brown
  - **Pregnancy**
    - Manufacturer advises avoid during first trimester. To be used only intermittently and only if dietary and lifestyle changes fail.
  - **Directions for Administration**
    - Take at night with at least 150 mL liquid.
  - **Medicinal Forms**
    - There can be variation in the licensing of different medicines containing the same drug.
      - **Granules**
        - **CAUTIONARY AND ADVISORY LABELS**
          - **25**
        - **Excipients:** May contain Sucrose
          - **Manevac** (Meda Pharmaceuticals Ltd)
            - Senna fruit 124 mg per 1 gram, Ispaghula 542 mg per 1 gram Manevac granules | 400 gram | £9.50 DT price = £9.50

- **Side-Effects, Further Information**
  - Prolonged or excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia.
- **Pregnancy**
  - Specialist sources indicate suitable for use in pregnancy.
- **Breast Feeding**
  - Specialist sources indicate suitable for use in breast-feeding in infants over 1 month.
- **Patient and Carer Advice**
  - Medicines for Children leaflet: Senna for constipation www.medicinesforchildren.org.uk/senna-for-constipation
- **National Funding/Access Decisions**
  - NHS restrictions Senokot® tablets.
- **Exceptions to Legal Category**
  - Senna is on sale to the public for use in children over 12 years; doses on packs may vary from those in BNF Publications.
**Sodium picosulfate**

(Sodium picosulphate)

**DRUG ACTION** Sodium picosulfate is a stimulant laxative. After metabolism in the colon it stimulates the mucosa thereby increasing the motility of the large intestine.

**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Child 1 month—3 years: 2.5–10 mg once daily, adjusted according to response
  - Child 4–17 years: 2.5–20 mg once daily, adjusted according to response
  - Adult: 5–10 mg once daily, dose to be taken at bedtime

**PHARMACOKINETICS**

Onset of action 6–12 hours.

**UNLICENSED USE** Sodium picosulfate doses in BNF

Publications adhere to national guidelines and may differ from those in product literature.

**CONTRA-INDICATIONS** Intestinal obstruction - undiagnosed abdominal pain

**SIDE-EFFECTS**

- Common or very common Abdominal cramp
- Uncommon Dizziness - nausea - vomiting
- Frequency not known Angioedema - pruritus - rash - syncope

**SIDE-EFFECTS, FURTHER INFORMATION**

Prolonged or excessive use can cause diarrhoea and related effects such as hypokalaemia.

**PREGNANCY**

Manufacturer states evidence limited but not known to be harmful.

**BREAST FEEDING**

(Specialist sources indicate suitable for use in breast-feeding in infants over 1 month—not known to be present in milk. [6])

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Sodium picosulfate for constipation www.medicinesforchildren.org.uk/sodium-picosulfate-for-constipation

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

EXCIPIENTS: May contain Alcohol

- **Sodium picosulfate (Non-proprietary)**
  - Sodium picosulfate 1 mg per 1 ml Sodium picosulfate 5mg/5ml oral solution sugar free sugar-free 100 ml £2.37 sugar-free | 300 ml £7.10 DT price = £7.10
  - **Dulco-Lax (sodium picosulfate)** (Boehringer Ingelheim Self-Medication Division)
  - Sodium picosulfate 1 mg per 1 ml Dulcolax Pico 5mg/5ml liquid sugar-free 100 ml £1.94 sugar-free | 300 ml £4.62 DT price = £7.10

**OPSIOD RECEPTOR ANTAGONISTS**

**Methylnaltrexone bromide**

**DRUG ACTION** Methylnaltrexone bromide is a peripherally acting opioid-receptor antagonist. It therefore blocks the gastro-intestinal (constipating) effects of opioids without altering their central analgesic effects.

**INDICATIONS AND DOSE**

**Opioid-induced constipation in patients with chronic pain (except palliative care patients with advanced illness)**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 12 mg once daily if required, to be given as 4–7 doses weekly

**Adjunct to other laxatives in opioid-induced constipation in advanced illness (palliative care patients)**

- **BY SUBCUTANEOUS INJECTION**
  - Adult (body-weight up to 38 kg): 150 micrograms/kg once daily on alternate days for maximum duration of treatment 4 months, two consecutive doses may be given 24 hours apart if no response to treatment on the preceding day
  - Adult (body-weight 38–61 kg): 8 mg once daily on alternate days for maximum duration of treatment 4 months, two consecutive doses may be given 24 hours apart if no response to treatment on the preceding day
  - Adult (body-weight 62–114 kg): 12 mg once daily on alternate days for maximum duration of treatment 4 months, two consecutive doses may be given 24 hours apart if no response to treatment on the preceding day
  - Adult (body-weight 115 kg and above): 150 micrograms/kg once daily on alternate days for maximum duration of treatment 4 months, two consecutive doses may be given 24 hours apart if no response to treatment on the preceding day

**PHARMACOKINETICS**

May act within 30–60 minutes.

**CONTRA-INDICATIONS** Acute surgical abdominal conditions - gastro-intestinal obstruction

**CAUTIONS** 

Diverticular disease (when active) - faecal impaction - gastro-intestinal tract lesions (known or suspected) - patients with colostomy - patients with peritoneal catheter

**SIDE-EFFECTS**

- Common or very common Abdominal pain - diarrhoea - dizziness - flatulence - injection site reactions - nausea - opioid withdrawal symptoms (usually mild to moderate) - vomiting
- Frequency not known Gastro-intestinal perforation

**Overdose**

Symptoms of overdosage include orthostatic hypotension.

**PREGNANCY**

Manufacturer advises avoid unless essential—toxicity at high doses in animal studies.

**BREAST FEEDING**

Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in severe impairment—no information available.

**RENAL IMPAIRMENT**

If eGFR less than 30 ml/minute/1.73 m², reduce dose as follows: body-weight under 62 kg, 75 micrograms/kg on alternate days; body-weight 62–114 kg, 8 mg on alternate days; body-weight over 114 kg, 75 micrograms/kg on alternate days.

**DIRECTIONS FOR ADMINISTRATION**

Rotate injection site.

**PRESCRIBING AND DISPENSING INFORMATION**

Palliative care

For further information on the use of methylnaltrexone in palliative care, see www.palliativedrugs.com/formulary/en/opioid-antagonists.html.

**HANDLING AND STORAGE**

Protect from light.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Relistor** (Swedish Orphan Biovitrum Ltd)
  - Methylnaltrexone bromide 20 mg per 1 ml
  - Solution for injection vials | 1 vial POM £21.05 | 7 vial POM £147.35
Naloxegol 20-Jun-2016

- **DRUG ACTION** Naloxegol is a peripherally acting opioid receptor antagonist. It therefore decreases the constipating effects of opioids without altering their central analgesic effects.

- **INDICATIONS AND DOSE**
  - **Opioid-induced constipation when response to laxatives inadequate**
    - **BY MOUTH**
    - Adult: 25 mg once daily, to be taken in the morning
  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
    - Use a lower starting dose of 12.5 mg once daily in patients taking concomitant moderate inhibitors of CYP3A4 (such as diltiazem and verapamil), increasing to 25 mg if well tolerated.

- **CONTRA-INDICATIONS** Gastro-intestinal or peritoneum malignancy (risk of gastro-intestinal perforation) - known or suspected — gastro-intestinal obstruction - patients at risk of recurrent gastro-intestinal obstruction - recurrent or advanced ovarian cancer (risk of gastro-intestinal perforation) - vascular endothelial growth factor (VEGF) inhibitor treatment (risk of gastro-intestinal perforation)

- **CAUTIONS**
  - Alzheimer’s disease (advanced) - cardiovascular disease - CNS metastases - congestive heart failure (symptomatic) - Crohn’s disease - diverticulitis (active or recurrent) - multiple sclerosis (active) - peptic ulcer disease (severe) - primary brain malignancies - QT interval over 500 milliseconds - recent history of myocardial infarction (within 6 months)

- **CAUTIONS, FURTHER INFORMATION**
  - Disruptions to blood-brain barrier: Manufacturer advises caution in patients with clinically important disruptions to the blood-brain barrier (e.g. advanced Alzheimer’s disease, active multiple sclerosis, primary brain malignancies) — risk of uptake into the CNS.
  - Cardiovascular disorders: Safety and efficacy has not been established in patients with these conditions.

- **INTERACTIONS** → Appendix 1 (naloxegol).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain (discontinue treatment if severe or persistent) - flatulence - headache - nausea - sweating - vomiting
  - **Uncommon** Opioid withdrawal syndrome (discontinue treatment)

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Gastro-intestinal effects: Manufacturer advises that gastro-intestinal side-effects typically occur shortly after initiation of treatment — consider reducing the dose.

- **PREGNANCY**
  - Manufacturer advises avoid — limited data available but toxicity at high doses in animal studies; theoretical risk of opioid withdrawal in foetuses.

- **BREAST FEEDING**
  - Manufacturer advises avoid — present in milk in animal studies and theoretical risk of opioid withdrawal in breast-fed infants.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in severe impairment — safety and efficacy not established.

- **RENAL IMPAIRMENT**
  - Manufacturer advises lower initial dose in moderate to severe impairment — initially 12.5 mg daily, increase to 25 mg if well tolerated.

- **DIRECTIONS FOR ADMINISTRATION**
  - Manufacturer advises tablets can be crushed, mixed with 120 mL of water and taken immediately if patients are unable to swallow tablets whole. The mixture may be administered via a nasogastric tube, if required.

- **PATIENT AND CARER ADVICE**
  - Manufacturer advises patients report severe, persistent or worsening gastro-intestinal effects (such as abdominal pain) to their prescriber.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Naloxegol for treating opioid-induced constipation (July 2015) NICE TA345
    - Naloxegol is recommended as a possible treatment for opioid induced constipation in patients whose response to laxatives is inadequate.
    - www.nice.org.uk/TA345

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 23
    - Moventig (Kyowa Kirin Ltd) ▼
    - Naloxegol (as Naloxegol oxalate) 12.5 mg ▼
      - 30 tablet (PoM) £55.20 DT price = £55.20
    - Naloxegol (as Naloxegol oxalate) 25 mg ▼
      - 30 tablet (PoM) £55.20 DT price = £55.20

3 Diarrhoea

**Acute diarrhoea**

Management of acute diarrhoea

The priority in acute diarrhoea, as in gastro-enteritis, is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in infants and in frail and elderly patients. **Oral rehydration preparations** are used in the prevention or reversal of fluid and electrolyte depletion. Severe depletion of fluid and electrolytes requires immediate admission to hospital and urgent replacement.

**Antimotility drugs**

Antimotility drugs relieve symptoms of acute diarrhoea by binding to opioid receptors in the gastrointestinal tract and thereby prolonging the duration of intestinal transit. They are used in the management of uncomplicated acute diarrhoea in adults, however, are not recommended for acute diarrhoea in young children; fluid and electrolyte replacement are of primary importance in severe cases of acute diarrhoea and may also be necessary in cases of dehydration.

Loperamide hydrochloride p. 63 is used due to its action on opioid receptors in the gastrointestinal tract and because it does not readily cross the blood-brain barrier. Loperamide hydrochloride can also be used for faecal incontinence [unlicensed indication] after the underlying cause of incontinence has been addressed.

Antimotility drugs have a role in Inflammatory bowel disease p. 35 and in Stoma care p. 91.

Antispasmodics

Antispasmodics are occasionally of value in treating abdominal cramp associated with diarrhoea but they should not be used for primary treatment. Antispasmodics and antiemetics should be avoided in young children with gastro-enteritis because they are rarely effective and have troublesome side-effects.

**Antibacterial drugs**

Antibacterial drugs are generally unnecessary in simple gastro-enteritis because the complaint usually resolves quickly without them, and infective diarrhoeas in the UK often have a viral cause. Systemic bacterial infection does, however, need appropriate systemic treatment. Ciprofloxacin p. 514 is occasionally used for prophylaxis against travellers’ diarrhoea, but routine use is not recommended. Lactobacillus preparations have not been shown to be effective.
Adsorbents and bulk-forming drugs
Adsorbents such as kaolin p. 64 are not recommended for acute diarrhoeas. Bulk-forming drugs, such as ispaghula husk p. 50, methylcellulose p. 50, and sterculia p. 51 are useful in controlling diarrhoea associated with diverticular disease. Coleestyramine p. 186 binds unabsorbed bile salts and provides symptomatic relief of diarrhoea following ileal disease or resection.

Enkephalinase inhibitors
Racacodotril p. 64 is a pro-drug of thiorphan. Thiorphan is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thereby reducing intestinal secretions. Racacodotril is licensed, as an adjunct to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea; it should only be used in children over 3 months of age when usual supportive measures, including oral rehydration, are insufficient to control the condition. Racacodotril does not affect the duration of intestinal transit.

Other drugs used for Diarrhoea Codeine phosphate, p. 421

ANTIDIARRHOEALS ➔ ANTIPROPULSIVES

Co-phenotrope

● INDICATIONS AND DOSE
  Adjunct to rehydration in acute diarrhoea
  ▶ BY MOUTH
  → Child 4-8 years: 1 tablet 3 times a day
  → Child 9-11 years: 1 tablet 4 times a day
  → Child 12-15 years: 2 tablets 3 times a day
  → Child 16-17 years: Initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled
  → Adult: Initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled

Control of faecal consistency after colostomy or ileostomy
  ▶ BY MOUTH
  → Child 4-8 years: 1 tablet 3 times a day
  → Child 9-11 years: 1 tablet 4 times a day
  → Child 12-15 years: 2 tablets 3 times a day
  → Child 16-17 years: Initially 4 tablets, then 2 tablets 4 times a day
  → Adult: Initially 4 tablets, then 2 tablets 4 times a day

● UNLICENSED USE Not licensed for use in children under 4 years.

● CONTRA-INDICATIONS Gastro-intestinal obstruction • intestinal atony • myasthenia gravis (but some antimuscarinics may be used to decrease muscarinic side-effects of anticholinesterases) • paralytic ileus • prostatic enlargement (in adults) • pyloric stenosis • severe ulcerative colitis • significant bladder outflow obstruction • toxic megacolon • urinary retention

● CAUTIONS Presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals or in overdosage • young children are particularly susceptible to overdosage; symptoms may be delayed and observation is needed for at least 48 hours after ingestion

● INTERACTIONS ➔ Appendix 1 (antimuscarinics, opioid analgesics).

● SIDE-EFFECTS ➔ Very rare Angle-closure glaucoma
  ➔ Frequency not known Abdominal pain • anorexia • confusion (particularly in the elderly) • constipation • dilution of the pupils with loss of accomodation • dry mouth • dryness of the skin • fever • flushing • giddiness • nausea • photophobia • reduced bronchial secretions • transient bradycardia (followed by tachycardia, palpitation and arrhythmias) • urinary retention • urinary urgency • vomiting

● PREGNANCY Manufacturer advises caution.

● BREAST FEEDING May be present in milk.

● HEPATIC IMPAIRMENT Avoid in jaundice.

● DIRECTIONS FOR ADMINISTRATION For administration by mouth tablets may be crushed.

● PRESCRIBING AND DISPENSING INFORMATION A mixture of diphenoxylate hydrochloride and atropine sulfate in the mass proportions 100 parts to 1 part respectively.

● EXCEPTIONS TO LEGAL CATEGORY Co-phenotrope 2.5/0.025 can be sold to the public for adults and children over 16 years (provided packs do not contain more than 20 tablets) as an adjunct to rehydration in acute diarrhoea (max. daily dose 10 tablets).

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
  ➔ Co-phenotrope (Non-proprietor) Atropine sulfate 25 microgram, Diphenoxylate hydrochloride 2.5 mg Lomotil 2.5mg/25microgram tablets | 100 tablet (PDT) no price available (CDS)

Kaolin with morphine

● INDICATIONS AND DOSE
  Acute diarrhoea
  ▶ BY MOUTH
  → Adult: 10 mL every 6 hours, dose to be given in water

● CONTRA-INDICATIONS Acute abdomen • delayed gastric emptying • heart failure secondary to chronic lung disease • phaeochromocytoma

● CAUTIONS Cardiac arrhythmias • pancreatitis • severe cor pulmonale

● SIDE-EFFECTS Abdominal pain • agitation • anorexia • anoxia • asthenia • bronchospasm • delirium • disorientation • dyspepsia • exacerabation of pancreatitis • excitation • hypertension • hypothermia • inhibition of cough reflex • malaise • muscle fasciculation • myoclonus • nyctagmus • paraesthesia • paralytic ileus • raised intracranial pressure • restlessless • rhabdomyolysis • seizures • syncope • taste disturbance

● BREAST FEEDING Therapeutic doses unlikely to affect infant.

● RENAL IMPAIRMENT Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

● PRESCRIBING AND DISPENSING INFORMATION When prepared extemporaneously, the BP states Kaolin and Morphine Mixture, BP consists of light kaolin or light kaolin (natural) 20%, sodium bicarbonate 5%, and chloroform and morphine tincture 4% in a suitable vehicle. Contains anhydrous morphine 550—800 micrograms/10 mL.

● LESS SUITABLE FOR PRESCRIBING Kaolin and Morphine Mixture, BP (Kaolin and Morphine Oral Suspension) is less suitable for prescribing.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral suspension
  ➔ Kaolin with morphine (Non-proprietor) Chloroform 5 ml per 1 litre, Kaolin light 200 mg per 1 ml, Morphine hydrochloride 91.6 microgram per 1 ml, Sodium bicarbonate 50 mg per 1 ml Kaolin and Morphine mixture | 200 ml £1.50 DT price = £1.50 (CDS)
Loperamide hydrochloride

**INDICATIONS AND DOSE**

**Symptomatic treatment of acute diarrhoea**
- BY MOUTH
  - Child 4–7 years: 1 mg 3–4 times a day for up to 3 days only
  - Child 8–11 years: 2 mg 3–4 times a day for up to 5 days
  - Child 12–17 years: Initially 4 mg, followed by 2 mg for up to 5 days, dose to be taken after each loose stool; usual dose 6–8 mg daily; maximum 16 mg per day
  - Adult: Initially 4 mg, followed by 2 mg for up to 5 days, dose to be taken after each loose stool; usual dose 6–8 mg daily; maximum 16 mg per day

**Chronic diarrhoea**
- BY MOUTH
- Adult: Initially 4–8 mg daily in divided doses, adjusted according to response; maintenance up to 16 mg daily in 2 divided doses

**Faecal incontinence**
- BY MOUTH
- Adult: Initially 500 micrograms daily, adjusted according to response, maximum daily dose to be given in divided doses; maximum 16 mg per day

**Pain of bowel colic in palliative care**
- BY MOUTH
- Adult: 2–4 mg 4 times a day

- **CONTRA-INDICATIONS** Active ulcerative colitis - antibiotic-associated colitis - conditions where abdominal distension develops - conditions where inhibition of peristalsis should be avoided
- **CAUTIONS** Not recommended for children under 12 years
- **INTERACTIONS** → Appendix 1 (loperamide).
- **SIDE-EFFECTS**
  - Common or very common Dizziness, flatulence, headache, nausea
  - Uncommon Abdominal pain, drowsiness, dry mouth, dyspepsia, rash, vomiting
  - Rare Fatigue, hypotonia, paralytic ileus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urinary retention
- **PREGNANCY** Manufacturers advise avoid—no information available.
- **BREAST FEEDING** Amount probably too small to be harmful.
- **HEPATIC IMPAIRMENT** Risk of accumulation—manufacturer advises caution.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - **Palliative care** For further information on the use of loperamide in palliative care, see www.palliativedrugs.com/formulary/en/loperamide.html.
  - **PATIENT AND CARER ADVICE**
    - Medicines for Children leaflet: Loperamide for diarrhoea www.medicinesforchildren.org.uk/loperamide-for-diarrhoea
  - **EXCEPTIONS TO LEGAL CATEGORY** Loperamide can be sold to the public, for use in adults and children over 12 years, provided it is licensed and labelled for the treatment of acute diarrhoea.
  - In adults Loperamide can be sold to the public, provided it is licensed and labelled for the treatment of acute diarrhoea associated with irritable bowel syndrome (after initial diagnosis by a doctor) in adults over 18 years of age.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Tablet**
  - Loperamide hydrochloride (Non-proprietary)
    - Loperamide hydrochloride 2 mg Loperamide 2 mg tablets | 30 tablet [POM] £2.15 DT price = £2.15
    - Norimode (Tillomed Laboratories Ltd)
      - Loperamide hydrochloride 2 mg Norimode 2 mg tablets | 30 tablet [POM] £2.15 DT price = £2.15
    - Normaloe (Tillomed Laboratories Ltd)
      - Loperamide hydrochloride 2 mg Normaloe 2 mg tablets | 12 tablet [P] £1.70
  - **Orodispersible tablet**
    - Imodium (McNeil Products Ltd)
      - Loperamide hydrochloride 2 mg Imodium Instant Melts 2 mg orodispersible tablets sugar-free | 12 tablet [P] £3.75 sugar-free | 18 tablet [P] £5.02 DT price = £5.02
  - **Capsule**
    - Loperamide hydrochloride (Non-proprietary)
      - Loperamide hydrochloride 2 mg Loperamide 2 mg capsules | 6 capsule [GEL] no price available | 12 capsule [P] £1.94 | 30 capsule [POM] £2.99 DT price = £1.01
    - Imodium (McNeil Products Ltd)
      - Loperamide hydrochloride 2 mg Imodium 2 mg Soft capsules | 12 capsule [P] £3.79
      - Imodium IBS Relief 2 mg capsules | 12 capsule [P] £3.79
  - **Oral solution**
    - Imodium (Janssen-Cilag Ltd)
      - Loperamide hydrochloride 200 microgram per 1 ml Imodium 1 mg/5ml oral solution sugar-free | 100 ml [POM] £1.17 DT price = £1.17

Loperamide with simeticone

The properties listed below are those particular to the combination only. For the properties of the components please consider, loperamide hydrochloride above, simeticone p. 68.

**INDICATIONS AND DOSE**

**Acute diarrhoea with abdominal colic**
- BY MOUTH
  - Child 12–17 years: Initially 1 tablet, then 1 tablet, after each loose stool, for up to 2 days; maximum 4 tablets per day
  - Adult: Initially 2 tablets, then 1 tablet, after each loose stool, for up to 2 days; maximum 4 tablets per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Imodium Plus (McNeil Products Ltd)
    - Loperamide hydrochloride 2 mg, Dimeticone (as Simeticone) 125 mg Imodium Plus caplets | 12 tablet [P] £3.66
**4 Disorders of gastric acid and ulceration**

### 4.1 Dyspepsia

**Overview**
Dyspepsia covers upper abdominal pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration and, gastric cancer, but most commonly it is of uncertain origin.

Urgent endoscopic investigation is required if dyspepsia is accompanied by ‘alarm features’ (e.g. bleeding, dysphagia, recurrent vomiting, or weight loss). Urgent investigation should also be considered for patients over 55 years with unexplained, recent-onset dyspepsia that has not responded to treatment.

Patients with dyspepsia should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, smoking cessation, and raising the head of the bed. Some medications may cause dyspepsia—these should be stopped, if possible.

Antacids may provide some symptomatic relief, however if symptoms persist in uninvestigated dyspepsia, treatment involves a proton pump inhibitor for up to 4 weeks. A proton pump inhibitor can be used intermittently to control symptoms long term. Patients with uninvestigated dyspepsia, who do not respond to an initial trial with a proton pump inhibitor, should be tested for Helicobacter pylori and given eradication therapy if *H. pylori* is present. Alternatively, particularly in populations where *H. pylori* infection is more likely, the ‘test and treat’ strategy for *H. pylori* can be used before a trial with a proton pump inhibitor.

If *H. pylori* is present in patients with functional (investigated, non-ulcer) dyspepsia, eradication therapy should be provided. If symptoms persist, treatment with either a proton pump inhibitor or a histamine *H₂*-receptor antagonist can be given for 4 weeks. These antisecretory drugs can be used intermittently to control symptoms long term. However, most patients with functional dyspepsia do not benefit symptomatically from *H. pylori* eradication therapy or antisecretory drugs.
ANTACIDS

Overview

Antacids (usually containing aluminium or magnesium compounds) can often relieve symptoms in ulcer dyspepsia and in non-erosive gastro-oesophageal reflux; they are also sometimes used in functional (non-ulcer) dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, although additional doses may be required. Conventional doses of liquid magnesium–aluminium antacids promote ulcer healing, but less well than antisecretory drugs; proof of a relationship between healing and neutralising capacity is lacking. Liquid preparations are more effective than tablet preparations.

Aluminium- and magnesium-containing antacids (e.g. aluminium hydroxide p. 925, magnesium carbonate p. 67, co-magaldrox p. 66 and magnesium trisilicate p. 67), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable for most antacid purposes. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium accumulation does not appear to be a risk if renal function is normal.

The acid-neutralising capacity of preparations that contain more than one antacid may be the same as simpler preparations. Complexes such as hydrotalcite confer no special advantage.

Sodium bicarbonate p. 910 should no longer be prescribed alone for the relief of dyspepsia but it is present as an ingredient in many indigestion remedies. However, it retains a place in the management of urinary-tract disorders and acidosis.

Bismuth-containing antacids (unless chelates) are not recommended because absorbed bismuth can be neurotoxic, causing encephalopathy; they tend to be constipating.

Calcium-containing antacids can induce rebound acid secretion: with modest doses the clinical significance is doubtful, but prolonged high doses also cause hypercalcemia and alkalosis, and can precipitate the milk-alkali syndrome.

Simeticone

Simeticone (activated dimeticone) p. 68 is added to an antacid as an antifoaming agent to relieve flatulence. These preparations may be useful for the relief of hiccup in palliative care.

Alginates

Alginates taken in combination with an antacid increase the viscosity of stomach contents and can protect the oesophageal mucosa from acid reflux. Some alginate-containing preparations form a viscous gel (‘raft’) that floats on the surface of the stomach contents, thereby reducing symptoms of reflux.

The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.

ANTACIDS > ALGINATE

Alginic acid

- INDICATIONS AND DOSE
  - GAVISCON INFANT® POWDER SACHETS
    - Management of gastro-oesophageal reflux disease
      - BY MOUTH
        - Child 1–23 months (body-weight up to 4.5 kg): 1 dose as required, to be mixed with feeds (or water, for breast-fed infants); maximum 6 doses per day
        - Child 1–23 months (body-weight 4.5 kg and above): 2 doses as required, to be mixed with feeds (or water, for breast-fed infants); maximum 12 doses per day
  - CONTRA-INDICATIONS
    - Intestinal obstruction - preterm neonates - where excessive water loss likely (e.g. fever, diarrhoea, vomiting, high room temperature)
  - INTERACTIONS
    - Appendix 1 (antacids).
    - Not to be used with other preparations containing thickening agents.
    - Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.
    - Antacids may damage enteric coatings designed to prevent dissolution in the stomach.
  - HEPATIC IMPAIRMENT
    - In patients with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.
  - RENAL IMPAIRMENT
    - In patients with fluid retention, avoid antacids containing large amounts of sodium.
  - PRESCRIBING AND DISPENSING INFORMATION
    - Each half of the dual-sachet is identified as ‘one dose’.
    - To avoid errors prescribe with directions in terms of ‘dose’.
  - MEDICINAL FORMS
    - There can be variation in the licensing of different medicines containing the same drug.
      - Powder
        - ELECTROLYTES: May contain Sodium
          - Gaviscon Infant (Forum Health Products Ltd)
            - Magnesium alginate 87.5 mg, Sodium alginate 225 mg Gaviscon Infant oral powder sachets sugar-free | 15 dual dose sachet £1.82

Sodium alginate with potassium bicarbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, alginic acid above.

- INDICATIONS AND DOSE
  - Management of mild symptoms of dyspepsia and gastro-oesophageal reflux disease
    - BY MOUTH USING CHEWABLE TABLETS
      - Child 6-11 years (under medical advice only): 1 tablet, to be chewed after meals and at bedtime
      - Child 12-17 years: 1–2 tablets, to be chewed after meals and at bedtime
      - Adult: 1–2 tablets, to be chewed after meals and at bedtime
    - BY MOUTH USING ORAL SUSPENSION
      - Child 2–11 years (under medical advice only): 2.5–5 mL, to be taken after meals and at bedtime
      - Child 12–17 years: 5–10 mL, to be taken after meals and at bedtime
      - Adult: 5–10 mL, to be taken after meals and at bedtime
Gastro-intestinal system

1 PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include aniseed or peppermint.

1 MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Chewable tablet
EXCIPIENTS: May contain Aspartame ELECTROLYTES: May contain Potassium, sodium
- Sodium alginate with potassium bicarbonate (Non-proprietary) Potassium bicarbonate 100 mg, Sodium alginate 500 mg. Sodium alginate 500mg / Potassium bicarbonate 100mg chewable tablets sugar free sugar-free | 60 tablet GSL no price available DT price = £3.07
- Brands may include Gaviscon Advance

Oral suspension
EXCIPIENTS: May contain Aspartame ELECTROLYTES: May contain Potassium, sodium
- Gaviscon Advance (Reckitt Benckiser Healthcare (UK) Ltd) Potassium bicarbonate 20 mg per 1 ml, Sodium alginate 100 mg per 1 ml Gaviscon Advance oral suspension anised sugar-free | 150 ml (P) £3.23 sugar-free | 300 ml (P) £5.82
- Gaviscon Advance oral suspension peppermint sugar-free | 300 ml (P) £5.82

ANTACIDS > ALUMINIUM AND MAGNESIUM

Co-magaldrox
The properties listed below are those particular to the combination only. For the properties of the components please consider, aluminium hydroxide p. 925, magnesium hydroxide p. 54.

1 INDICATIONS AND DOSE

MAALOX®
Dyspepsia
- BY MOUTH
  - Child 12–17 years: 10–20 mL, to be taken 20–60 minutes after meals, and at bedtime when required
  - Adult: 10–20 mL, to be taken 20–60 minutes after meals, and at bedtime when required

MUCOGEL®
Dyspepsia
- BY MOUTH
  - Child 12–17 years: 10–20 mL 3 times a day, to be taken 20–60 minutes after meals, and at bedtime, or when required
  - Adult: 10–20 mL 3 times a day, to be taken 20–60 minutes after meals, and at bedtime, or when required

1 PRESCRIBING AND DISPENSING INFORMATION Co-magaldrox is a mixture of aluminium hydroxide and magnesium hydroxide; the proportions are expressed in the form x/y where x and y are the strengths in milligrams per unit dose of magnesium hydroxide and aluminium hydroxide respectively.

MUCOGEL® Mucogel® suspension is low in sodium.
MAALOX® Maalox® suspension is low in sodium.

1 MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral suspension
- Maalox (Sanofi)
  - Magnesium hydroxide 39 mg per 1 ml, Aluminium hydroxide gel dried 44 mg per 1 ml Maalox oral suspension sugar-free | 500 ml (GSL) £3.35 DT price = £2.99
- Mucogel (Chemidex Pharma Ltd)
  - Magnesium hydroxide 39 mg per 1 ml, Aluminium hydroxide gel dried 44 mg per 1 ml Mucogel oral suspension sugar-free | 500 ml (GSL) £2.99 DT price = £2.99

Co-simalcite

1 INDICATIONS AND DOSE
Dyspepsia
- BY MOUTH
  - Child 8–11 years: 5 mL 4 times a day as required, to be taken between meals and at bedtime
  - Child 12–17 years: 10 mL 4 times a day as required, to be taken between meals and at bedtime
  - Adult: 10 mL 4 times a day as required, to be taken between meals and at bedtime

1 CONTRA-INDICATIONS Hypophosphataemia · infants · neonates

CONTRA-INDICATIONS, FURTHER INFORMATION
- Aluminium-containing antacids Aluminium-containing antacids should not be used in neonates and infants because accumulation may lead to increased plasma-aluminium concentrations.

INTERACTIONS ➔ Appendix 1 (antacids). Antacids should preferably not be taken at the same time as other drugs since they may impair absorption. Antacids may damage enteric coatings designed to prevent dissolution in the stomach.

1 SIDE-EFFECTS
SIDE-EFFECTS, FURTHER INFORMATION
- Constipation and diarrhoea Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects.

HEPATIC IMPAIRMENT Avoid; can cause constipation which can precipitate coma. Avoid in hepatic coma; risk of renal failure.

RENSAL IMPAIRMENT Antacids containing magnesium salts should be avoided or used at a reduced dose because there is an increased risk of toxicity.
- In adults There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics).
- In children Aluminium-containing antacids should not be used in children with renal impairment, because accumulation may lead to increased plasma-aluminium concentrations.

1 PRESCRIBING AND DISPENSING INFORMATION Altacite Plus® is low in Na⁺.

1 MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral suspension
- Altacite Plus (Peckforton Pharmaceuticals Ltd)
  - Simeticone 25 mg per 1 ml, Hydrotalcite 100 mg per 1 ml Altacite Plus oral suspension sugar-free | 100 ml (P) £4.00 sugar-free | 500 ml (P) £5.20 DT price = £5.20
Simeticone with aluminium hydroxide and magnesium hydroxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, simeticone p. 68, aluminium hydroxide p. 925.

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **BY MOUTH**
      - Child 12-17 years: 5–10 mL 4 times a day, to be taken after meals and at bedtime, or when required
      - Adult: 5–10 mL 4 times a day, to be taken after meals and at bedtime, or when required

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Oral suspension**
  - Simeticone 5 mg per 1 ml, Magnesium hydroxide 39 mg per 1 ml, Aluminium hydroxide gel dried 44 mg per 1 ml
  - Maalox Plus oral suspension sugar-free | 500 ml | £3.90

**ANTACIDS > MAGNESIUM**

Magnesium carbonate

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **BY MOUTH USING ORAL SUSPENSION**
    - Adult: 10 mL 3 times a day, dose to be taken in water

- **CONTRA-INDICATIONS**
  - **Hypophosphataemia**

- **INTERACTIONS**
  - **Appendix 1 (antacids).**
    - Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.
    - Antacids may damage enteric coatings designed to prevent dissolution in the stomach.

- **SIDE-EFFECTS**
  - Belching due to liberated carbon dioxide

- **HEPATIC IMPAIRMENT**
  - In patients with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.

- **RENAI IMPAIRMENT**
  - Avoid or use at a reduced dose; increased risk of toxicity. Magnesium carbonate mixture has a high sodium content; avoid in patients with fluid retention.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Aromatic Magnesium Carbonate Mixture, BP consists of light magnesium carbonate 3%, sodium bicarbonate 5%, in a suitable vehicle containing aromatic cardamom tincture.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.
  No licensed medicines identified.

Magnesium trisilicate

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **BY MOUTH USING CHEWABLE TABLETS**
    - Adult: 1–2 tablets as required

- **CONTRA-INDICATIONS**
  - **Hypophosphataemia**

- **INTERACTIONS**
  - **Appendix 1 (antacids).**
    - Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.
    - Antacids may damage enteric coatings designed to prevent dissolution in the stomach.

- **SIDE-EFFECTS**
  - Belching due to liberated carbon dioxide

- **HEPATIC IMPAIRMENT**
  - In patients with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.

- **RENAI IMPAIRMENT**
  - Magnesium trisilicate and magnesium carbonate mixtures have high sodium content; avoid in patients with fluid retention.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Magnesium Trisilicate Mixture, BP consists of 5% each of magnesium trisilicate, light magnesium carbonate, and sodium bicarbonate in a suitable vehicle with a peppermint flavour.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

- Magnesium trisilicate with magnesium carbonate and sodium bicarbonate (Non-proprietary)
  - Magnesium carbonate light 50 mg per 1 ml, Magnesium trisilicate 50 mg per 1 ml | 200 ml | £1.50 DT price = £1.50
ANTIFOAMING DRUGS

Simeticone

(Activated dimeticone)

- **DRUG ACTION** Simeticone (activated dimeticone) is an antifoaming agent.

- **INDICATIONS AND DOSE**

  - **DENTINOX®**
    - **Colic | Wind pains**
      - **BY MOUTH**
      - Child 1 month-1 year: 2.5 mL, to be taken with or after each feed; may be added to bottle feed; maximum 6 doses per day
    - **INFACOL®**
      - **Colic | Wind pains**
        - **BY MOUTH**
        - Child 1 month-1 year: 0.5–1 mL, to be taken before feeds

- **PRESCRIBING AND DISPENSING INFORMATION**
  - **DENTINOX®** The brand name Dentinox® is also used for other preparations including teething gel.

- **PATIENT AND CARER ADVICE**
  - **INFACOL®** Patients or carers should be given advice on use of the Infacol® dropper.
  - **LESS SUITABLE FOR PRESCRIBING**
    - **INFACOL®** Infacol® is less suitable for prescribing (evidence of benefit in infantile colic uncertain).
    - **DENTINOX®** Dentinox® colic drops are less suitable for prescribing (evidence of benefit in infantile colic uncertain).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Oral suspension**
    - **Infacol®** (Forest Laboratories UK Ltd)
      - Simeticone 40 mg per 1 ml Infacol 40 mg/ml oral suspension sugar-free | 50 ml [GSL] £2.71 DT price = £2.71
  - **Oral drops**
    - **Dentinox Infant®** (Dendron Ltd)
      - Simeticone 8.4 mg per 1 ml Dentinox Infant colic drops | 100 mL [GSL] £1.73
  - **Combinations available:** Simeticone with aluminium hydroxide and magnesium hydroxide, p. 67

4.2 Gastric and duodenal ulceration

Peptic ulceration

Overview

Peptic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma. Healing can be promoted by general measures, stopping smoking and taking antacids and by antisecretory drug treatment, but relapse is common when treatment ceases. Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by Helicobacter pylori.

**Helicobacter pylori infection**

Eradication of Helicobacter pylori reduces recurrence of gastric and duodenal ulcers and the risk of rebleeding. It also causes regression of most localised gastric mucosa associated lymphoid-tissue (MALT) lymphomas. The presence of *H. pylori* should be confirmed before starting eradication treatment. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*; reinfection is rare. Antibiotic associated colitis is an uncommon risk.

For initial treatment, a one-week triple-therapy regimen that comprises a proton pump inhibitor, clarithromycin p. 496, and either amoxicillin p. 506 or metronidazole p. 499 can be used. However, if a patient has been treated with metronidazole for other infections, a regimen containing a proton pump inhibitor, amoxicillin and clarithromycin is preferred for initial therapy. If a patient has been treated with a macrolide for other infections, a regimen containing a proton pump inhibitor, amoxicillin and metronidazole is preferred for initial therapy. These regimens eradicate *H. pylori* in about 85% of cases. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H₂-receptor antagonist), however, if the ulcer is large, or complicated by haemorrhage or perforation, then antisecretory treatment is continued for a further 3 weeks. Treatment failure usually indicates antibacterial resistance or poor compliance. Resistance to amoxicillin is rare. However, resistance to clarithromycin and metronidazole is common and can develop during treatment.

Two-week triple-therapy regimens offer the possibility of higher eradication rates compared to one-week regimens, but adverse effects are common and poor compliance is likely to offset any possible gain.

Two-week dual-therapy regimens using a proton pump inhibitor and a single antibacterial are licensed, but produce low rates of *H. pylori* eradication and are not recommended. Tinidazole p. 501 is also used occasionally for *H. pylori* eradication as an alternative to metronidazole; tinidazole should be combined with antisecretory drugs and other antibacterials.

Routine retesting, to confirm eradication, is not necessary unless the patient has gastric MALT lymphoma or complicated *H. pylori* associated peptic ulcer.

A two-week regimen comprising a proton pump inhibitor plus tripotassium dicitratobismuthate p. 70, plus tetracycline p. 523, plus metronidazole can be used for eradication failure. Alternatively, the patient can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

See under NSAID–associated ulcers for the role of *H. pylori* eradication therapy in patients starting or taking a NSAID. Also see Dyspepsia p. 64 for *H. pylori* eradication in patients with dyspepsia.

**Test for Helicobacter pylori**

¹³C-Urea breath test kits are available for the diagnosis of gastro-duodenal infection with *Helicobacter pylori*. The test involves collection of breath samples before and after ingestion of an oral solution of ¹³C-urea; the samples are sent for analysis by an appropriate laboratory. The test should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of treatment with an antisecretory drug. A specific ¹⁴C-urea breath test kit for children is available (Helicobacter Test INFAI for children of the age 3–11®). However, the appropriateness of testing for *H. pylori* infection in children has not been established.

**NSAID–associated ulcers**

Gastro-intestinal bleeding and ulceration can occur with NSAID use. The risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs. Whenever possible, the NSAID should be withdrawn if an ulcer occurs.

Patients at high risk of developing gastro-intestinal complications with a NSAID include those aged over 65 years, those with a history of peptic ulcer disease or serious gastro-intestinal complication, those taking other medicines that increase the risk of gastro-intestinal side-effects, or those with serious co-morbidity (e.g.
cardiovascular disease, diabetes, renal or hepatic impairment). In those at risk of ulceration, a proton pump inhibitor can be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs; a H₂-receptor antagonist such as ranitidine p. 72 given at twice the usual dose or misoprostol p. 73 are alternatives. Colic and diarrhoea may limit the dose of misoprostol. Its use is most appropriate for the frail or very elderly from whom NSAIDs cannot be withdrawn. A combination of a cyclo-oxygenase-2 selective inhibitor with a proton pump inhibitor may be more appropriate for those with a history of upper gastro-intestinal bleeding or 3 or more risk factors for gastro-intestinal ulceration, but see NSAIDs and Cardiovascular Events.

NSAID use and H. pylori infection are independent risk factors for gastro-intestinal bleeding and ulceration. In patients already taking a NSAID, eradication of H. pylori is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in patients with dyspepsia or a history of gastric or duodenal ulcer, who are H. pylori positive, and who are about to start long-term treatment with a non-selective NSAID, eradication of H. pylori may reduce the overall risk of ulceration.

In a patient who has developed an ulcer, if the NSAID can be discontinued, a proton pump inhibitor usually produces the most rapid healing; alternatively, the ulcer can be treated with a H₂-receptor antagonist or misoprostol. On healing, patients should be tested for H. pylori and given eradication therapy if H. pylori is present (see also Test for Helicobacter pylori).

If treatment with a non-selective NSAID needs to continue, the following options are suitable:

- Treat ulcer with a proton pump inhibitor and on healing continue the proton pump inhibitor (dose not normally reduced because asymptomatic ulcer recurrence may occur);
- Treat ulcer with a proton pump inhibitor and on healing switch to misoprostol for maintenance therapy (colic and diarrhoea may limit the dose of misoprostol);
- Treat ulcer with a proton pump inhibitor and switch non-selective NSAID to a cyclo-oxygenase-2 selective inhibitor, but see NSAIDs and Cardiovascular Events; on healing, continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

If treatment with a cyclo-oxygenase-2 selective inhibitor needs to continue, treat ulcer with a proton pump inhibitor; on healing continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

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### GASTROPROTECTIVE COMPLEXES AND CHELATORS

#### Chelates and complexes

**Overview**

Tripotassium dicitrato bismuthate p. 70 is a bismuth chelate effective in healing gastric and duodenal ulcers. See under Peptic ulceration p. 68 for the role of tripotassium dicitrato bismuthate in a Helicobacter pylori eradication regimen for those who have not responded to first-line regimens.

The bismuth content of tripotassium dicitrato bismuthate is low but absorption has been reported; encephalopathy (described with older high-dose bismuth preparations) has not been reported.

Sucralfate below may act by protecting the mucosa from acid-pepsin attack in gastric and duodenal ulcers. It is a complex of aluminium hydroxide and sulfated sucrose but has minimal antacid properties.

---

### Sucralfate

**INDICATIONS AND DOSE**

**Benign gastric ulceration | Benign duodenal ulceration**

- **BY MOUTH**
  - Child 15–17 years: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks, or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day
  - Adult: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks, or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day

**Chronic gastritis**

- **BY MOUTH**
  - Adult: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day

**Prophylaxis of stress ulceration in child under intensive care**

- **BY MOUTH**
  - Child 15–17 years: 1 g 6 times a day; maximum 8 g per day

**Recommended regimens for Helicobacter pylori eradication**

<table>
<thead>
<tr>
<th>Acid suppressant</th>
<th>Antibacterial</th>
<th>Price for 7-day course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Esomeprazole 20 mg</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>twice daily</td>
<td>250 mg twice daily</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>twice daily</td>
<td>250 mg twice daily</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>twice daily</td>
<td>500 mg 3 times a day</td>
<td>400 mg 3 times a day</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>twice daily</td>
<td>250 mg twice daily</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td>Rabeprazole sodium</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>20 mg twice daily</td>
<td>250 mg twice daily</td>
<td>400 mg twice daily</td>
</tr>
</tbody>
</table>
Prophylaxis of stress ulceration

- **BY MOUTH**
- Adult: 1 g 6 times a day; maximum 8 g per day

**UNLICENSED USE** Not licensed for use in children under 15 years. Tablets not licensed for prophylaxis of stress ulceration.

**CAUTIONS** Patients under intensive care (Important: reports of bezoar formation)

**CAUTIONS, FURTHER INFORMATION**

- Bezoar formation Following reports of bezoar formation associated with sucralfate, caution is advised in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.

**INTERACTIONS** → Appendix 1 (sucralfate).

**SIDE-EFFECTS**

- **Common or very common** Constipation
- **Uncommon** Back pain, bezoar formation, diarrhoea, dizziness, drowsiness, dry mouth, headache, flatulence, gastric discomfort, indigestion, nausea, rash

**PREGNANCY** No evidence of harm; absorption from gastrointestinal tract negligible.

**BREAST FEEDING** Amount probably too small to be harmful.

**RENAL IMPAIRMENT** Use with caution; aluminium is absorbed and may accumulate.

**DIRECTIONS FOR ADMINISTRATION** Administration of sucralfate and enteral feeds should be separated by 1 hour and for administration by mouth, sucralfate should be given 1 hour before meals. Oral suspension blocks fine-bore feeding tubes. Crushed tablets may be dispersed in water.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include aniseed and caramel.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 5
- Sucralfate (Non-proprietary)
  - Sucralfate 1 gram
  - Sulfacrat 1 g tablets | 100 tablet no price available

### Tripotassium dicitratobismuthate

**INDICATIONS AND DOSE**

- **Eradication failure of Helicobacter pylori infection (in combination with omeprazole, tetracycline and metronidazole)**
  - **BY MOUTH**
  - Adult: 120 mg 4 times a day for 2 weeks

- **Benign gastric and duodenal ulceration**
  - **BY MOUTH**
  - Adult: 240 mg twice daily, alternatively 120 mg 4 times a day both dosage regimens taken for 28 days followed by a further 28 days if necessary, maintenance dose not indicated but course may be repeated after interval of 1 month

**INTERACTIONS** → Appendix 1 (tripotassium dicitratobismuthate).

**SIDE-EFFECTS**

- **Common or very common** May blacken faeces, may darken tongue
- **Uncommon** Constipation, diarrhoea, nausea, pruritus, rash, vomiting

**PREGNANCY** Manufacturer advises avoid on theoretical grounds.

### H2-receptor antagonists

**Overview**

Histamine H2-receptor antagonists heal gastric and duodenal ulcers by reducing gastric acid output as a result of histamine H2-receptor blockade; they are also used to relieve symptoms of gastro-oesophageal reflux disease. H2-receptor antagonists should not normally be used for Zollinger-Ellison syndrome because proton pump inhibitors are more effective.

Maintenance treatment with low doses for the prevention of peptic ulcer disease has largely been replaced in Helicobacter pylori positive patients by eradication regimens. In adults, H2-receptor antagonists are used for the treatment of functional dyspepsia and may be used for the treatment of uninvestigated dyspepsia without alarm features. H2-receptor antagonist therapy can promote healing of NSAID-associated ulcers (particularly duodenal).

Treatment with a H2-receptor antagonist has not been shown to be beneficial in haematemesis and melaena, but prophylactic use reduces the frequency of bleeding from gastroduodenal erosions in hepatic coma, and possibly in other conditions requiring intensive care. H2-receptor antagonists also reduce the risk of acid aspiration in obstetric patients at delivery (Mendelson’s syndrome).

**CAUTIONS** Signs and symptoms of gastric cancer (in adults)

**CAUTIONS, FURTHER INFORMATION**

- **Gastric cancer**
  - In adults H2-receptor antagonists might mask symptoms of gastric cancer; particular care is required in patients presenting with 'alarm features' in such cases gastric malignancy should be ruled out before treatment.

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea, dizziness, headache
- **Uncommon** Erythema multiforme, rash, toxic epidermal necrolysis
- **Rare** Arthralgia, blood disorders, bradycardia, cholestatic jaundice, confusion, depression, hallucinations, hepatitis, leucopenia, myalgia, pancytopenia, psychiatric reactions, thrombocytopenia
- **Frequency not known** Gynaecomastia, impotence

**SIDE-EFFECTS, FURTHER INFORMATION**

Psychiatric reactions, including confusion, depression, and hallucinations occur particularly in the elderly or the very ill.
**Cimetidine**

**INDICATIONS AND DOSE**

**Benign duodenal ulceration**
- **BY MOUTH**
  - Adult: 400 mg twice daily for at least 4 weeks, to be taken with breakfast and at night, alternatively 800 mg once daily for at least 4 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg once daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

**Benign gastric ulceration**
- **BY MOUTH**
  - Adult: 400 mg twice daily for 6 weeks, to be taken with breakfast and at night, alternatively 800 mg daily for 6 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg once daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

**NSAID-associated ulceration**
- **BY MOUTH**
  - Adult: 400 mg twice daily for 8 weeks, to be taken with breakfast and at night, alternatively 800 mg daily for 8 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

**Reflux oesophagitis**
- **BY MOUTH**
  - Adult: 400 mg 4 times a day for 4–8 weeks

**Prophylaxis of stress ulceration**
- **BY MOUTH**
  - Adult: 200–400 mg every 4–6 hours

**Gastric acid reduction in obstetrics**
- **BY MOUTH**
  - Adult: Initially 400 mg, to be administered at start of labour, then increased if necessary up to 400 mg every 4 hours, do not use syrup in prophylaxis of acid aspiration; maximum 2.4 g per day

**Gastric acid reduction during surgical procedures**
- **BY MOUTH**
  - Adult: 400 mg, to be given 90–120 minutes before induction of general anaesthesia

**Short-bowel syndrome**
- **BY MOUTH**
  - Adult: 400 mg twice daily, adjusted according to response, to be taken with breakfast and at bedtime

**To reduce degradation of pancreatic enzyme supplements**
- **BY MOUTH**
  - Adult: 0.8–1.6 g daily in 4 divided doses, dose to be taken 1–1½ hours before meals

**INTERACTIONS** → Appendix 1 (histamine H₂-antagonists).

**SIDE-EFFECTS**
- Common or very common Malaise
- Uncommon Tachycardia
- Rare Interstitial nephritis
- Very rare Alopecia • galactorrhoea • pancreatitis • vasculitis
- **PREGNANCY** Manufacturer advises avoid unless essential.
- **BREAST FEEDING** Significant amount present in milk—not known to be harmful but manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** Reduce dose. Increased risk of confusion.
- **RENAL IMPAIRMENT** Reduce dose to 200 mg 4 times daily if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 200 mg 3 times daily if eGFR 15–30 mL/minute/1.73 m². Reduce dose to 200 mg twice daily if eGFR less than 15 mL/minute/1.73 m². Occasional risk of confusion.

**EXCEPTIONS TO LEGAL CATEGORY** Cimetidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity (max. single dose 200 mg, max. daily dose 800 mg), and for the prophylactic management of nocturnal heartburn (single night-time dose 100 mg).

**EXCIPIENTS: May contain Propylene glycol**

**Gastro-oesophageal reflux disease**
- **Omeprazole 20 mg**
  - Adult: 20 mg daily, taken in the morning and at night

**Tagamet (Chemidex Pharma Ltd)**
- **Cimetidine 200 mg**
  - Adult: 200 mg twice daily; maintenance
  - **Cimetidine 400 mg**
  - Adult: 400 mg twice daily; maximum
  - **Cimetidine 800 mg**
  - Adult: 800 mg twice daily; maximum

**Famotidine**

**INDICATIONS AND DOSE**

**Treatment of benign gastric and duodenal ulceration**
- **BY MOUTH**
  - Adult: 40 mg once daily for 4–8 weeks, to be taken at night

**Maintenance treatment of duodenal ulceration**
- **BY MOUTH**
  - Adult: 20 mg once daily, to be taken at night

**Reflux oesophagitis**
- **BY MOUTH**
  - Adult: 20–40 mg twice daily for 6–12 weeks; maintenance 20 mg twice daily

**INTERACTIONS** → Appendix 1 (histamine H₂-antagonists).

**SIDE-EFFECTS**
- Common or very common Constipation
- Uncommon Fatigue • vomiting • anorexia • dry mouth • flatulence • nausea • taste disorders
- Very rare Chest tightness • interstitial pneumonia • paraesthesia • seizures
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.
- **BREAST FEEDING** Present in milk—not known to be harmful but manufacturer advises avoid.
- **RENAL IMPAIRMENT** Use normal dose every 36–48 hours or use half normal dose if eGFR less than 50 mL/minute/1.73 m². Seizures reported very rarely.

**EXCEPTIONS TO LEGAL CATEGORY** Famotidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of nocturnal heartburn.
Gastro-intestinal system

Disorders of gastric acid and ulceration

这些症状当与食物或饮料的消费有关，其中会引起睡眠障碍（最大单剂量10 mg，每日剂量20 mg）。

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Famotidine (Non-proprietary)

  Famotidine 20 mg | 28 tablet £22.00 DT price = £21.62
  Famotidine 40 mg | 28 tablet £39.00 DT price = £38.98

**Nizatidine**

**INDICATIONS AND DOSE**

Benign gastric, duodenal or NSAID-associated ulceration
- **BY MOUTH**
  - Adult: 300 mg once daily for 4–8 weeks, dose to be taken in the evening, alternatively 150 mg twice daily for 4–8 weeks; maintenance 150 mg once daily, dose to be taken at night

Gastro-oesophageal reflux disease
- **BY MOUTH**
  - Adult: 150–300 mg twice daily for up to 12 weeks

**SIDE-EFFECTS**
- Common or very common Sweating
- Rare Fever • hyperuricaemia • nausea • vasculitis

**PREGNANCY**

Manufacturer advises avoid unless essential.

**BREAST FEEDING**

Amount too small to be harmful.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution.

**RENAL IMPAIRMENT**

Use half normal dose if eGFR 20–50 mL/minute/1.73 m². Use one-quarter normal dose if eGFR less than 20 mL/minute/1.73 m².

**EXCEPTIONS TO LEGAL CATEGORY**

Nizatidine can be sold to 20 years: 2 mg/kg twice daily (max. per dose 300 mg, to be given over at least 2 minutes, alternatively (by mouth) 150 mg, to be given 2 hours before induction of anaesthesia and also when possible on the preceding evening.

**Prophylaxis of stress ulceration**

Initially by slow intravenous injection
- Adult: 50 mg every 8 hours, dose to be diluted to 20 mL and given over at least 2 minutes, (by mouth) 150 mg twice daily, may be given when oral feeding commences

**Reflux oesophagitis and other conditions where gastric acid reduction is beneficial**

- **BY MOUTH**
  - Child 1–5 months: 1 mg/kg 3 times a day (max. per dose 3 mg/kg 3 times a day)
  - Child 6 months–2 years: 2–4 mg/kg twice daily
  - Child 3–11 years: 2–4 mg/kg twice daily (max. per dose 150 mg)
  - Child 12–17 years: 150 mg twice daily, alternatively 300 mg once daily, dose to be taken at night
  - Adult: 150 mg twice daily for 4–8 weeks, alternatively 300 mg once daily for 4–8 weeks, dose to be taken at night

**Ranitidine**

**INDICATIONS AND DOSE**

Benign gastric ulceration | Duodenal ulceration
- **BY MOUTH**
  - Child 1–5 months: 1 mg/kg 3 times a day (max. per dose 3 mg/kg 3 times a day)
  - Child 6 months–2 years: 2–4 mg/kg twice daily
  - Child 3–11 years: 2–4 mg/kg twice daily (max. per dose 150 mg); increased to up to 5 mg/kg twice daily (max. per dose 300 mg), dose increase for severe gastro-oesophageal ulceration
  - Child 12–17 years: 150 mg twice daily, alternatively 300 mg once daily, dose to be taken at night, then increased if necessary to 300 mg twice daily for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease, alternatively increased if necessary to 150 mg 4 times a day for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease

**Chronic episodic dyspepsia**
- **BY MOUTH**
  - Adult: 150 mg twice daily for 6 weeks, alternatively 300 mg once daily for 6 weeks, dose to be taken at night

NSAID-associated gastric ulceration
- **BY MOUTH**
  - Adult: 150 mg twice daily for up to 8 weeks, alternatively 300 mg once daily for up to 8 weeks, dose to be taken at night

NSAID-associated duodenal ulcer
- **BY MOUTH**
  - Adult: 300 mg twice daily for 4 weeks, to achieve a higher healing rate

Prophylaxis of NSAID-associated gastric ulcer

Prophylaxis of NSAID-associated duodenal ulcer
- **BY MOUTH**
  - Adult: 300 mg twice daily

Gastro-oesophageal reflux disease
- **BY MOUTH**
  - Adult: 300 mg daily in 2–4 divided doses for up to 12 weeks

Long-term treatment of healed gastro-oesophageal reflux disease
- **BY MOUTH**
  - Adult: 150 mg twice daily

Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics
- **BY MOUTH**
  - Adult: 150 mg, dose to be given at onset of labour, then 150 mg every 6 hours

Gastric acid reduction (prophylaxis of acid aspiration) in surgical procedures

Initially by intramuscular injection, or by slow intravenous injection
- Adult: 50 mg, to be given 45–60 minutes before induction of anaesthesia, intravenous injection diluted to 20 mL and given over at least 2 minutes, alternatively (by mouth) 150 mg, to be given 2 hours before induction of anaesthesia and also when possible on the preceding evening

Prophylaxis of stress ulceration

Initially by slow intravenous injection
- Adult: 50 mg every 8 hours, dose to be diluted to 20 mL and given over at least 2 minutes, then (by mouth) 150 mg twice daily, may be given when oral feeding commences.
Gastric and duodenal ulceration

### Conditions where reduction of gastric acidity is beneficial and oral route not available

- **By Intramuscular injection**
  - Adult: 50 mg every 6–8 hours
- **By Slow Intravenous injection**
  - Adult: 50 mg, dose to be diluted to 20 mL and given over at least 2 minutes; may be repeated every 6–8 hours

### UNLICENSED USE

- In children: Oral preparations not licensed for use in children under 3 years.
- In adults: Doses given for prophylaxis of NSAID-associated gastric or duodenal ulcer, and prophylaxis of stress ulceration, are not licensed.

### INTERACTIONS

→ Appendix 1 (histamine H₂-antagonists).

### SIDE-EFFECTS

- Uncommon: Blurred vision
- Frequency not known: Alopecia, interstitial nephritis, involuntary movement disorders, pancreatitis

### PREGNANCY

Manufacturer advises avoid unless essential, but not known to be harmful.

### BREAST FEEDING

Significant amount present in milk, but not known to be harmful.

### RENAL IMPAIRMENT

- In adults: Use half normal dose if eGFR less than 50 mL/minute/1.73 m².
- In children: Use half normal dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m².

### DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Zantac®), give intermittently in Glucose 5% or Sodium Chloride 0.9%.

### PATIENT AND CARER ADVICE

In fat malabsorption syndrome, give oral doses 1–2 hours before food to enhance effects of pancreatic enzyme replacement.

Medicines for Children leaflet: Ranitidine for acid reflux
www.medicinesforchildren.org.uk/ranitidine-for-acid-reflux

### EXCEPTIONS TO LEGAL CATEGORY

Ranitidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink (max. single dose 75 mg, max. daily dose 300 mg).

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, infusion.

#### Tablet

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 75 mg Ranitidine 75 mg tablets | 6 tablet | GSL £1.76 | 12 tablet | GSL £26.75
  - Ranitidine (as Ranitidine hydrochloride) 150 mg Ranitidine 150 mg tablets | 60 tablet | POS £1.28 DT price = £1.31 | 60 tablet | GPO no price available DT price = £1.31
  - Ranitidine (as Ranitidine hydrochloride) 300 mg Ranitidine 300 mg tablets | 30 tablet | GPO no price available DT price = £1.29
  - Ranitidine (as Ranitidine hydrochloride) 300 mg | 30 tablet | POS £1.29 DT price = £1.29
  - Ranitidil (Tillomed Laboratories Ltd)
  - Ranitidine (as Ranitidine hydrochloride) 150 mg Ranitil 150 mg tablets | 60 tablet | POS £18.13 DT price = £1.31
  - Ranitidine (as Ranitidine hydrochloride) 300 mg Ranitil 300 mg tablets | 30 tablet | POS £17.64 DT price = £1.29
  - Zantac (Omega Pharma Ltd, GlaxoSmithKline UK Ltd)
  - Ranitidine (as Ranitidine hydrochloride) 150 mg Zantac 150 mg tablets | 60 tablet | POS £1.28 DT price = £1.31
  - Ranitidine (as Ranitidine hydrochloride) 300 mg Zantac 300 mg tablets | 30 tablet | POS £1.28 DT price = £1.29

#### Oral solution

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 15 mg per 1 ml Ranitidine 15 mg/5 mL oral solution sugar free sugar-free | 100 ml | POS £2.75–3.75 DT price = £2.75
  - Ranitidine (as Ranitidine hydrochloride) 30 mg per 1 ml Ranitidine 30 mg/5 mL oral solution sugar-free | 100 ml | POS £4.20–5.20 DT price = £4.25

#### Injectable

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 15 mg | 20 mg per 1 ml Ranitidine (as Ranitidine hydrochloride) 15 mg | 20 mg per 1 ml | POS £2.50–4.50 DT price = £2.75
  - Ranitidine (as Ranitidine hydrochloride) 30 mg | 40 mg per 1 ml Ranitidine (as Ranitidine hydrochloride) 30 mg | 40 mg per 1 ml | POS £4.50–6.50 DT price = £4.65

### Effervescent tablet

#### CAUTIONARY AND ADVISORY LABELS

- **13 ELECTROLYTES**: May contain Sodium

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 150 mg Ranitidine 150 mg effervescent tablets | 60 tablet | POS £1.28 DT price = £1.31
  - Ranitidine (as Ranitidine hydrochloride) 300 mg Ranitidine 300 mg effervescent tablets | 30 tablet | POS £6.50 DT price = £6.50

### Oral solution

- **EXCIPIENTS**: May contain Alcohol

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 15 mg per 1 ml Ranitidine 15 mg/5 mL oral solution sugar free sugar-free | 100 ml | POS £1.65–2.65 DT price = £1.75
  - Ranitidine (as Ranitidine hydrochloride) 30 mg per 1 ml Ranitidine 30 mg/5 mL oral solution sugar-free | 100 ml | POS £2.65–3.65 DT price = £2.75

### Solution for injection

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 25 mg per 1 ml Ranitidine 25 mg/5 mL solution for injection ampoules | 5 ampoule | POS £2.45–3.45 DT price = £2.45
  - Ranitidine (as Ranitidine hydrochloride) 50 mg per 1 ml Ranitidine 50 mg/5 mL solution for injection ampoules | 5 ampoule | POS £3.95–4.95 DT price = £3.95

### PROSTAGLANDIN ANALOGUES AND PROSTAMIDES

#### PROSTAGLANDINS, GASTROPROTECTIVE

### Misoprostol

#### Drug action

Misoprostol is a synthetic prostaglandin analogue that has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers. It also acts as a potent uterine stimulant.

#### Indications and dose

- **Benign gastric ulceration**
- **Benign duodenal ulceration**
- **NSAID-associated ulceration**

- **By mouth**
  - Adult: 800 micrograms daily in 2–4 divided doses continued for at least 4 weeks or may be continued for up to 8 weeks if required, dose to be taken with breakfast (or main meals) and at bedtime.
  - Adult: 200 micrograms 4 times a day, reduced if not tolerated to 200 micrograms 2–3 times a day, use lower dose is less effective.

#### Caution

Conditions where hypotension might precipitate severe complications (e.g. cerebrovascular disease, cardiovascular disease) - inflammatory bowel disease

#### Interactions

→ Appendix 1 (misoprostol)

#### Side-effects

- Common or very common: Diarrhoea
- Frequency not known: Abdominal pain, abnormal vaginal bleeding, dizziness, dyspepsia, flatulence, intermenstrual bleeding, menorrhagia, nausea, postmenopausal bleeding, rashes, vomiting

#### Side-effects, further information

- Diarrhoea: May occasionally be severe and require withdrawal, reduced by giving single doses not exceeding 200 micrograms and by avoiding magnesium-containing antacids.

#### Conception and contraception

Manufacturer advises that misoprostol should not be used in women of...
childbearing age unless pregnancy has been excluded. In such patients it is advised that misoprostol should only be used if the patient takes effective contraceptive measures and has been advised of the risks of taking misoprostol if pregnant.

- **PREGNANCY** Avoid—potent uterine stimulant (has been used to induce abortion). Teratogenic risk in first trimester.
- **BREAST FEEDING** Present in milk, but amount probably too small to be harmful.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **Cyto tec** (Pfizer Ltd)
  - Misoprostol 200 microgram: Cyto tec 200microgram tablets | 56 tablet [po] no price available | 60 tablet [po] £10.03 DT price = £0.03

**PROTON PUMP INHIBITORS**

**Proton pump inhibitors**

**Overview**

Proton pump inhibitors are effective short-term treatments for gastric and duodenal ulcers; they are also used in combination with antibiotics for the eradication of Helicobacter pylori (see specific regimens). Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose proton pump inhibitor reduces the risk of rebleeding and the need for surgery. Proton pump inhibitors can be used for the treatment of dyspepsia and gastro-oesophageal reflux disease.

Proton pump inhibitors are also used for the prevention and treatment of NSAID-associated ulcers. In patients who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur.

A proton pump inhibitor can be used to reduce the degradation of pancreatic enzyme supplements in patients with cystic fibrosis. They can also be used to control excessive secretion of gastric acid in Zollinger–Ellison syndrome; high doses are often required.

**Proton pump inhibitors**

- **DRUG ACTION** Proton pump inhibitors inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell.

  - **in most cases, symptoms resolve on PPI withdrawal; topical or systemic steroids might be necessary for treatment of SCLE only if there are no signs of remission after a few weeks or months.**

- **CAUTIONS** Can increase the risk of fractures (particularly when used at high doses for over a year in the elderly) (in adults) may increase the risk of gastro-intestinal infections (including Clostridium difficile infection) - may mask the symptoms of gastric cancer (in adults) - patients at risk of osteoporosis

**CAUTIONS, FURTHER INFORMATION**

- **Risk of osteoporosis** Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D, and if necessary, receive other preventative therapy.
- **Gastric cancer** In adults Particular care is required in those presenting with ’alarm features’, in such cases gastric malignancy should be ruled out before treatment.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - constipation - diarrhoea - flatulence - gastro-intestinal disturbances - headache - nausea - vomiting
- **Uncommon** Arthralgia - dizziness - dry mouth - fatigue - myalgia - paraesthesia - peripheral oedema - pruritus - rash - sleep disturbances
- **Rare** Alopecia - anaphylaxis - blood disorders - bronchoospasm - confusion - depression - fever - gynaecomastia - hallucinations - hepatitis - hypersensitivity reactions - hypomagnesaemia (usually after 1 year of treatment, but sometimes after 3 months of treatment) - hyponatraemia - interstitial nephritis - jaundice - leucocytosis - leucopenia - pancytopenia - photosensitivity - Stevens-Johnson syndrome - stomatitis - sweating - taste disturbance - thrombocytopenia - toxic epidermal necrolysis - visual disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

Rebound acid hypersecretion and protracted dyspepsia may occur after stopping prolonged treatment with a proton pump inhibitor.

**MONITORING REQUIREMENTS** Measurement of serum-magnesium concentrations should be considered before and during prolonged treatment with a proton pump inhibitor, especially when used with other drugs that cause hypomagnesaemia or with digoxin.

**PRESCRIBING AND DISPENSING INFORMATION** A proton pump inhibitor should be prescribed for appropriate indications at the lowest effective dose for the shortest period; the need for long-term treatment should be reviewed periodically.

**Esomeprazole**

- **INDICATIONS AND DOSE**

  **NSAID-associated gastric ulcer**
  - **BY MOUTH**
    - Adult: 20 mg once daily for 4–8 weeks
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - Adult: 20 mg daily continue until oral administration possible, injection to be given over at least 3 minutes

  **Prophylaxis of NSAID-associated gastric ulcer in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment**
  - **BY MOUTH**
    - Adult: 20 mg daily
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - Adult: 20 mg daily continue until oral administration possible, injection to be given over at least 3 minutes
Gastro-oesophageal reflux disease (in the presence of erosive reflux oesophagitis)

► By mouth
- Child 1-11 years (body-weight 10-19 kg): 10 mg once daily for 8 weeks
- Child 1-11 years (body-weight 20 kg and above): 10–20 mg once daily for 8 weeks
- Child 12-17 years: Initially 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily
- Adult: Initially 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily

► By intravenous injection, or by intravenous infusion
- Adult: 40 mg daily continue until oral administration possible, injection to be given over at least 3 minutes

Symptomatic treatment of gastro-oesophageal reflux disease (in the absence of oesophagitis)

► By mouth
- Child 1-11 years (body-weight 10 kg and above): 10 mg once daily for up to 8 weeks
- Child 12-17 years: 20 mg once daily for up to 4 weeks
- Adult: 20 mg once daily for up to 4 weeks, then 20 mg daily if required

► By intravenous injection, or by intravenous infusion
- Adult: 20 mg daily continue until oral administration is possible, injection to be given over at least 3 minutes

Zollinger–Ellison syndrome

► By mouth
- Adult: Initially 40 mg twice daily, adjusted according to response; usual dose 80–160 mg daily, daily doses above 80 mg should be given in 2 divided doses

Severe peptic ulcer bleeding (following endoscopic treatment)

► Initially by intravenous infusion
- Adult: Initially 80 mg, to be given over 30 minutes, then (by continuous intravenous infusion) 8 mg/hour for 72 hours, then (by mouth) 40 mg once daily for 4 weeks

Helicobacter pylori eradication in combination with clarithromycin and amoxicillin or metronidazole

► By mouth
- Adult: 20 mg twice daily

- With oral use Do not chew or crush capsules; swallow whole or mix capsule contents in water and drink within 30 minutes. Do not chew or crush tablets; swallow whole or disperse in water and drink within 30 minutes. Disperse the contents of each sachet of gastro-resistant granules in approx. 15 mL water. Stir and leave to thicken for a few minutes; stir again before administration and use within 30 minutes; rinse container with 15 mL water to obtain full dose. For administration through a gastric tube, consult product literature.

- With oral use Counselling on administration of gastro-resistant capsules, tablets, and granules advised.

- Medicinal forms
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Gastro-resistant tablet

► Esomeprazole (Non-proprietary)
  - Esomeprazole (as Esomeprazole magnesium trihydrate) 20 mg Esomeprazole 20 mg gastro-resistant tablets | 28 tablet (Pom) £18.50 DT price = £2.97
  - Esomeprazole (as Esomeprazole magnesium trihydrate) 40 mg Esomeprazole 40 mg gastro-resistant tablets | 28 tablet (Pom) £25.19 DT price = £3.54
  - Nexium (AstraZeneca UK Ltd, Pfizer Consumer Healthcare Ltd) Esomeprazole (as Esomeprazole magnesium trihydrate) 20 mg Nexium 20 mg gastro-resistant tablets | 28 tablet (Pom) £18.50 DT price = £2.97
  - Esomeprazole (as Esomeprazole magnesium trihydrate) 40 mg Nexium 40 mg gastro-resistant tablets | 28 tablet (Pom) £25.19 DT price = £3.54

Gastro-resistant capsule

► Esomeprazole (Non-proprietary)
  - Esomeprazole (as Esomeprazole magnesium dihydrate) 20 mg Esomeprazole 20 mg gastro-resistant capsules | 28 capsule (Pom) £12.95 DT price = £3.40
  - Esomeprazole (as Esomeprazole magnesium dihydrate) 40 mg Esomeprazole 40 mg gastro-resistant capsules | 28 capsule (Pom) £17.63 DT price = £3.96
  - Emozul (Consilient Health Ltd) Esomeprazole (as Esomeprazole magnesium dihydrate) 20 mg Emozul 20 mg gastro-resistant capsules | 28 capsule (Pom) £3.40 DT price = £3.40
  - Esomeprazole (as Esomeprazole magnesium dihydrate) 40 mg Emozul 40 mg gastro-resistant capsules | 28 capsule (Pom) £3.96 DT price = £3.96

Gastro-resistant granules

- Cautionary and advisory labels 25

- Nexium (AstraZeneca UK Ltd)
  - Esomeprazole (as Esomeprazole magnesium trihydrate) 10 mg Nexium 10 mg gastro-resistant granules sachets | 28 sachet (Pom) £25.19 DT price = £25.19

Powder for solution for injection

► Esomeprazole (Non-proprietary)
  - Esomeprazole (as Esomeprazole sodium) 40 mg Esomeprazole 40 mg powder for solution for injection vials | 1 vial (Pom) £3.07–£3.13 (Hospital only)
  - Nexium (AstraZeneca UK Ltd)
    - Esomeprazole (as Esomeprazole sodium) 40 mg Nexium LV 40 mg powder for solution for injection vials | 1 vial (Pom) £4.25 (Hospital only)

Lansoprazole

- Indications and dose
  - Helicobacter pylori eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole
    - By mouth
      - Adult: 30 mg twice daily

Unrestricted use
- Tablets and capsules not licensed for use in children 1–11 years.

Interactions
- Appendix 1 (proton pump inhibitors).

Pregnancy
- Manufacturer advises caution—no information available.

Breast feeding
- Manufacturer advises avoid—no information available.

Hepatic impairment
- In adults In severe hepatic impairment max. 20 mg daily. Severe peptic ulcer bleeding in severe hepatic impairment, initial intravenous infusion of 80 mg, then by continuous intravenous infusion, 4 mg/hour for 72 hours.
- In children 1–11 years max. 10 mg daily in severe impairment. 12–17 years max. 20 mg daily in severe impairment.

Renal impairment
- Manufacturer advises caution in severe renal insufficiency.

Directions for administration
- With intravenous use in adults For intravenous infusion (Nexium®), give continuously or intermittently in Sodium Chloride 0.9%; reconstitute 40–80 mg with up to 100 mL infusion fluid; for intermittent infusion, give requisite dose over 10–30 minutes; stable for 12 hours in Sodium Chloride 0.9%.
Benign gastric ulcer

- **BY MOUTH**
  - Adult: 30 mg once daily for 8 weeks, dose to be taken in the morning

Duodenal ulcer

- **BY MOUTH**
  - Adult: 30 mg once daily for 4 weeks, dose to be taken in the morning; maintenance 15 mg once daily

**NSAID-associated duodenal ulcer** | **NSAID-associated gastric ulcer**

- **BY MOUTH**
  - Adult: 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed

**Prophylaxis of NSAID-associated duodenal ulcer** | **Prophylaxis of NSAID-associated gastric ulcer**

- **BY MOUTH**
  - Adult: 15–30 mg once daily

Gastro-oesophageal reflux disease

- **BY MOUTH**
  - Adult: 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 15–30 mg once daily, dose to be taken in the morning

**Acid-related dyspepsia**

- **BY MOUTH**
  - Adult: 15–30 mg once daily for 2–4 weeks, doses to be taken in the morning

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**INDICATIONS AND DOSE**

*Helicobacter pylori* eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole

- **BY MOUTH**
  - Adult: 20 mg twice daily

Eradication failure of *Helicobacter pylori* infection in combination with tripotassium dicitratobismuthate, tetracycline and metronidazole

- **BY MOUTH**
  - Adult: 20 mg twice daily

**Benign gastric ulceration**

- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, increased if necessary to 40 mg once daily, in severe or recurrent cases

**Duodenal ulceration**

- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, increased if necessary to 40 mg once daily, in severe or recurrent cases

**Prevention of relapse in gastric ulcer**

- **BY MOUTH**
  - Adult: 20 mg once daily, dose may range between 10–40 mg daily

**Prevention of relapse in duodenal ulcer**

- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, continued for a further 4 weeks if not fully healed

**Prophylaxis in patients with a history of NSAID-associated duodenal ulcer who require continued NSAID treatment** | **Prophylaxis in patients with a history of NSAID-associated gastric ulcer** | **NSAID-associated gastroduodenal erosions**

- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, continued for a further 4 weeks if not fully healed

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**Gastro-resistant capsule**

CAUTIONARY AND ADVISORY LABELS 5, 22, 25
be given in 2 divided doses, injection to be given over 5 minutes, infusion to be given over 20–30 minutes

**Gastro-oesophageal reflux disease**
- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, continued for a further 4–8 weeks if not fully healed; maintenance 20 mg once daily

**Gastro-oesophageal reflux disease refractory to other treatment**
- **BY MOUTH**
  - Adult: 40 mg once daily for 8 weeks; maintenance 20 mg once daily

**Acid reflux disease (long-term management)**
- **BY MOUTH**
  - Adult: 10 mg once daily, increased to 20 mg once daily, dose only increased if symptoms return

**Acid-related dyspepsia**
- **BY MOUTH**
  - Adult: 10–20 mg once daily for 2–4 weeks according to response

**Treatment and prevention of benign gastric ulcers**
**Treatment and prevention of duodenal ulcers**
**Treatment and prevention of NSAID-associated ulcers**
**Treatment and prevention of gastro-oesophageal reflux disease**
- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 40 mg once daily until oral administration possible, injection to be given over 5 minutes, infusion to be given over 20–30 minutes

**Major peptic ulcer bleeding (following endoscopic treatment)**
- **INITIALLY BY INTRAVENOUS INFUSION**
  - Adult: Initially 80 mg, to be given over 40–60 minutes, then (by continuous intravenous infusion) 8 mg/hour for 72 hours, subsequent dose then changed to oral therapy

**UNLICENSED USE** Treatment of major peptic ulcer bleeding (following endoscopic treatment) is an unlicensed indication.

**INTERACTIONS** → Appendix 1 (proton pump inhibitors).

**SIDE-EFFECTS** Agitation - impotence

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk but not known to be harmful.

**HEPATIC IMPAIRMENT** Not more than 20 mg daily should be needed.

**DIRECTIONS FOR ADMINISTRATION** For administration by mouth, swallow whole, or disperse Losec MUPS® tablets in water, or mix capsule contents or Losec MUPS® tablets with fruit juice or yoghurt. Preparations consisting of an e/c tablet within a capsule should not be opened.

- With intravenous use For intravenous infusion (Losec®), give intermittently or continuously in Glucose 5% or Sodium chloride 0.9%; reconstitute each 40 mg vial with infusion fluid and dilute to 100 mL; for intermittent infusion give 40 mg over 20–30 minutes; stable for 3 hours in glucose 5% or 12 hours in sodium chloride 0.9%.

**PATIENT AND CARER ADVICE**
- With oral use Counselling on administration advised.

**PROFESSION SPECIFIC INFORMATION**
Dental practitioners’ formulary
Gastro-resistant omeprazole capsules may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY**
- With oral use Omeprazole 10 mg tablets can be sold to the public for the short-term relief of reflux-like symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks, and a pack size of 28 tablets.

**MEDICINAL FORMS**

- **Omeprazole (Non-proprietary)**
  - Omeprazole 10 mg Omeprazole 10mg gastro-resistant capsules | 28 capsule £9.30 DT price = £0.90
  - Omeprazole 20 mg Omeprazole 20mg gastro-resistant capsules | 28 capsule £13.50 DT price = £0.91
  - Omeprazole 40 mg Omeprazole 40mg gastro-resistant capsules | 7 capsule £6.96 DT price = £0.75 | 28 capsule £19.72
  - **Losec** (AstraZeneca UK Ltd)
    - Omeprazole (as Omeprazole magnesium) 10 mg Losec MUPS 10mg gastro-resistant tablets | 28 tablet £7.75 DT price = £0.75
    - Omeprazole (as Omeprazole magnesium) 20 mg Losec MUPS 20mg gastro-resistant tablets | 28 tablet £11.60 DT price = £1.10
  - **Mezopram** (Sandoz Ltd)
    - Omeprazole (as Omeprazole magnesium) 10 mg Mezopram 10mg gastro-resistant tablets | 28 tablet £5.80 DT price = £0.50
    - Mezopram 20mg gastro-resistant tablets | 28 tablet £9.86 DT price = £1.10
  - Omeprazole (as Omeprazole magnesium) 40 mg Mezopram 40mg gastro-resistant tablets | 7 tablet £4.93 DT price = £0.50

**Gastro-resistant capsule**
- **Omeprazole (Non-proprietary)**
  - Omeprazole 10 mg Omeprazole 10mg gastro-resistant capsules | 28 capsule £9.30 DT price = £0.90
  - Omeprazole 20 mg Omeprazole 20mg gastro-resistant capsules | 28 capsule £13.50 DT price = £0.91
  - Omeprazole 40 mg Omeprazole 40mg gastro-resistant capsules | 7 capsule £6.96 DT price = £0.75 | 28 capsule £19.72
  - **Losec** (AstraZeneca UK Ltd)
    - Omeprazole 10 mg Losec 10mg gastro-resistant capsules | 28 capsule £9.30 DT price = £0.90
    - Omeprazole 20 mg Losec 20mg gastro-resistant capsules | 28 capsule £13.92 DT price = £0.91
    - Omeprazole 40 mg Losec 40mg gastro-resistant capsules | 7 capsule £6.96 DT price = £0.75
  - **Mepradec** (Discovery Pharmaceuticals)
    - Omeprazole 10 mg Mepradec 10mg gastro-resistant capsules | 28 capsule £0.83 DT price = £0.90
    - Omeprazole 20 mg Mepradec 20mg gastro-resistant capsules | 28 capsule £0.83 DT price = £0.90

**Powder for solution for infusion**
- **Omeprazole (Non-proprietary)**
  - Omeprazole (as Omeprazole sodium) 40 mg Omeprazole 40mg powder for solution for infusion vials | 5 vial £32.45 (Hospital only) | 5 vial £16.54

**Pantoprazole**

**INDICATIONS AND DOSE**

- **Helicobacter pylori** eradication in combination with amoxicillin and clarithromycin; or in combination with clarithromycin and metronidazole
  - **BY MOUTH**
    - Adult: 40 mg twice daily

- **Benign gastric ulcer**
  - **BY MOUTH**
    - Adult: 40 mg daily for 8 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases
**Gastro-intestinal system**

**MEDICINAL FORMS**

**DIRECTIONS FOR ADMINISTRATION**

**HEPATIC IMPAIRMENT**

**BREAST FEEDING**

**PREGNANCY**

**INTERACTIONS**

**Rabeprazole sodium**

**INDICATIONS AND DOSE**

**Benign gastric ulcer**

**Duodenal ulcer**

**Gastro-oesophageal reflux disease**

**Zollinger–Ellison syndrome (and other hypersecretory conditions)**

**Gastric ulcer**

- By Intravenous Injection, or by Intravenous infusion
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

**Duodenal ulcer**

- By Mouth
- Adult: 40 mg daily for 4 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases
- By Intravenous injection, or by Intravenous infusion
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

**Gastro-oesophageal reflux disease**

- By Mouth
- Adult: 20–80 mg daily for 4 weeks, continued for further 4 weeks if not fully healed, dose to be taken in the morning; maintenance 20 mg daily and increased to 40 mg daily, increased only if symptoms return
- By Intravenous injection, or by Intravenous infusion
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

**Zollinger–Ellison syndrome (and other hypersecretory conditions)**

- By Mouth
- Adult: Initially 80 mg daily (max. per dose 80 mg), adjusted according to response
- Elderly: 40 mg daily
- By Intravenous injection, or by Intravenous infusion
- Adult: Initially 80 mg, alternatively 160 mg in 2 divided doses, if rapid acid control required, then 80 mg once daily (max. per dose 80 mg), adjusted according to response

**INTERACTIONS** → Appendix 1 (proton pump inhibitors).

**SIDE-EFFECTS**

- Hyperlipidaemia - weight changes
- Pregnancy: Manufacturer advises avoid unless potential benefit outweighs risks—fetotoxic in animals.
- Breast Feeding: Manufacturer advises avoid unless potential benefit outweighs risks—small amount present in milk.
- Hepatic Impairment: Max. 20 mg daily in severe impairment and cirrhosis. Monitor liver function in hepatic impairment (discontinue if deterioration).
- Renal Impairment: Max. oral dose 40 mg daily.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Protium®), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute 40 mg with 10 mL sodium chloride 0.9% and dilute with 100 mL of infusion fluid; give 40 mg over 15 minutes.

**EXCEPTIONS TO LEGAL CATEGORY**

Pantoprazole 20 mg tablets can be sold to the public for the short-term treatment of reflux symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Gastro-resistant tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

- Pantoprazole (Non-proprietary)
- Pantoprazole (as Pantoprazole sodium sesquihydrate)

<table>
<thead>
<tr>
<th>20 mg</th>
<th>Pantoprazole 20mg gastro-resistant tablets</th>
<th>28 tablet £0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£11.83 DT price = £0.99</td>
<td></td>
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</tbody>
</table>

**Pantoprazole (as Pantoprazole sodium sesquihydrate)**

<table>
<thead>
<tr>
<th>40 mg</th>
<th>Pantoprazole 40mg gastro-resistant tablets</th>
<th>28 tablet £0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£20.57 DT price = £1.16</td>
<td></td>
</tr>
</tbody>
</table>

**Powder for solution for injection**

- Pantoprazole (Non-proprietary)
- Pantoprazole (as Pantoprazole sodium sesquihydrate)

<table>
<thead>
<tr>
<th>40 mg</th>
<th>Pantoprazole 40mg powder for solution for injection vials</th>
<th>1 vial £0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£5.00</td>
<td>5 vial</td>
</tr>
<tr>
<td></td>
<td>£22.50–£23.25</td>
<td></td>
</tr>
</tbody>
</table>

- Protium (Takeda UK Ltd)
- Pantoprazole (as Pantoprazole sodium sesquihydrate)

<table>
<thead>
<tr>
<th>40 mg</th>
<th>Protium I.V. 40mg powder for solution for injection vials</th>
<th>5 vial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£25.53</td>
<td></td>
</tr>
</tbody>
</table>

**Rabeprazole sodium**

**INDICATIONS AND DOSE**

**Benign gastric ulcer**

- By Mouth
- Adult: 20 mg daily for 8 weeks, dose to be taken in the morning

**Duodenal ulcer**

- By Mouth
- Adult: 20 mg daily for 4 weeks, dose to be taken in the morning

**Gastro-oesophageal reflux disease**

- By Mouth
- Adult: 20 mg once daily for 4–8 weeks; maintenance 10–20 mg daily

**Gastro-oesophageal reflux disease (symptomatic treatment in the absence of oesophagitis)**

- By Mouth
- Adult: 10 mg daily for up to 4 weeks, then 10 mg daily if required

**Zollinger–Ellison syndrome**

- By Mouth
- Adult: Initially 60 mg once daily, adjusted according to response, doses above 100 mg daily given in 2 divided doses; maximum 120 mg per day

**Helicobacter pylori eradication in combination with amoxicillin or metronidazole and clarithromycin**

- By Mouth
- Adult: 20 mg twice daily

**INTERACTIONS** → Appendix 1 (proton pump inhibitors).

**SIDE-EFFECTS**

<table>
<thead>
<tr>
<th>Common or very common</th>
<th>Cough · influenza like syndrome · rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Chest pain · nervousness</td>
</tr>
<tr>
<td>Rare</td>
<td>Anorexia · weight gain</td>
</tr>
</tbody>
</table>

**PREGNANCY**

Manufacturer advises avoid—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in severe hepatic dysfunction.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

- Rabeprazole sodium (Non-proprietary)
- Rabeprazole sodium 10 mg Rabeprazole 10mg gastro-resistant tablets | 28 tablet £0.57 DT price = £1.57
- Rabeprazole sodium 20 mg Rabeprazole 20mg gastro-resistant tablets | 28 tablet £0.99 DT price = £1.92
- Pariet (Eisai Ltd)
- Rabeprazole sodium 10 mg Pariet 10mg gastro-resistant tablets | 28 tablet £0.57 DT price = £1.57
- Rabeprazole sodium 20 mg Pariet 20mg gastro-resistant tablets | 28 tablet £1.34 DT price = £1.92
4.3 Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease

Management

Gastro-oesophageal reflux disease (including non-erosive gastro-oesophageal reflux and erosive oesophagitis) is associated with heartburn, acid regurgitation, and sometimes, difficulty in swallowing (dysphagia); oesophageal inflammation (oesophagitis), ulceration, and stricture formation may occur and there is an association with asthma.

The management of gastro-oesophageal reflux disease includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms and treatment is then adjusted according to response. The extent of healing depends on the severity of the disease, the treatment chosen, and the duration of therapy.

Patients with gastro-oesophageal reflux disease should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, smoking cessation, and raising the head of the bed.

For mild symptoms of gastro-oesophageal reflux disease, initial management may include the use of antacids and alginate. Alginate-containing antacids can form a ‘raft’ that floats on the surface of the stomach contents to reduce reflux and protect the oesophageal mucosa. Histamine H₂-receptor antagonists may relieve symptoms and permit reduction in antacid consumption. However, proton pump inhibitors provide more effective relief of symptoms than H₂-receptor antagonists. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by giving treatment intermittently.

For severe symptoms of gastro-oesophageal reflux disease or for patients with a proven or severe pathology (e.g. oesophagitis, oesophageal ulceration, oesophagopharyngeal reflux, Barrett’s oesophagus), initial management involves the use of a proton pump inhibitor; patients need to be reassessed if symptoms persist despite treatment for 4–6 weeks with a proton pump inhibitor. If symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by reducing the dose of the proton pump inhibitor or by giving it intermittently, or by substituting treatment with a histamine H₂-receptor antagonist).

However, for endoscopically confirmed erosive, ulcerative, or strictureing disease, or Barrett’s oesophagus, treatment with a proton pump inhibitor usually needs to be maintained at the minimum effective dose.

Pregnancy

If dietary and lifestyle changes fail to control gastro-oesophageal reflux disease in pregnancy, an antacid or an alginate can be used. If this is ineffective, ranitidine p. 72 can be tried. Omeprazole p. 76 is reserved for women with severe or complicated reflux disease.

Gastro-oesophageal reflux disease in children

Gastro-oesophageal reflux disease is common in infancy but most symptoms resolve without treatment between 12 and 18 months of age. In infants, mild or moderate reflux without complications can be managed initially by changing the frequency and volume of feed; a feed thickener or thickened formula feed can be used (with advice of a dietician). If necessary, a suitable alginate-containing preparation can be used instead of thickened feeds. For older children, life-style changes similar to those for adults may be helpful followed if necessary by treatment with an alginate-containing preparation.

Children who do not respond to these measures or who have problems such as respiratory disorders or suspected oesophagitis need to be referred to hospital; an H₂-receptor antagonist may be needed to reduce acid secretion. If the oesophagitis is resistant to H₂-receptor blockade, the proton pump inhibitor omeprazole can be tried.

Other drugs used for Gastro-oesophageal reflux disease

Cimetidine, p. 71 • Esomeprazole, p. 74 • Famotidine, p. 71 • Lansoprazole, p. 75 • Nizatidine, p. 72 • Pantoprazole, p. 77 • Rabeprazole sodium, p. 78

Antacids > Alginate

Sodium alginate with calcium carbonate and sodium bicarbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, alginic acid p. 65, sodium bicarbonate p. 910, calcium carbonate p. 919.

- Indications and dose

Mild symptoms of gastro-oesophageal reflux disease

- By mouth
  - Child 6–11 years: 5–10 mL, to be taken after meals and at bedtime
  - Child 12–17 years: 10–20 mL, to be taken after meals and at bedtime
  - Adult: 10–20 mL, to be taken after meals and at bedtime

- Prescribing and dispensing information

Flavours of oral liquid formulations may include aniseed or peppermint.

- Patient and carer advice

Medicines for Children leaflet: Gaviscon for gastro-oesophageal reflux disease www.medicinesforchildren.org.uk/gaviscon-gastro-oesophageal-reflux-disease

- Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Oral suspension

Electrolytes: May contain Sodium

- Sodium alginate with calcium carbonate and sodium bicarbonate (Non-proprietary)
  - Calcium carbonate 16 mg per 1 mL, Sodium bicarbonate 26.7 mg per 1 mL, Sodium alginate 50 mg per 1 mL Alginate raft-forming oral suspension sugar free peppermint sugar-free | 500 mL [GSL] no price available DT price = £1.95
  - Alginate raft-forming oral suspension sugar free aniseed sugar-free | 500 mL [GSL] no price available DT price = £1.95
  - Alginate raft-forming oral suspension sugar free sugar-free | 500 mL [GSL] no price available DT price = £1.95
  - Brands may include Acidex, Entrocalm Heartburn and Indigestion Relief, Gaviscon, Gaviscon Cool, Gaviscon Liquid Relief, Peptac

- Forms

Alginate raft-forming oral suspension sugar free aniseed sugar-free 500 ml | 1
Alginate raft-forming oral suspension sugar free peppermint sugar-free | 500 ml [GSL] no price available DT price = £1.95
Alginate raft-forming oral suspension sugar free aniseed sugar-free | 500 ml [GSL] no price available DT price = £1.95
Alginate raft-forming oral suspension sugar free sugar-free | 500 ml [GSL] no price available DT price = £1.95

- Brands

- Common names

- Active ingredients

- Excipients

- Available from

- Special precautions

- Side effects
4.4 *Helicobacter pylori* diagnosis

**DIAGNOSTIC AGENTS**

### Urea (13c)

- **INDICATIONS AND DOSE**
  - Diagnosis of gastro-duodenal *Helicobacter pylori* infection
  - **BY MOUTH**
  - Adult: (consult product literature)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Diabact UBT (Seahorse Laboratories Ltd)
      - Urea [13-C] 50 mg: diabact UBT 50mg tablets | 1 tablet | £21.25 | 10 tablet | £196.20
    - Urea [13-C] 100 mg: Diabact breath test kit | 1 kit | £20.75
  - **Soluble tablet**
    - Pylobactell (Turbet Laboratories Ltd)
      - Urea [13-C] 45 mg: Helicobacter Test INFAI for children breath test kit sugar-free | 1 kit | £19.10
      - Urea [13-C] 75 mg: Helicobacter Test INFAI breath test kit sugar-free | 1 kit | £21.70

### Antimuscarinics

*Antimuscarinics* (formerly termed ‘anticholinergics’) are the class of drugs that are used for gastro-intestinal smooth muscle spasm and are less likely to cross the blood–brain barrier.

- They have no serious adverse effects but, like all antispasmodics, should be avoided in paralytic ileus.

#### Other antispasmodics

Alverine citrate p. 82, mebeverine hydrochloride p. 82, and peppermint oil p. 43 are believed to be direct relaxants of intestinal smooth muscle and may relieve pain in irritable bowel syndrome. They have no serious adverse effects but, like all antispasmodics, should be avoided in paralytic ileus.

#### **Dicycloverine hydrochloride**

(Dicyclomine hydrochloride)

- **INDICATIONS AND DOSE**
  - Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm
  - **BY MOUTH**
    - Child 6–23 months: 5–10 mg 3–4 times a day, dose to be taken 15 minutes before feeds
    - Child 2–11 years: 10 mg 3 times a day
    - Child 12–17 years: 10–20 mg 3 times a day
    - Adult: 10–20 mg 3 times a day

- **CONTRA-INDICATIONS**
  - Child under 6 months

- **PREGNANCY**
  - Not known to be harmful; manufacturer advises use only if essential.

- **BREAST FEEDING**
  - Avoid—present in milk; apnoea reported in infant.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Dicycloverine hydrochloride can be sold to the public provided that max. single dose is 10 mg and max. daily dose is 60 mg.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Dicycloverine hydrochloride (Non-proprietary)
      - Dicycloverine hydrochloride 10 mg: Dicycloverine 10mg tablets | 100 tablet | £201.22 | DT price = £184.25
      - Dicycloverine hydrochloride 20 mg: Dicycloverine 20mg tablets | 84 tablet | £203.42 | DT price = £196.69
  - **Oral solution**
    - Dicycloverine hydrochloride (Non-proprietary)
      - Dicycloverine hydrochloride 2 mg per 1 ml: Dicycloverine 10mg/5ml oral solution | 100 ml | no price available | 120 ml | £196.36 | DT price = £183.27 | 300 ml | no price available

#### Antispasmodics

**Antimuscarinics**

The intestinal smooth muscle relaxant properties of antimuscarinic and other antispasmodic drugs may be useful in irritable bowel syndrome.

Antimuscarinics (formerly termed ‘anticholinergics’) reduce intestinal motility. They can be used for the management of irritable bowel syndrome.

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amines atropine sulfate p. 1022 and dicycloverine hydrochloride below and the quaternary ammonium compounds propantheline bromide p. 81 and hyoscyamine butyryl bromide p. 81. The quaternary ammonium compounds are less lipid soluble than atropine sulfate and are less likely to cross the blood–brain barrier; they are also less well absorbed from the gastro-intestinal tract.

Dicycloverine hydrochloride has a much less marked antimuscarinic action than atropine sulfate and may also have some direct action on smooth muscle. Hyoscine butyryl bromide is advocated as a gastro-intestinal antispasmodic, but it is poorly absorbed; the injection is useful in endoscopy and radiology. Atropine sulfate and the belladonna alkaloids are outmoded treatments, any clinical virtues being outweighed by atropinic side-effects.

Other indications for antimuscarinic drugs include arrhythmias, asthma and airways disease, motion sickness, parkinsonism, urinary incontinence, mydriasis and cycloplegia, premedication, and as an antidote to organophosphorus poisoning.

### **5 Food allergy**

#### Food allergy

**Management**

Allergy with classical symptoms of vomiting, colic and diarrhoea caused by specific foods such as cow’s milk or shellfish should be managed by strict avoidance. The condition should be distinguished from symptoms of occasional food intolerance in those with irritable bowel syndrome. Sodium cromoglicate p. 253 may be helpful as an adjunct to dietary avoidance.

Other drugs used for Food allergy Chlorphenamine maleate, p. 266

### **6 Gastro-intestinal smooth muscle spasm**

#### Antispasmodics

**Antimuscarinics**

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Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amines atropine sulfate p. 1022 and dicycloverine hydrochloride below and the quaternary ammonium compounds propantheline bromide p. 81 and hyoscyamine butyryl bromide p. 81. The quaternary ammonium compounds are less lipid soluble than atropine sulfate and are less likely to cross the blood–brain barrier;
Diclofenac sodium with aluminium hydroxide, magnesium oxide and simeticone

The properties listed below are those particular to the combination only. For the properties of the components please consider, diclofenac sodium p. 80, aluminium hydroxide p. 925, simeticone p. 68.

## INDICATIONS AND DOSE

### Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

- **By mouth**
  - Child 12-17 years: 10–20 mL every 4 hours as required
  - Adult: 10–20 mL every 4 hours as required

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Hyoscine butylbromide

17-Oct-2016

## INDICATIONS AND DOSE

### Symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm

- **By mouth**
  - Child 6-11 years: 10 mg 3 times a day
  - Child 12-17 years: 20 mg 4 times a day
  - Adult: 20 mg 4 times a day

### Irritable bowel syndrome

- **By mouth**
  - Adult: 10 mg 3 times a day; increased if necessary up to 20 mg 4 times a day

### Acute spasm | Spasm in diagnostic procedures

- Initially by intramuscular injection, or by slow intravenous injection
  - Adult: 20 mg, then (by intramuscular injection or by slow intravenous injection) 20 mg after 30 minutes if required, dose may be repeated more frequently in endoscopy; maximum 100 mg per day

### Excessive respiratory secretions in palliative care

- **By mouth**
  - Child 1 month-1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
  - Child 2–4 years: 5 mg 3–4 times a day
  - Child 5–11 years: 10 mg 3–4 times a day
  - Child 12–17 years: 10–20 mg 3–4 times a day
  - **By intramuscular injection, or by intravenous injection**
  - Child 1 month-4 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
  - Child 5–11 years: 5–10 mg 3–4 times a day
  - Child 12–17 years: 10–20 mg 3–4 times a day

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Propantheline bromide

## INDICATIONS AND DOSE

### Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

- **By mouth**
  - Child 5-11 years: 10 mg 3–4 times a day
  - Child 12-17 years: 10–20 mg 3–4 times a day
  - **By intramuscular injection, or by intravenous injection**
  - Child 1 month-4 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
  - Child 5–11 years: 5–10 mg 3–4 times a day
  - Child 12–17 years: 10–20 mg 3–4 times a day
  - **By subcutaneous injection**
  - Adult: 20 mg every 4 hours if required, adjusted according to response to up to 20 mg every 1 hour
  - **By subcutaneous infusion**
  - Adult: 20–120 mg/24 hours

### Bowel colic (in palliative care)

- **By mouth**
  - Child 1 month-1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
  - Child 2–4 years: 5 mg 3–4 times a day
Gastro-intestinal smooth muscle spasm

Mebeverine hydrochloride

- **INDICATIONS AND DOSE**
  Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm
  - BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
    - Child 10–17 years: 135–150 mg 3 times a day, dose preferably taken 20 minutes before meals
    - Adult: 135–150 mg 3 times a day, dose preferably taken 20 minutes before meals
  - Irritable bowel syndrome
    - BY MOUTH USING MODIFIED-RELEASE MEDICINES
    - Child 12–17 years: 200 mg twice daily
    - Adult: 200 mg twice daily

- **UNLICENSED USE**

- **CONTRA-INDICATIONS**
  Paralytic ileus

- **SIDE-EFFECTS**
  Allergic reactions - angioedema - rash - urticaria

- **PREGNANCY**
  Not known to be harmful—manufacturers advise avoid.

- **BREAST FEEDING**
  Manufacturers advise avoid—no information available.

- **PATIENT AND CARER ADVICE**
  Medicines for Children leaflet: Mebeverine for intestinal spasm www.medicinesforchildren.org.uk/mebeverine-for-intestinal-spasms
  Patients or carers should be given advice on the timing of administration of mebeverine hydrochloride tablets and oral suspension.

- **EXCEPTIONS TO LEGAL CATEGORY**
  In adults Mebeverine hydrochloride can be sold to the public for symptomatic relief of irritable bowel syndrome provided that max. single dose is 135 mg and max. daily dose is 405 mg; for uses other than symptomatic relief of irritable bowel syndrome provided that max. single dose is 100 mg and max. daily dose is 300 mg.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Mebeverine hydrochloride (Non-proprietary)
    - Mebeverine hydrochloride 135 mg Mebeverine 135 mg tablets | 100 tablet 🟢 £20.00 DT price = £7.02
    - Colofac (BGP Products Ltd)
      - Mebeverine hydrochloride 135 mg Colofac 135 mg tablets | 100 tablet 🟢 £9.02 DT price = £7.02
  - Mebeverine hydrochloride (as Mebeverine pamoate) 10 mg per 1 ml Mebeverine 50 mg/5 ml oral suspension sugar free sugar-free | 300 ml 🟢 £163.43–187.00 DT price = £163.43

## Antispasmodics

### Alverine citrate

- **INDICATIONS AND DOSE**
  Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm | Dysmenorrhoea
  - BY MOUTH
    - Child 12–17 years: 60–120 mg 1–3 times a day
    - Adult: 60–120 mg 1–3 times a day

- **CONTRA-INDICATIONS**
  Intestinal obstruction - paralytic ileus

- **SIDE-EFFECTS**
  Dizziness - dyspnoea - headache - hepatitis - jaundice (resolves with cessation) - nausea - pruritus - wheezing

- **PREGNANCY**
  Manufacturer advises avoid—limited information available

- **BREAST FEEDING**
  Manufacturer advises avoid—limited information available.

- **PATIENT AND CARER ADVICE**
  Driving and skilled tasks
  Dizziness may affect performance of skilled tasks (e.g. driving).

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - Alverine citrate (Non-proprietary)
    - Alverine citrate 60 mg Alverine 60 mg capsules | 100 capsule 🟢 £19.49 DT price = £9.48
    - Alverine citrate 120 mg Alverine 120 mg capsules | 60 capsule 🟢 £22.28 DT price = £33.28
  - Audmonal (Teva UK Ltd)
    - Alverine citrate 60 mg Audmonal 60 mg capsules | 100 capsule 🟢 £14.80 DT price = £9.48
    - Alverine citrate 120 mg Audmonal Forte 120 mg capsules | 60 capsule 🟢 £17.75 DT price = £33.28
  - Gielism (HFA Healthcare Products Ltd)
    - Alverine citrate 60 mg Gielism 60 mg capsules | 100 capsule 🟢 £19.48 DT price = £9.48
    - Alverine citrate 120 mg Gielism Forte 120 mg capsules | 60 capsule 🟢 £19.42 DT price = £33.28
  - Spasmonal (Meda Pharmaceuticals Ltd)
    - Alverine citrate 60 mg Spasmonal 60 mg capsules | 100 capsule 🟢 £16.45 DT price = £19.48
    - Alverine citrate 120 mg Spasmonal Forte 120 mg capsules | 60 capsule 🟢 £19.42 DT price = £33.28

- **UNLICENSED USE**
  Tablets not licensed for use in children under 12 years.
7 Liver disorders and related conditions

7.1 Biliary disorders

Biliary disorders

Drugs affecting biliary composition and flow

The use of laparoscopic cholecystectomy and of endoscopic biliary techniques has limited the place of the bile acid ursodeoxycholic acid p. 84 in gallstone disease. Ursodeoxycholic acid is suitable for patients with unimpaired gall bladder function, small or medium-sized radiolucent stones, and whose mild symptoms are not amenable to other treatment. Long-term prophylaxis may be needed after complete dissolution of the gallstones has been confirmed because they may recur in up to 25% of patients within one year of stopping treatment.

Ursodeoxycholic acid is also used in primary biliary cirrhosis; liver tests improve in most patients but the effect on overall survival is uncertain.

Cholic acid p. 84 may be used to improve the flow of bile in those with inborn errors of primary bile acid synthesis. A terpene mixture (Rowachol®) raises biliary cholesterol solubility. It is not considered to be a useful adjunct.

Bile acid sequestrants

Colestyramine p. 186 is an anion-exchange resin that is not absorbed from the gastro-intestinal tract. It relieves diarrhoea and pruritus by forming an insoluble complex with bile acids in the intestine.

Exocrine pancreatic insufficiency

14-Dec-2016

Description of condition

Exocrine pancreatic insufficiency is characterised by reduced secretion of pancreatic enzymes into the duodenum. The main clinical manifestations are malabsorption of lipids and carbohydrates, and lack of proteolysis.

Patients also present with gastro-intestinal symptoms such as borborygmus, flatulence, abdominal pain, bloating, nausea, and anorexia. Fat absorption is impaired and dietary fats are malabsorbed. Levels of fat-soluble vitamins and micronutrients (such as vitamin A, vitamin D, vitamin E, and vitamin K) are low. Lipoprotein profiles are abnormal, with an increase in very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) concentrations and a decrease in high-density lipoprotein (HDL) levels.

Aims of treatment

The aim of treatment is to relieve gastro-intestinal symptoms and to achieve a normal nutritional status.

Drug treatment

Pancreatic enzyme replacement therapy with pancreatin p. 90 is the mainstay of treatment for exocrine pancreatic insufficiency.

Pancreatin contains the three main groups of digestive enzymes: lipase, amylase and protease. These enzymes respectively digest fats, carbohydrates and proteins into their basic components so that they can be absorbed and utilised by the body. Pancreatin should be administered with meals and snacks. The dose should be adjusted, as necessary, to the lowest effective dose according to the symptoms of malabsorption and malnutrition. Fibrosering colonopathy is known to occur in patients with cystic fibrosis taking high-dose pancreatic enzyme replacement therapy (in excess of 10 000 units/kg/day of lipase). Possible risk factors are gender (in children, boys are at greater risk than girls), more severe cystic fibrosis, and concomitant use of laxatives. The peak age for developing fibrosering colonopathy is between 2 and 8 years.

Manufacturers of Pancrease HL® and Nutrizym 22® recommend that the total dose of pancreatin used in patients with cystic fibrosis should not usually exceed 10 000 units/kg/day of lipase. Manufacturers of pancreatin recommend that if a patient taking pancreatin develops new abdominal symptoms (or any change in existing abdominal symptoms) the patient should be reviewed to exclude the possibility of colonic damage.

There is limited evidence that acid suppression may improve the effectiveness of pancreatin. Acid-suppressing drugs (proton pump inhibitors or H₂-receptor antagonists) may be trialled in patients who continue to experience symptoms despite high doses of pancreatin.

Levels of fat-soluble vitamins and micronutrients (such as zinc and selenium) should be routinely assessed and supplementation advised whenever necessary.

Pancreatin preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Protease units</th>
<th>Amylase units</th>
<th>Lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon® 10 000 capsule, e/c granules</td>
<td>600</td>
<td>8000</td>
<td>10 000</td>
</tr>
<tr>
<td>Creon® Micro e/c granules (per 100 mg)</td>
<td>200</td>
<td>3600</td>
<td>5000</td>
</tr>
<tr>
<td>Pancrex® granules (per gram)</td>
<td>300</td>
<td>4000</td>
<td>5000</td>
</tr>
<tr>
<td>Pancrex V® capsule, powder</td>
<td>430</td>
<td>9000</td>
<td>8000</td>
</tr>
<tr>
<td>Pancrex V® 125® capsule, powder</td>
<td>160</td>
<td>3300</td>
<td>2950</td>
</tr>
<tr>
<td>Pancrex V® e/c tablet</td>
<td>110</td>
<td>1700</td>
<td>1900</td>
</tr>
<tr>
<td>Pancrex V® Forte e/c tablet</td>
<td>330</td>
<td>5000</td>
<td>5600</td>
</tr>
<tr>
<td>Pancrex V® powder (per gram)</td>
<td>1400</td>
<td>30 000</td>
<td>25 000</td>
</tr>
</tbody>
</table>

Higher-strength pancreatin preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Protease units</th>
<th>Amylase units</th>
<th>Lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon® 25 000 capsule, e/c pellets</td>
<td>1000</td>
<td>18000</td>
<td>25 000</td>
</tr>
<tr>
<td>Creon® 40000 capsule, e/c granules</td>
<td>1600</td>
<td>25 000</td>
<td>40 000</td>
</tr>
<tr>
<td>Nutrizym 22® capsule, e/c minitablets</td>
<td>1100</td>
<td>19 800</td>
<td>22 000</td>
</tr>
<tr>
<td>Pancrease HL® capsule, e/c minitablets</td>
<td>1250</td>
<td>22 500</td>
<td>25 000</td>
</tr>
</tbody>
</table>

Non-drug treatment

Dietary advice should be provided. Food intake should be distributed between three main meals per day, and two or three snacks. Food that is difficult to digest should be avoided, such as legumes (peas, beans, lentils) and high-fibre foods. Alcohol should be avoided completely. Reduced fat diets are not recommended.

Medium-chain triglycerides (see MCT oil, in Borderline substances), which are directly absorbed by the intestinal mucosa, were thought to be useful in some patients. However evidence has shown that MCT-enriched preparations offer no advantage over a normal balanced diet.

Gastro-intestinal system
## BILE ACIDS

### Cholic acid

**DRUG ACTION** Cholic acid is the predominant primary bile acid in humans, which can be used to provide a source of bile acid in patients with inborn deficiencies in bile acid synthesis.

**INDICATIONS AND DOSE**

**Inborn errors of primary bile acid synthesis (initiated by a specialist)**
- **BY MOUTH**
  - **Adult:** Usual dose 5–15 mg/kg daily; increased in steps of 50 mg daily in divided doses if required, dose to be given with food at the same time each day; Usual maximum 500 mg/24 hours

**INTERACTIONS** → Appendix 1 (bile acids).

**SIDE-EFFECTS** Diarrhoea • gallstones (long term use) • pruritus

SIDE-EFFECTS, FURTHER INFORMATION
Patients presenting with pruritus and/or persistent pruritus should be investigated for potential overdose by a serum and/or urine bile acid assay.

**PREGNANCY** Limited data available—known to be harmful
Manufacturer advises monitor patient parameters more frequently in pregnancy.

**BREAST FEEDING** Present in milk but not known to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises monitor closely.

**MONITORING REQUIREMENTS** Manufacturer advises monitor serum and/or urine bile-acid concentrations every 3 months for the first year, then every 6 months for three years, then annually; monitor liver function tests at the same or greater frequency.

**DIRECTIONS FOR ADMINISTRATION** Manufacturer advises capsules may be opened and the content added to infant formula, juice, fruit compote, or yoghurt for administration.

**PATIENT AND CARER ADVICE** Counselling advised on administration.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

CAUTIONARY AND ADVISORY LABELS 25
- **Kolbam (Retrophin Inc)**
  - Cholic acid 50 mg | 90 capsule (POM) £3.240.00
  - Cholic acid 250 mg | 90 capsule (POM) £11.340.00
- **Orphacol (Laboratoires CTRS)**
  - Cholic acid 50 mg | 60 capsule (POM) £3.720.00
  - Cholic acid 250 mg | 60 capsule (POM) £6.630.00

### Ursodeoxycholic acid

**INDICATIONS AND DOSE**

**Dissolution of gallstones**
- **BY MOUTH**
  - **Adult:** 8–12 mg/kg once daily, dose to be taken at bedtime, alternatively 8–12 mg/kg daily in 2 divided doses for up to 2 years; treatment is continued for 3–4 months after stones dissolve

**CONTRA-INDICATIONS** Acute inflammation of the gall bladder • frequent episodes of biliary colic • inflammatory diseases and other conditions of the colon, liver or small intestine which interfere with enterohepatic circulation of bile salts • non-functioning gall bladder • radio-opaque stones

**CAUTIONS** Liver disease

**INTERACTIONS** → Appendix 1 (bile acids).

**SIDE-EFFECTS**
- Common or very common Diarrhoea
- Very rare Abdominal pain • gallstone calcification • urticaria

**PREGNANCY** No evidence of harm but manufacturer advises avoid.

**BREAST FEEDING** Not known to be harmful but manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Avoid in chronic liver disease (but used in primary biliary cirrhosis).

**MONITORING REQUIREMENTS** In primary biliary cirrhosis, monitor liver function every 4 weeks for 3 months, then every 3 months.

**PATIENT AND CARER ADVICE** Patients should be given dietary advice (including avoidance of excessive cholesterol and calories).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21
- **Ursodeoxycholic acid (Non-proprietary)**
  - Ursodeoxycholic acid 150 mg | 60 tablet (POM) £19.02 DT price = £19.02
  - Ursodeoxycholic acid 300 mg | 60 tablet (POM) £47.63 DT price = £47.63
- **Cholurso (HFA Healthcare Products Ltd)**
  - Ursodeoxycholic acid 250 mg | 60 tablet (POM) £18.00
  - Ursodeoxycholic acid 500 mg | 60 tablet (POM) £45.00
- **Destolit (Norgine Pharmaceuticals Ltd)**
  - Ursodeoxycholic acid 150 mg | 60 tablet (POM) £18.39 DT price = £18.02
- **Ursofalk (Dr. Falk Pharma UK Ltd)**
  - Ursodeoxycholic acid 500 mg | 100 tablet (POM) £80.00

**Capsule**

CAUTIONARY AND ADVISORY LABELS 21
- **Ursodeoxycholic acid (Non-proprietary)**
  - Ursodeoxycholic acid 250 mg | 60 capsule (POM) £31.50 DT price = £25.29
- **Ursofalk (Dr. Falk Pharma UK Ltd)**
  - Ursodeoxycholic acid 250 mg | 60 capsule (POM) £30.17 DT price = £25.29

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 21
- **Ursofalk (Dr. Falk Pharma UK Ltd)**
  - Ursodeoxycholic acid 50 mg per 1 ml | 250 ml (POM) £26.98 DT price = £26.98
PITUITARY AND HYPOTHALAMIC HORMONES

TERPENES

Borneol with camphene, cineole, menthol, menthone and pinene

- **INDICATIONS AND DOSE**
  - Biliary disorders
    - **BY MOUTH**
    - Adult: 1–2 capsules 3 times a day, to be taken before food

- **LESS SUITABLE FOR PRESCRIBING** Rowachol® is less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Gastro-resistant capsule**
    - **CAUTIONARY AND ADVISORY LABELS 22**
    - **Rowachol** (Meadow Laboratories Ltd)
      - Cineole 2 mg, Borneol 5 mg, Camphene 5 mg, Menthene 6 mg, Pinene 17 mg, Menthol 32 mg Rowachol gastro-resistant capsules | 50 capsule [PON] £7.35

7.2 Oesophageal varices

Other drugs used for Oesophageal varices Vasopressin, p. 613

PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > VASOPRESSIN AND ANALOGUES

Terlipressin acetate

- **INDICATIONS AND DOSE**
  - **GLYPRESSIN® INJECTION**
    - **Bleeding from oesophageal varices**
      - **BY INTRAVENOUS INJECTION**
        - Adult (body-weight up to 50 kg): Initially 2 mg every 4 hours until bleeding controlled, then reduced to 1 mg every 4 hours if required, maximum duration 48 hours
        - Adult (body-weight 50 kg and above): Initially 2 mg every 4 hours until bleeding controlled, reduced if not tolerated to 1 mg every 4 hours, maximum duration 48 hours
  - **VARIQUEL® INJECTION**
    - **Bleeding from oesophageal varices**
      - **BY INTRAVENOUS INJECTION**
        - Adult (body-weight up to 50 kg): Initially 1 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute
        - Adult (body-weight 50–69 kg): Initially 1.5 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute
        - Adult (body-weight 70 kg and above): Initially 2 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute

- **CAUTIONS**
  - Arrhythmia · elderly · electrolyte and fluid disturbances · heart disease · history of QT-interval prolongation · respiratory disease · septic shock · uncontrolled hypertenstion · vascular disease

- **INTERACTIONS**
  - Caution with concomitant use of drugs that prolong the QT-interval.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal cramps · arrhythmia · bradycardia · diarrhoea · headache · hypertension · hypotension · pallor · peripheral ischaemia
  - **Uncommon** Angina · bronchospasm · convulsions · hot flushes · hyponatraemia · intestinal ischaemia · myocardial infarction · nausea · pulmonary oedema · respiratory failure · tachycardia · vomiting
  - **Rare** Dyspnoea
  - **Very rare** Hyperglycaemia · stroke
  - **Frequency not known** Heart failure · skin necrosis

- **PREGNANCY** Avoid unless benefits outweigh risk—uterine contractions and increased intra-uterine pressure in early pregnancy, and decreased uterine blood flow reported.

- **BREAST FEEDING** Avoid unless benefits outweigh risk—no information available.

- **RENAL IMPAIRMENT** Use with caution in chronic renal failure.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **Glypressin** (Ferring Pharmaceuticals Ltd)
      - Terlipressin acetate 120 microgram per 1 ml Glypressin 1mg/8.5ml solution for injection ampoules | 5 ampoule [POM] £98.98 (Hospital only)
    - **VARIQUEL** (Sinclair IS Pharma Plc)
      - Terlipressin acetate 200 microgram per 1 ml Variquel 1mg/5ml solution for injection vials | 5 vial [POM] £89.48
  - **Powder and solvent for solution for injection**
    - **Glypressin** (Ferring Pharmaceuticals Ltd)
      - Terlipressin acetate 1 mg Glypressin 1mg powder and solvent for solution for injection vials | 5 vial [POM] £92.33
    - **VARIQUEL** (Alliance Pharmaceuticals Ltd)
      - Terlipressin acetate 1 mg Variquel 1mg powder and solvent for solution for injection vials | 5 vial [POM] £89.48

8 Obesity

**Description of condition**

Obesity is directly linked to many health problems including cardiovascular disease, type 2 diabetes, fatty liver disease, gallstones, and gastro-oesophageal reflux disease. It is also linked to psychological and psychiatric morbidities.

In adults, obesity is generally classified as a body mass index (BMI) of ≥ 30 kg/m², though BMI should be interpreted with caution as it is not a direct measure of adiposity, particularly in patients who are very muscular or have muscle weakness or atrophy.

Waist circumference should also be considered as it may provide an indication of total body fat and a risk of obesity-related health problems. Men with a waist circumference ≥ 94 cm (≥ 90 cm for Asian men), and women with a waist circumference of ≥ 80 cm are at increased risk of obesity-related health problems. A waist circumference of ≥ 102 cm in men and ≥ 88 cm in women indicates a very high risk of obesity-related health problems.

**Aims of treatment**

Management should be aimed at modest, sustainable weight loss and maintenance of a healthy weight, to reduce the risk factors associated with obesity.

**Overview**

Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity. Patients should be monitored for changes in weight,
as well as changes in blood pressure and blood lipids, and for other associated conditions. 

An initial assessment should consider potential underlying causes (e.g. hypothyroidism) and a review of the appropriateness of current medications which are known to cause weight gain, e.g. atypical antipsychotics, beta-adrenoceptor blocking drugs, insulin (when used in the treatment of type 2 diabetes), lithium carbonate, lithium citrate, sodium valproate, sulphonylureas, thiazolidinediones, and tricyclic antidepressants. 

Lifestyle changes
Patients should be encouraged to engage in a sustainable weight management programme which includes strategies to change behaviour, increase physical activity, and improve diet and eating behaviour. 

**Drug treatment**
Drug treatment should never be used as the sole element of treatment and should be used as part of an overall weight management plan. An anti-obesity drug should be considered only for those with a BMI of \( \geq 30 \text{ kg/m}^2 \), in whom diet, exercise and behaviour changes fail to achieve a realistic reduction in weight. In the presence of associated risk factors, it may be appropriate to prescribe an anti-obesity drug to individuals with a BMI of \( \geq 28 \text{ kg/m}^2 \). A vitamin and mineral supplement may also be considered if there is concern about inadequate micronutrient intake, particularly for vulnerable groups such as in the elderly and younger patients.

The effect of management should be monitored on a regular basis with reinforcement of supporting lifestyle advice. Rates of weight loss may be slower in patients with type 2 diabetes, so less strict goals than in those without diabetes may be appropriate.

Orlistat, below, is the only drug currently available in the UK that is recommended specifically for the management of obesity; it acts by reducing the absorption of dietary fat.

Orlistat is licensed for use as an adjunct in the management of obesity in patients with a BMI of \( \geq 30 \text{ kg/m}^2 \), or, in individuals with a BMI of \( \geq 28 \text{ kg/m}^2 \) in the presence of other risk factors. Treatment with orlistat may also be used to maintain weight loss rather than to continue to lose weight. Discontinuation of treatment with orlistat should be considered after 12 weeks if weight loss has not exceeded 5% since the start of treatment. 

Drugs which produce a feeling of satiety (such as methylcellulose p. 50 and sterculia p. 51 [unlicensed indications]) have been used in an attempt to control appetite, but there is little evidence for their efficacy. Various centrally acting appetite suppressants, including stimulants and serotonergic drugs (such as dexfenfluramine, fenfluramine, sibutramine, and rimonabant), have been used in the management of obesity but have been withdrawn or are no longer recommended due to serious safety concerns or their addictive potential.

**Surgery**
Bariatric surgery may be considered for patients who have a BMI of \( \geq 40 \text{ kg/m}^2 \) (Obesity III, morbid obesity), or between 35–39.9 \text{ kg/m}^2 (Obesity II) and a significant disease (such as type 2 diabetes or high blood pressure) which could be improved with weight loss, and if all appropriate non-surgical measures have been tried but clinically beneficial weight loss has not been achieved or maintained. 

**Useful Resources**

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**PERIPHERALLY ACTING ANTI-OBESEITY DRUGS**

**LIPASE INHIBITORS**

**Orlistat**
- **DRUG ACTION** Orlistat, a lipase inhibitor, reduces the absorption of dietary fat.
- **INDICATIONS AND DOSE** Adjunct in obesity (in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of \( \geq 30 \text{ kg/m}^2 \) or more in individuals with a BMI of \( \geq 28 \text{ kg/m}^2 \) or more in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia)
  - **BY MOUTH**
    - Adult: 120 mg up to 3 times a day, dose to be taken immediately before, during, or up to 1 hour after each main meal, continue treatment beyond 12 weeks only if weight loss since start of treatment exceeds 5% (target for initial weight loss may be lower in patients with type 2 diabetes), if a meal is missed or contains no fat, the dose of orlistat should be omitted.
- **CONTRA-INDICATIONS** Cholestasis - chronic malabsorption syndrome
- **CAUTIONS** Chronic kidney disease - may impair absorption of fat-soluble vitamins - volume depletion

**CAUTIONS, FURTHER INFORMATION**
Vitamin supplementation (especially of vitamin D) may be considered if there is concern about deficiency of fat-soluble vitamins.

**INTERACTIONS** Appendix 1 (orlistat).
- **Multivitamins** If a multivitamin supplement is required, it should be taken at least 2 hours after orlistat dose or at bedtime.
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal distension (gastro-intestinal effects minimised by reduced fat intake) - abdominal pain (gastro-intestinal effects minimised by reduced fat intake) - anxiety - faecal incontinence - faecal urgency - flatulence - gingival disorders - headache - hypoglycaemia - liquid stools - malaise - menstrual disturbances - oily leakage from rectum - oily stools - respiratory infections - tooth disorders - urinary tract infection
  - **Frequency not known** Bullous eruptions - cholelithiasis - diverticulitis - hepatitis - hypothyroidism - oxalate nephropathy - rectal bleeding
- **PREGNANCY** Use with caution.
- **BREAST FEEDING** Avoid — no information available.
- **MEDIcular FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - Orlistat (Non-proprietary)
      - Orlistat 120 mg Orlistat 120 mg capsules | 84 capsule POM £30.05 DT price = £18.44
      - Alli (GlaxoSmithKline Consumer Healthcare)
        - Orlistat 60 mg Alli 60 mg capsules | 84 capsule P £29.10 DT price = £18.44
      - Beacita (Actavis UK Ltd)
        - Orlistat 120 mg Beacita 120 mg capsules | 84 capsule POM £31.63 DT price = £18.44
      - Xenical (Roche Products Ltd)
        - Orlistat 120 mg Xenical 120 mg capsules | 84 capsule POM £31.63 DT price = £18.44
9 Rectal and anal disorders

Rectal and anal disorders

Overview
Anal and perianal pruritus, soreness, and excoriation are best treated by application of bland ointments and suppositories. These conditions occur commonly in patients suffering from haemorrhoids, fistulas, and proctitis. Cleansing with attention to any minor faecal soiling, adjustment of the diet to avoid hard stools, the use of bulk-forming materials such as bran and a high residue diet are helpful. In proctitis these measures may supplement treatment with corticosteroids or sulfasalazine p. 39.

When necessary, topical preparations containing local anaesthetics or corticosteroids are used, provided perianal thrush has been excluded. Perianal thrush is treated with a topical antifungal preparation.

For the management of other anal disorders, see also Anal fissure below.

Soothing haemorrhoidal preparations
Soothing preparations containing mild astringents such as bismuth subgallate, zinc oxide, and hamamelis may give symptomatic relief in haemorrhoids. Many proprietary preparations also contain lubricants, vasoconstrictors, or mild antiseptics.

Local anaesthetics, such as lidocaine hydrochloride, are used to relieve pain associated with haemorrhoids and pruritus ani but good evidence is lacking. Alternative local anaesthetics include tetracaine, cinchocaine (dibucaine), and pramoxaine (pramoxine), but they are more irritant. Local anaesthetic ointments can be absorbed through the rectal mucosa (avoid excessive application) and pruritus ani (pramoxine), but they are more irritant.

Compound haemorrhoidal preparations with corticosteroids
Corticosteroids are often combined with local anaesthetics and soothing agents in preparations for haemorrhoids. They are suitable for occasional short-term use after exclusion of infections, such as herpes simplex; prolonged use can cause atrophy of the anal skin.

Rectal sclerosants
Oily phenol injection is used to inject haemorrhoids particularly when unprolapsed.

Rectal and anal disorders in children
Haemorrhoids in children are rare. Treatment is usually symptomatic and the use of a locally applied cream is appropriate for short periods; however, local anaesthetics can cause stinging initially and this may aggravate the child’s fear of defaecation.

9.1 Anal fissures

Anal fissure

Description of condition
An anal fissure is a tear or ulcer in the lining of the anal canal, immediately within the anal margin. Clinical features of anal fissure include bleeding and persistent pain on defaecation, and a linear split in the anal mucosa.

Drug treatment

Acute anal fissure

Initial management of acute anal fissures (present for less than 6 weeks) should focus on ensuring that stools are soft and easily passed. Bulk-forming laxatives (such as ispaghula husk p. 50) are recommended and an osmotic laxative (such as lactulose p. 52) can be considered as an alternative—see also Constipation p. 48, for further information about these laxatives. Short-term use of a topical preparation containing a local anaesthetic (such as lidocaine hydrochloride) or a simple analgesic (such as paracetamol p. 414 or ibuprofen p. 999) may be offered for prolonged burning pain following defaecation. If these measures are inadequate, the patient should be referred for specialist treatment in hospital.

Chronic anal fissure

Chronic anal fissures (present for 6 weeks or longer), and associated pain, may be treated with glyceryl trinitrate rectal ointment 0.4% or 0.2% [unlicensed] p. 207 (available from Special-order manufacturers p. 1422 or specialist importing companies). Limited evidence suggests that the strength used does not influence the effectiveness, but that the higher strength potentially increases the incidence of side-effects. Healing rates with topical glyceryl trinitrate are marginally superior to placebo, but the incidence of headache as an adverse effect is quite high (about 20–30% of patients). Recurrence of the fissure after treatment is common.

As an alternative to glyceryl trinitrate rectal ointment, chronic anal fissure may also be treated with topical diltiazem hydrochloride 2% [unlicensed] or nifedipine 0.2–0.5% [unlicensed] (available from Special-order manufacturers p. 1422 or specialist importing companies), which have a lower incidence of adverse effects than topical glyceryl trinitrate. Oral nifedipine [unlicensed indication] and oral diltiazem hydrochloride [unlicensed indication] may be as effective as topical treatment, but the incidence of adverse effects are likely to be higher and topical preparations are preferred.

Patients who do not respond to first-line treatment may be referred to a specialist for local injection of botulinum toxin type A [unlicensed indication].

Non-drug treatment

Surgery is an effective option for the management of chronic anal fissure in adults but is generally reserved for those who do not respond to drug treatment.

9.2 Haemorrhoids

CORTICOSTEROIDS

Benzyl benzoate with bismuth oxide, bismuth subgallate, hydrocortisone acetate, peru balsam and zinc oxide

- INDICATIONS AND DOSE

Haemorrhoids / Pruritus ani
- BY RECTUM USING OINTMENT
- Adult: Apply twice daily for no longer than 7 days, to be applied morning and night, an additional dose should be applied after a bowel movement
- BY RECTUM USING SUPPOSITORIES
- Adult: 1 suppository twice daily for no longer than 7 days, to be inserted night and morning, additional dose after a bowel movement

- CAUTIONS

Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application)
local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**PRESCRIBING AND DISPENSING INFORMATION** A proprietary brand Anusol Plus HC® (ointment and suppositories) is on sale to the public.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Suppository**
- Anusol-Hc (McNeil Products Ltd)
  Hydrocortisone acetate 10 mg, Bismuth oxide 24 mg, Benzyl benzoate 33 mg, Peru Balsam 49 mg, Bismuth subgallate 59 mg, Zinc oxide 296 mg Anusol HC suppositories | 12 suppository £1.74
  Anusol Plus HC suppositories | 12 suppository £3.03

**Ointment**
- Anusol-Hc (McNeil Products Ltd)
  Hydrocortisone acetate 2.5 mg per 1 gram, Bismuth oxide 8.75 mg per 1 gram, Benzyl benzoate 12.5 mg per 1 gram, Peru Balsam 18.75 mg per 1 gram, Bismuth subgallate 22.5 mg per 1 gram, Zinc oxide 107.5 mg per 1 gram Anusol HC ointment | 15 gram £3.03
  Anusol HC ointment | 30 gram £2.49

**Benzyl benzoate with bismuth oxide, hydrocortisone acetate, peru balsam, pramocaine hydrochloride and zinc oxide**

**INDICATIONS AND DOSE**

**Haemorrhoids | Pruritus ani**
- **BY RECTUM**
  - Adult: Apply twice daily for no longer than 7 days, to be applied morning and night and after a bowel movement

**CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- Anugesc-Hc (Pfizer Ltd)
  Hydrocortisone acetate 5 mg per 1 gram, Bismuth oxide 8.75 mg per 1 gram, Pramocaine hydrochloride 10 mg per 1 gram, Benzyl benzoate 12 mg per 1 gram, Peru Balsam 18.5 mg per 1 gram, Zinc oxide 123.5 mg per 1 gram Anugesc HC cream | 30 gram £3.71

**Cinchocaine hydrochloride with fluocortolone caproate and fluocortolone pivalate**

**INDICATIONS AND DOSE**

**Haemorrhoids | Pruritus ani**
- **BY RECTUM USING OINTMENT**
  - Adult: Apply twice daily for 5–7 days, apply 3–4 times a day if required, on the first day of treatment, then apply once daily for a few days after symptoms have cleared
  - **BY RECTUM USING SUPPOSITORIES**
  - Adult: Initially 1 suppository daily for 5–7 days, to be inserted after a bowel movement, then 1 suppository once daily on alternate days for 1 week

**CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**Suppository**
- Anusol-Hc (McNeil Products Ltd)
  Cinchocaine hydrochloride 1 mg, Fluocortolone pivalate 610 microgram, Fluocortolone pivalate 630 microgram Ultraproct suppositories | 12 suppository £4.06
- Anusol Plus HC suppositories | 12 suppository £6.30

**Ointment**
- Anusol-Hc (McNeil Products Ltd)
  Cinchocaine hydrochloride 5 mg per 1 gram, Fluocortolone pivalate 920 microgram per 1 gram, Fluocortolone caproate 950 microgram per 1 gram Ultraproct ointment | 30 gram £8.27

**Cinchocaine hydrochloride with hydrocortisone**

**INDICATIONS AND DOSE**

**PROCTOSEDYL® OINTMENT**

**Haemorrhoids | Pruritus ani**
- **TO THE SKIN, OR BY RECTUM**
  - Child: Apply twice daily, to be administered morning and night and after a bowel movement. Apply externally or by rectum. Do not use for longer than 7 days
  - Adult: Apply twice daily, to be administered morning and night and after a bowel movement. Apply externally or by rectum. Do not use for longer than 7 days

**PROCTOSEDYL® SUPPOSITORIES**

**Haemorrhoids | Pruritus ani**
- **BY RECTUM**
  - Child 12-17 years: 1 suppository, insert suppository night and morning and after a bowel movement. Do not use for longer than 7 days
  - Adult: 1 suppository, insert suppository night and morning and after a bowel movement. Do not use for longer than 7 days

**UNIROID-HC® OINTMENT**

**Haemorrhoids | Pruritus ani**
- **TO THE SKIN, OR BY RECTUM**
  - Child 12-17 years: Apply twice daily, and apply after a bowel movement, apply externally or by rectum, do not use for longer than 7 days
  - Adult: Apply twice daily, and apply after a bowel movement, apply externally or by rectum, do not use for longer than 7 days

**UNIROID-HC® SUPPOSITORIES**

**Haemorrhoids | Pruritus ani**
- **BY RECTUM**
  - Child 12-17 years: 1 suppository, insert twice daily and after a bowel movement. Do not use for longer than 7 days
  - Adult: 1 suppository, insert twice daily and after a bowel movement. Do not use for longer than 7 days

**CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)
Hydrocortisone with lidocaine

**INDICATIONS AND DOSE**

- **Haemorrhoids** | **Pruritus ani**
  - **BY RECTUM USING OINTMENT**
    - Adult: Apply twice daily for 5–7 days, apply 3–4 times a day on the first day if necessary, then apply once daily for a few days after symptoms have cleared
  - **BY RECTUM USING SUPPOSITORIES**
    - Adult: 1 suppository daily for 5–7 days, to be inserted after a bowel movement

- **Haemorrhoids (severe cases)** | **Pruritus ani (severe cases)**
  - **BY RECTUM USING SUPPOSITORIES**
    - Adult: Initially 1 suppository 2–3 times a day, then 1 suppository daily for a total of 5–7 days, to be inserted after a bowel movement

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Suppository**
  - **Scheriproct** (Bayer Plc)
    - Cinchocaine hydrochloride 1 mg, Prednisolone hexanoate 1.3 mg | 12 suppository [POM] £1.38 DT price = £1.38
  - **Ointment**
    - **Scheriproct** (Bayer Plc)
      - Prednisolone hexanoate 1.9 mg per 1 gram, Cinchocaine hydrochloride 5 mg per 1 gram | 30 gram [POM] £2.94 DT price = £2.94

**CAUTIONS**

Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

---

Hydrocortisone with pramocaine

**INDICATIONS AND DOSE**

- **Haemorrhoids** | **Pruritus ani**
  - **BY RECTUM**
    - Adult: 1 applicatorful 2–3 times a day and 1 applicatorful, after a bowel movement, do not use for longer than 7 days; maximum 4 applicatorfuls per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Foam**
  - **Proctofoam HC** (Meda Pharmaceuticals Ltd)
    - Hydrocortisone acetate 10 mg per 1 gram, Pramocaine hydrochloride 10 mg per 1 gram | 40 dose [POM] £6.07 DT price = £6.07

**SCLerosants**

**Phenol**

**INDICATIONS AND DOSE**

- **Haemorrhoids (particularly when unprolapsed)**
  - **BY SUBMUCOSAL INJECTION**
    - Adult: 2–3 mL, dose (using phenol 5%) to be injected into the submucosal layer at the base of the pile; several injections may be given at different sites, max. total injected 10 mL at any one time

**SIDE-EFFECTS**

Irritation - tissue necrosis

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Oily Phenol Injection, BP consists of phenol 5% in a suitable fixed oil.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - **Phenol (Non-proprietary)**
    - Phenol 50 mg per 1 ml Oily phenol 5% solution for injection 5ml ampoules | 10 ampoule [POM] £55.34
      - Oily phenol 5% solution for injection 2ml ampoules | 10 ampoule [POM] £38.03
10 Reduced exocrine secretions

PANCREATIC ENZYMES

Pancreatin

- **DRUG ACTION** Supplements of pancreatin are given to compensate for reduced or absent exocrine secretion. They assist the digestion of starch, fat, and protein.

- **INDICATIONS AND DOSE**

  - **CREON® 10000**
    - **Pancreatic insufficiency**
    - **BY MOUTH**
    - Child: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
    - Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

  - **CREON® 25000**
    - **Pancreatic insufficiency**
    - **BY MOUTH**
    - Child 2-17 years: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
    - Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

  - **CREON® 40000**
    - **Pancreatic insufficiency**
    - **BY MOUTH**
    - Child 2-17 years: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
    - Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

  - **CREON® MICRO**
    - **Pancreatic insufficiency**
    - **BY MOUTH**
    - Child: Initially 100 mg, to be taken before each feed or meal; granules can be mixed with a small amount of milk or soft food and administered immediately (manufacturer recommends mixing with acidic liquid or pureed fruit before administration), granules should not be chewed before swallowing
    - Adult: Initially 100 mg, to be taken before each feed or meal; granules can be mixed with a small amount of milk or soft food and administered immediately (manufacturer recommends mixing with acidic liquid or pureed fruit before administration), granules should not be chewed before swallowing

- **DOSE EQUIVALENCE AND CONVERSION**
  - For Creon® Micro: 100 mg granules = one measured scoopful (scoop supplied with product).

- **NUTRIZYM 22® GASTRO-RESISTANT CAPSULES**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Adult: Initially 1–2 capsules, dose to be taken with meals and 1 capsule as required, dose to be taken with snacks, doses should be swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing)

- **PANCREASE HL®**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Child 15-17 years: Initially 1–2 capsules, dose to be taken during each meal and 1 capsule, to be taken with snacks, all doses either taken whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing)
  - Adult: Initially 1–2 capsules, dose to be taken during each meal and 1 capsule, to be taken with snacks, all doses either taken whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing)

- **PANCREX®**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Child 2-17 years: 5–10 g, to be taken just before meals, washed down or mixed with milk or water
  - Adult: 5–10 g, to be taken just before meals, washed down or mixed with milk or water

- **PANCREX® V**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Child 1-11 months: 1–2 capsules, contents of capsule to be mixed with feeds
  - Child 1-17 years: 2–6 capsules, dose to be taken with each meal either swallowed whole or sprinkled on food
  - Adult: 2–6 capsules, dose to be taken with each meal either swallowed whole or sprinkled on food

- **PANCREX® V POWDER**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Child: 0.5–2 g, to be taken before or with meals, washed down or mixed with milk or water
  - Adult: 0.5–2 g, to be taken before or with meals, washed down or mixed with milk or water

- **PANCREX® V TABLETS**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Child 2-17 years: 5–15 tablets, to be taken before meals
  - Adult: 5–15 tablets, to be taken before meals

- **PANCREX® V TABLETS FORTE**

  - **Pancreatic insufficiency**
  - **BY MOUTH**
  - Child 2-17 years: 6–10 tablets, to be taken before meals
  - Adult: 6–10 tablets, to be taken before meals

- **CONTRA-INDICATIONS**
  - **PANCREASE HL®** Should not be used in children aged 15 years or less with cystic fibrosis
  - **NUTRIZYM 22® GASTRO-RESISTANT CAPSULES** Should not be used in children aged 15 years or less with cystic fibrosis

- **CAUTIONS** Can irritate the perioral skin and buccal mucosa if retained in the mouth; excessive doses can cause perianal irritation

- **INTERACTIONS** → Appendix 1 (pancreatin).

- **SIDE-EFFECTS** Abdominal discomfort, hyperuricaemia (associated with very high doses), hyperuricosuria (associated with very high doses), mucosal irritation, nausea, skin irritation, vomiting
Stoma care

11 Stoma care

Description of condition
A stoma is an artificial opening on the abdomen to divert flow of faeces or urine into an external pouch located outside of the body. This procedure may be temporary or permanent. Colostomy and ileostomy are the most common forms of stoma but a gastrostomy, jejunostomy, duodenostomy or caecostomy may also be performed. Understanding the type and extent of surgical intervention in each patient is crucial in managing the patient’s pharmaceutical needs correctly.

Overview
Prescribing for patients with stoma calls for special care due to modifications in drug delivery, resulting in a higher risk of sub-optimal absorption. The following is a brief account of some of the main points to be borne in mind.

Enteric-coated and modified-release medicines are unsuitable, particularly in patients with an ileostomy, as there may not be sufficient release of active ingredient. Soluble tablets, liquids, capsules or uncoated tablets are more suitable due to their quicker dissolution. When a solid-dose form such as a capsule or a tablet is given, the contents of the ostomy bag should be checked for any remnants.

Preparations containing sorbitol as an excipient should be avoided, due to its laxative side effects.

Analgesics
Opioid analgesics may cause troublesome constipation in colostomy patients. When a non-opioid analgesic is required, paracetamol is usually suitable. Anti-inflammatory analgesics may cause gastric irritation and bleeding; faecal output should be monitored for traces of blood.

Antacids
The tendency to diarrhoea from magnesium salts or constipation from aluminium or calcium salts may be increased in patients with stoma.

Antisecretory drugs
The gastric acid secretion often increases stoma output. Proton pump inhibitors and somatostatin analogues (octreotide p. 846 and lanreotide p. 845) are often used to reduce this risk.

Antidiarrhoeal drugs
Loperamide hydrochloride p. 63 and codeine phosphate p. 421 reduce intestinal motility and decrease water and sodium output from an ileostomy. Loperamide hydrochloride circulates through the enterohepatic circulation, which is disrupted in patients with a short bowel; high doses of loperamide hydrochloride may be required.
Codeine phosphate can be added if response with loperamide hydrochloride alone is inadequate.

**Digoxin**
Patients with a stoma are particularly susceptible to hypokalaemia if taking digoxin p. 103, due to fluid and sodium depletion. Potassium supplements or a potassium-sparing diuretic may be advisable with monitoring for early signs of toxicity.

**Diuretics**
Diuretics should be used with caution in patients with an ileostomy or with urostomy as they may become excessively dehydrated and potassium depletion may easily occur. It is usually advisable to use a potassium-sparing diuretic.

**Iron preparations**
Iron preparations may cause loose stools and sore skin in these patients. If this is troublesome and if iron is definitely indicated, an intramuscular iron preparation should be used. Modified-release preparations should be avoided for the reasons given above.

**Laxatives**
Laxatives should not be used in patients with an ileostomy where possible as they may cause rapid and severe loss of water and electrolytes.

Colostomy patients may suffer from constipation and whenever possible should be treated by increasing fluid intake or dietary fibre. Bulk-forming drugs can be tried. If they are insufficient, as small a dose as possible of a stimulant laxative such as senna p. 59 can be used with caution.

**Potassium supplements**
Liquid formulations are preferred to modified-release formulations. The daily dose should be split to avoid osmotic diarrhoea.

**Care of stoma**
Patients and their carers are usually given advice about the use of cleansing agents, protective creams, lotions, deodorants, or sealants whilst in hospital, either by the surgeon or by stoma care nurses. Voluntary organisations offer help and support to patients with stoma.
Chapter 2
Cardiovascular system

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1 Arrhythmias

Arrhythmias

Overview
Management of an arrhythmia requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment.

Ectopic beats
If ectopic beats are spontaneous and the patient has a normal heart, treatment is rarely required and reassurance to the patient will often suffice. If they are particularly troublesome, beta-blockers are sometimes effective and may be safer than other suppressant drugs.

Atrial fibrillation
Treatment of patients with atrial fibrillation aims to reduce symptoms and prevent complications, especially stroke. All patients with atrial fibrillation should be assessed for their risk of stroke and thromboembolism. Atrial fibrillation can be managed by either controlling the ventricular rate (‘rate control’) or by attempting to restore and maintain sinus rhythm (‘rhythm control’). At any stage if treatment fails to control symptoms, or, if symptoms reoccur after cardioversion and specialised management is required, referral should be made within 4 weeks. If drug treatment fails to control the symptoms of atrial fibrillation or is unsuitable, ablation strategies can be considered. Review anticoagulation, stroke, and bleeding risk at least annually in all patients with atrial fibrillation.

Acute presentation
All patients with life-threatening haemodynamic instability caused by new-onset atrial fibrillation should undergo emergency electrical cardioversion without delaying to achieve anticoagulation. In patients presenting acutely but without life-threatening haemodynamic instability, rate or rhythm control can be offered if the onset of arrhythmia is less than 48 hours; rate control is preferred if onset is more than 48 hours or uncertain. Consideration of pharmacological or electrical cardioversion should be based on clinical circumstances. If pharmacological cardioversion has been agreed, intravenous amiodarone hydrochloride p. 99, or alternatively flecainide acetate p. 97, can be used (amiodarone hydrochloride is preferred if there is structural heart disease). If urgent rate control is required, a beta-blocker or verapamil hydrochloride p. 155 can be given intravenously.

Cardioversion
Sinus rhythm can be restored by electrical cardioversion, or pharmacological cardioversion with an oral or intravenous antiarrhythmic drug e.g. flecainide acetate or amiodarone hydrochloride. If atrial fibrillation has been present for more than 48 hours, electrical cardioversion is preferred and should not be attempted until the patient has been fully anticoagulated for at least 3 weeks; if this is not possible, parenteral anticoagulation should be commenced, and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks; prior to cardioversion, offer rate control as appropriate.

Drug treatment
Rate control is the preferred first-line drug treatment strategy for atrial fibrillation except in patients with new-onset atrial fibrillation, heart failure secondary to atrial fibrillation, atrial flutter suitable for an ablation strategy, atrial fibrillation with a reversible cause, or if rhythm control is more suitable based on clinical judgement. Ventricular rate can be controlled with a standard beta-blocker (not sotalol hydrochloride p. 102) or a rate-limiting calcium channel blocker such as diltiazem hydrochloride p. 148 [unlicensed indication], or verapamil hydrochloride as monotherapy. Choice of drug should be based on individual symptoms, heart rate, comorbidities, and patient preference. Digoxin p. 103 is usually only effective for controlling the ventricular rate at rest, and should therefore only be used as monotherapy in predominantly sedentary patients with non-paroxysmal atrial fibrillation. When a single drug fails to adequately control the ventricular rate, a combination of two drugs including a beta-blocker, digoxin, or diltiazem hydrochloride can be used. If symptoms are not controlled with a combination of two drugs, a rhythm-control strategy should be considered. If ventricular function is diminished, the combination of a beta-blocker (that is licensed for use in heart failure) and digoxin is preferred. Digoxin is also used when atrial fibrillation is accompanied by congestive heart failure.
If drug treatment is required to maintain sinus rhythm (‘rhythm control’) post-cardioversion, a standard beta-blocker is used. If a standard beta-blocker is not appropriate or is ineffective, consider an oral anti-arrhythmic drug such as sotalol hydrochloride, flecainide acetate, propafenone hydrochloride p. 98, or amiodarone hydrochloride; dronedarone p. 100 may be considered in paroxysmal or persistent atrial fibrillation (see NICE guidance). If necessary, amiodarone hydrochloride can be started 4 weeks before and continuing for up to 12 months after electrical cardioversion to increase success of the procedure, and to maintain sinus rhythm. Flecainide acetate or propafenone hydrochloride should not be given when there is known ischaemic or structural heart disease. Consider amiodarone hydrochloride in patients with left ventricular impairment or heart failure.

### Paroxysmal atrial fibrillation

In symptomatic paroxysmal atrial fibrillation, ventricular rhythm is controlled with a standard beta-blocker. Alternatively, if symptoms persist or a standard beta-blocker is not appropriate, an oral anti-arrhythmic drug such as dronedarone (see NICE guidance), sotalol hydrochloride, flecainide acetate, propafenone hydrochloride, or amiodarone hydrochloride can be given (see also Paroxysmal supraventricular tachycardia and Supraventricular arrhythmias). In selected patients with infrequent episodes of symptomatic paroxysmal atrial fibrillation, sinus rhythm can be restored using the ‘pill-in-the-pocket’ approach; this involves the patient taking oral flecainide acetate or propafenone hydrochloride to self-treat an episode of atrial fibrillation when it occurs.

### Stroke prevention

All patients with atrial fibrillation should be assessed for their risk of stroke and the need for thromboprophylaxis; this needs to be balanced with the patient’s risk of bleeding; a NICE guideline (NICE clinical guideline 180 (June 2014)). Atrial fibrillation: The management of atrial fibrillation recommends using the CHA2DS2-VASc assessment tool for stroke risk and the HAS-BLED tool for bleeding risk prior to anticoagulation. Risk factors for stroke taken into account by CHA2DS2-VASc include prior ischaemic stroke, transient ischaemic attacks, or thromboembolic events, heart failure, left ventricular systolic dysfunction, vascular disease, diabetes, hypertension, females, and patients over 65 years. Patients with a very low risk of stroke (CHA2DS2-VASc score of 0 for men or 1 for women) do not require any antithrombotic for stroke prevention. Parenteral anticoagulation should be offered to patients with new-onset atrial fibrillation who are receiving subtherapeutic or no anticoagulation therapy until assessment is made, and appropriate anticoagulation is started. Oral anticoagulation should be offered to patients with confirmed diagnosis of atrial fibrillation in whom sinus rhythm has not been successfully restored within 48 hours of onset, patients who have had, or are at high risk of recurrence of atrial fibrillation such as those with structural heart disease, prolonged history of atrial fibrillation (more than 12 months), a history of failed attempts at cardioversion, and patients whom the risk of stroke outweighs the risk of bleeding. Anticoagulation treatment should not be withheld solely because of the risk of falls, and choice of treatment should be based on clinical features and patient preferences. Oral anticoagulation may be with a vitamin K antagonist (e.g. warfarin sodium p. 131, or in non-valvular atrial fibrillation with apixaban p. 117, dabigatran etexilate p. 128, or rivaroxaban p. 120. Anticoagulants are also indicated during cardioversion procedures. Aspirin p. 114 is less effective than warfarin sodium at preventing emboli; the modest benefit is offset by the risk of bleeding, and aspirin should not be offered as monotherapy solely for stroke prevention in atrial fibrillation. If anticoagulant treatment is contra-indicated or not tolerated, left atrial appendage occlusion can be considered.

### Atrial flutter

Like atrial fibrillation, treatment options for atrial flutter involve either controlling the ventricular rate or attempting to restore and maintain sinus rhythm. However, atrial flutter generally responds less well to drug treatment than atrial fibrillation.

Control of the ventricular rate is usually an interim measure pending restoration of sinus rhythm. Ventricular rate can be controlled by administration of a beta-blocker, diltiazem hydrochloride p. 148 [unlicensed indication], or verapamil hydrochloride p. 155; an intravenous beta-blocker or verapamil hydrochloride is preferred for rapid control. Digoxin p. 103 can be added if rate control remains inadequate, and may be particularly useful in those with heart failure.

Conversion to sinus rhythm can be achieved by electrical cardioversion (by cardiac pacing or direct current), pharmacological cardioversion, or catheter ablation. If the duration of atrial flutter is unknown, or it has lasted for over 48 hours, cardioversion should not be attempted until the patient has been fully anticoagulated for at least 3 weeks; if this is not possible, parenteral anticoagulation should be commenced and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks.

Direct current cardioversion is usually the treatment of choice when rapid conversion to sinus rhythm is necessary (e.g. when atrial flutter is associated with haemodynamic compromise); catheter ablation is preferred for the treatment of recurrent atrial flutter. There is a limited role for anti-arrhythmic drugs as their use is not always successful. Flecainide acetate p. 97 or propafenone hydrochloride p. 98 can slow atrial flutter, resulting in 1:1 conduction to the ventricles, and should therefore be prescribed in conjunction with a ventricular rate controlling drug such as a beta-blocker, diltiazem hydrochloride [unlicensed indication], or verapamil hydrochloride. Amiodarone hydrochloride p. 99 can be used when other drug treatments are contra-indicated or ineffective.

All patients should be assessed for their risk of stroke and the need for thromboprophylaxis; the choice of anticoagulant is based on the same criteria as for atrial fibrillation.

### Paroxysmal supraventricular tachycardia

This will often terminate spontaneously or with reflex vagal stimulation such as a Valsalva manoeuvre, immersing the face in ice-cold water, or carotid sinus massage; such manoeuvres should be performed with ECG monitoring. If the effects of reflex vagal stimulation are transient or ineffective, or if the arrhythmia is causing severe symptoms, intravenous adenosine p. 101 should be given. If adenosine is ineffective or contra-indicated, intravenous verapamil hydrochloride is an alternative, but it should be avoided in patients recently treated with beta-blockers.

Failure to terminate paroxysmal supraventricular tachycardia with reflex vagal stimulation or drug treatment may suggest an arrhythmia of atrial origin, such as focal atrial tachycardia or atrial flutter.

Treatment with direct current cardioversion is needed in haemodynamically unstable patients or when the above measures have failed to restore sinus rhythm (and an alternative diagnosis has not been found).

Recurrent episodes of paroxysmal supraventricular tachycardia can be treated by catheter ablation, or prevented with drugs such as diltiazem hydrochloride, verapamil hydrochloride, beta-blockers including sotalol hydrochloride p. 102, flecainide acetate or propafenone hydrochloride.
Arrhythmias after myocardial infarction

In patients with a paroxysmal tachycardia or rapid irregularity of the pulse it is best not to administer an anti-arrhythmic until an ECG record has been obtained. Bradycardia, particularly if complicated by hypotension, should be treated with an intravenous dose of atropine sulfate p. 1022 the dose may be repeated if necessary. If there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine sulfate, adrenaline/epinephrine p. 211 should be given by intravenous infusion, and the dose adjusted according to response.

For further advice, refer to the most recent recommendations of the Resuscitation Council (UK) available at www.resus.org.uk.

Ventricular tachycardia

Pulseless ventricular tachycardia or ventricular fibrillation should be treated with immediate defibrillation (see Cardiopulmonary resuscitation).

Patients with unstable sustained ventricular tachycardia, who continue to deteriorate with signs of hypotension or reduced cardiac output, should receive direct current cardioversion to restore sinus rhythm. If this fails, intravenous amiodarone hydrochloride should be administered and direct current cardioversion repeated.

Patients with sustained ventricular tachycardia who are haemodynamically stable can be treated with intravenous anti-arrhythmic drugs. Amiodarone hydrochloride is the preferred drug. Flecainide acetate, propafenone hydrochloride, and, although less effective, lidocaine hydrochloride p. 97 have all been used. If sinus rhythm is not restored, direct current cardioversion or pacing should be considered. Cather ablation is an alternative if cessation of the arrhythmia is not urgent. Non-sustained ventricular tachycardia can be treated with a beta-blocker.

All patients presenting with ventricular tachycardia should be referred to a specialist. Following restoration of sinus rhythm, patients who remain at high risk of cardiac arrest will require maintenance therapy. Most patients will be treated with an implantable cardioverter defibrillator. Beta-blockers or sotalol hydrochloride (in place of a standard beta-blocker), or amiodarone hydrochloride (in combination with a standard beta-blocker), can be used in addition to the device in some patients; alternatively, they can be used alone when use of an implantable cardioverter defibrillator is not appropriate.

Torsade de pointes

Torsade de pointes is a form of ventricular tachycardia associated with a long QT syndrome (usually drug-induced, but other factors including hypokalaemia, severe bradycardia, and genetic predisposition are also implicated). Episodes are usually self-limiting, but are frequently recurrent and can cause impairment or loss of consciousness. If not controlled, the arrhythmia can progress to ventricular fibrillation and sometimes death. Intravenous infusion of magnesium sulfate p. 924 is usually effective. A beta-blocker (but not sotalol hydrochloride) and atrial (or ventricular) pacing can be considered. Anti-arrhythmic can further prolong the QT interval, thus worsening the condition.

Drugs for arrhythmias

Anti-arrhythmic drugs can be classified clinically into those that act on supraventricular arrhythmias (e.g. verapamil hydrochloride), those that act on both supraventricular and ventricular arrhythmias (e.g. amiodarone hydrochloride), and those that act on ventricular arrhythmias (e.g. lidocaine hydrochloride).

Anti-arrhythmic drugs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

- **Class I**: membrane stabilising drugs (e.g. lidocaine, flecainide)
- **Class II**: beta-blockers
- **Class III**: amiodarone; sotalol (also Class II)
- **Class IV**: calcium-channel blockers (includes verapamil but not dihydropyridines)

The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired. Most drugs that are effective in countering arrhythmias can also provoke them in some circumstances; moreover, hypokalaemia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.

Supraventricular arrhythmias

Adenosine p. 101 is usually the treatment of choice for terminating paroxysmal supraventricular tachycardia. As it has a very short duration of action (half-life only about 8 to 10 seconds, but prolonged in those taking dipyridamole p. 116), most side-effects are short lived. Unlike verapamil hydrochloride p. 155, adenosine can be used after a beta-blocker. Verapamil hydrochloride may be preferable to adenosine in asthma.

Oral administration of a **cardiac glycoside** (such as digoxin p. 103) slows the ventricular response in cases of atrial fibrillation and atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate. Cardiac glycosides are contra-indicated in supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome).

Verapamil hydrochloride is usually effective for supraventricular tachycardias. An initial intravenous dose (**important**: serious beta-blocker interaction hazard) may be followed by oral treatment; hypotension may occur with large doses. It should not be used for tachyarrhythmias where the QRS complex is wide (i.e. broad complex) unless a supraventricular origin has been established beyond reasonable doubt. It is also contra-indicated in atrial fibrillation or atrial flutter associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). It should not be used in children with arrhythmias without specialist advice; some supraventricular arrhythmias in childhood can be accelerated by verapamil hydrochloride with dangerous consequences.

Intravenous administration of a **beta-blocker** such as esmolol hydrochloride p. 145 or propranolol hydrochloride p. 142, can achieve rapid control of the ventricular rate. Drugs for both supraventricular and ventricular arrhythmias include amiodarone hydrochloride p. 99, beta-blockers, disopyramide p. 96, flecainide acetate p. 97, procainamide (available from 'special-order' manufacturers or specialist importing companies), and propafenone hydrochloride p. 98.

Supraventricular and ventricular arrhythmias

Amiodarone hydrochloride is used in the treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated. It can be used for paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It can also be used for tachyarrhythmias associated with Wolff-Parkinson-White syndrome. It should be initiated only under hospital or specialist supervision. Amiodarone hydrochloride may be given by intravenous infusion as well as by mouth, and has the advantage of causing little or no myocardial depression. Unlike oral amiodarone hydrochloride, intravenous amiodarone hydrochloride acts relatively rapidly.

Intravenous injection of amiodarone hydrochloride can be used in cardiopulmonary resuscitation for ventricular
fibrillation or pulseless tachycardia unresponsive to other interventions.

Amiodarone hydrochloride has a very long half-life (extending to several weeks) and only needs to be given once daily (but high doses can cause nausea unless divided). Many weeks or months may be required to achieve steady-state plasma-amiodarone concentration; this is particularly important when drug interactions are likely.

Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. Sotalol has a role in the management of ventricular arrhythmias.

Disopyramide can be given by intravenous injection to control arrhythmias after myocardial infarction (including those not responding to lidocaine hydrochloride p. 97), but it impairs cardiac contractility. Oral administration of disopyramide is useful, but it has an antimuscarinic effect which limits its use in patients susceptible to angle-closure glaucoma or with prostatic hyperplasia.

Flecainide acetate belongs to the same general class as lidocaine hydrochloride and may be of value for serious symptomatic ventricular arrhythmias. It may also be indicated for junctional re-entry tachycardias and for paroxysmal atrial fibrillation. However, it can precipitate serious arrhythmias in a small minority of patients (including those with otherwise normal hearts).

Propafenone hydrochloride is used for the prophylaxis and treatment of ventricular arrhythmias and also for some supraventricular arrhythmias. It has complex mechanisms of action, including weak beta-blocking activity (therefore caution is needed in obstructive airways disease—contra-indicated if severe).

Drugs for supraventricular arrhythmias include adenosine, cardiac glycosides, and verapamil hydrochloride. Drugs for ventricular arrhythmias include lidocaine hydrochloride.

Mexitel and procarainamide are both available from ‘special-order’ manufacturers or specialist importing companies. Mexitel can be used for life-threatening ventricular arrhythmias; procainamide is given by intravenous injection to control ventricular arrhythmias.

Ventricular arrhythmias

Intravenous lidocaine hydrochloride can be used for the treatment of ventricular tachycardia in haemodynamically stable patients, and ventricular fibrillation and pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation, however it is no longer the anti-arrhythmic drug of first choice.

Drugs for both supraventricular and ventricular arrhythmias include amiodarone hydrochloride, beta-blockers, disopyramide, flecainide acetate, procarainamide (available from ‘special-order’ manufacturers or specialist importing companies), and propafenone hydrochloride.

Mexitel is available from ‘special-order’ manufacturers or specialist importing companies for treatment of life-threatening ventricular arrhythmias.

Other drugs used for Arrhythmias

Acebutolol, p. 143
Atenolol, p. 143
Metoprolol tartrate, p. 145
Nadolol, p. 141
Oxeprenol hydrochloride, p. 141

ANTIARRHYTHMICS > CLASS IA

Disopyramide

- INDICATIONS AND DOSE
  Prevention and treatment of ventricular and supraventricular arrhythmias, including after myocardial infarction | Maintenance of sinus rhythm after cardioversion
  - BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
    - Adult: 300—800 mg daily in divided doses
  - BY MOUTH USING MODIFIED-RELEASE MEDICINES
    - Adult: 250—375 mg every 12 hours

- CONTRA-INDICATIONS
  Bundle-branch block associated with first-degree AV block | second- and third-degree AV block or bifascicular block (unless pacemaker fitted) | severe heart failure (unless secondary to arrhythmia) | severe sinus node dysfunction

- CAUTIONS
  Atrial flutter or atrial tachycardia with partial block | avoid in acute porphyrias p. 930 | elderly | heart failure (avoid if severe) | myasthenia gravis | prostatic enlargement | structural heart disease | susceptibility to angle-closure glaucoma

- INTERACTIONS
  → Appendix 1 (disopyramide).

- SIDE-EFFECTS
  Angle-closure glaucoma | antimuscarinic effects | AV block | blurred vision | cholestatic jaundice | dry mouth | gastro-intestinal irritation | hypoglycaemia | hypotension | myocardial depression | psychosis | urinary retention | ventricular tachycardia | ventricular fibrillation or torsade de pointes (usually associated with prolongation of QRS complex or QT interval)

- PREGNANCY
  Manufacturer advises use only if potential benefit outweighs risk; may induce labour if used in third trimester.

- BREAST FEEDING
  Present in milk—use only if essential.

  Monitor infant for antimuscarinic effects.

- HEPATIC IMPAIRMENT
  Half-life prolonged—may need dose reduction. Avoid modified-release preparation.

- RENAL IMPAIRMENT
  Reduce dose by increasing dose interval; adjust according to response. Avoid modified-release preparation.

- MONITORING REQUIREMENTS
  Monitor for hypotension, hypoglycaemia, ventricular tachycardia, ventricular fibrillation or torsade de pointes (discontinue if occur).

  Monitor serum potassium.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

  Modified-release tablet

  CAUTIONARY AND ADVISORY LABELS 25
  - Rythmodan Retard (Sanofi)
    Disopyramide (as Disopyramide phosphate) 250 mg Rythmodan Retard 250mg tablets | 60 tablet £32.08 DT price = £32.08
  - Capsule
    - Rythmodan (Sanofi)
      Disopyramide 100 mg Rythmodan 100mg capsules | 84 capsule £22.09

  Disopyramide 150 mg Disopyramide 150mg capsules | 84 capsule £33.40 DT price = £27.58

  Disopyramide 100 mg Rythmodan 100mg capsules | 84 capsule £14.14 DT price = £22.09
ANTIARRHYTHMICS › CLASS IB

Lidocaine hydrochloride
(Lignocaine hydrochloride)

● INDICATIONS AND DOSE
Cardiopulmonary resuscitation (as an alternative if amiodarone is not available)
▶ BY INTRAVENOUS INJECTION
Adult: 1 mg/kg, do not exceed 3 mg/kg over the first hour
Ventricular arrhythmias, especially after myocardial infarction in patients without gross circulatory impairment
▶ INITIALLY BY INTRAVENOUS INJECTION
Adult: 100 mg, to be given as a bolus dose over a few minutes, followed immediately by (by intravenous infusion) 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then (by intravenous infusion) 1 mg/minute, reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion), following intravenous injection lidocaine has a short duration of action (lasting for 15–20 minutes). If an intravenous infusion is not immediately available the initial intravenous injection of 100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes
Ventricular arrhythmias, especially after myocardial infarction in lighter patients or those whose circulation is severely impaired
▶ INITIALLY BY INTRAVENOUS INJECTION
Adult: Initially 50 mg, to be given as a bolus dose over a few minutes, followed immediately by (by intravenous infusion) 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then (by intravenous infusion) 1 mg/minute, reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion), following intravenous injection lidocaine has a short duration of action (lasting for 15–20 minutes). If an intravenous infusion is not immediately available the initial intravenous injection of 50 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

● CONTRA-INDICATIONS
All grades of atioventricular block • severe myocardial depression • sino-atrial disorders

● CAUTIONS
Acute porphyria (consider infusion with glucose for its anti-porphyrinogenic effects) • congestive cardiac failure (consider lower dose) • post cardiac surgery (consider lower dose)

● INTERACTIONS
▶ Appendix 1 (lidocaine).

● SIDE-EFFECTS
▶ Common or very common
Bradycardia (may lead to cardiac arrest) • confusion • convulsions • dizziness (particularly if injection too rapid) • drowsiness (particularly if injection too rapid) • hypotension (may lead to cardiac arrest) • paraesthesia (particularly if injection too rapid) • respiratory depression
▶ Rare
Anaphylaxis

● PREGNANCY
Crosses the placenta but not known to be harmful in animal studies—use if benefit outweighs risk.

● BREAST FEEDING
Present in milk but amount too small to be harmful.

● HEPATIC IMPAIRMENT
Caution—increased risk of side-effects.

● RENAL IMPAIRMENT
Possible accumulation of lidocaine and active metabolite; caution in severe impairment.

● MONITORING REQUIREMENTS
Monitor ECG and have resuscitation facilities available.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
▶ Lidocaine hydrochloride (Non-proprietary)
Lidocaine hydrochloride 5 mg per 1 ml Lidocaine 50mg/10ml (0.5%) solution for injection ampoules | 10 ampoule (PSt) £7.00
Lidocaine hydrochloride 10 mg per 1 ml Lidocaine 100mg/10ml (1%) solution for injection Mini-Plasco ampoules | 20 ampoule (PSt) £10.89
Lidocaine 100mg/10ml (1%) solution for injection ampoules | 10 ampoule (PSt) £4.40 DT price = £4.01
Lidocaine 100mg/10ml (1%) solution for injection Sure-Amp ampoules | 20 ampoule (PSt) £8.80
Lidocaine 200mg/20ml (1%) solution for injection vials | 10 vial (PSt) £9.00
Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 ampoule (PSt) £7.00–£9.63 DT price = £8.75
Lidocaine 50mg/5ml (1%) solution for injection ampoules | 10 ampoule (PSt) £2.35–£3.10 DT price = £2.36
Lidocaine 20mg/2ml (1%) solution for injection ampoules | 10 ampoule (PSt) £3.50 DT price = £1.98
Lidocaine 50mg/5ml (1%) solution for injection Sure-Amp ampoules | 20 ampoule (PSt) £8.00
Lidocaine hydrochloride 20 mg per 1 ml Lidocaine 100mg/5ml (2%) solution for injection ampoules | 10 ampoule (PSt) £2.40–£3.80 DT price = £2.41
Lidocaine 400mg/20ml (2%) solution for injection vials | 10 vial (PSt) £19.50
Lidocaine 200mg/10ml (2%) solution for injection Mini-Plasco ampoules | 20 ampoule (PSt) £14.52
Lidocaine 40mg/2ml (2%) solution for injection ampoules | 10 ampoule (PSt) £4.00 DT price = £2.11
Lidocaine 100mg/5ml (2%) solution for injection Sure-Amp ampoules | 20 ampoule (PSt) £6.00
Lidocaine 400mg/20ml (2%) solution for injection ampoules | 10 ampoule (PSt) £8.00–£9.90 DT price = £9.00

ANTIARRHYTHMICS › CLASS IC

Flecainide acetate

● INDICATIONS AND DOSE
AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily) (specialist supervision in hospital) | Ventricular tachyarrhythmias resistant to other treatment (specialist supervision in hospital)
▶ INITIALLY BY SLOW INTRAVENOUS INJECTION
Adult: Initially 2 mg/kg (max. per dose 150 mg), to be given over 10–30 minutes with ECG monitoring, followed by (by intravenous infusion) 1.5 mg/kg/hour if required for 1 hour, then (by intravenous infusion) reduced to 0.100–250 micrograms/kg/hour for up to 24 hours, maximum cumulative dose of 600 mg in first 24 hours, then transfer to oral treatment

Supraventricular arrhythmias
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: Initially 50 mg twice daily, increased if necessary up to 300 mg daily
▶ BY MOUTH USING MODIFIED-RELEASE MEDICINES
Adult: 200 mg daily

Ventricular arrhythmias (initiated under direction of hospital consultant)
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: Initially 100 mg twice daily for 3–5 days, maximum 400 mg daily reserved for rapid control or in heavily built patients; for maintenance, reduce to the lowest dose that controls the arrhythmia continued →
DOSE EQUIVALENCE AND CONVERSION
- Patients stabilised on 200 mg daily immediate-release flecainide may be transferred to modified-release medicines.

- **UNEQUALIZED USE** Capsules, tablets and injection: licensed for AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff–Parkinson–White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily). Immediate-release tablets only: licensed for symptomatic sustained ventricular tachycardia, disabling symptoms of premature ventricular contractions and/or non-sustained ventricular tachycardia in patients resistant to or intolerant of other therapy. Injection only: licensed for ventricular tachyarrhythmias resistant to other treatment.

- **CONTRA-INDICATIONS** Abnormal left ventricular function • atrial conduction defects (unless pacing rescue available) • bundle branch block (unless pacing rescue available) • control of arrhythmias in acute situations (for modified-release forms only) • distal block (unless pacing rescue available) • haemodynamically significant valvular heart disease • heart failure • history of myocardial infarction and either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia • long-standing atrial fibrillation where conversion to sinus rhythm not attempted • second-degree or greater AV block (unless pacing rescue available) • sinus node dysfunction (unless pacing rescue available)

- **CAUTIONS** Atrial fibrillation following heart surgery • elderly (accumulation may occur) • patients with pacemakers (especially those who may be pacemaker dependent because stimulation threshold may rise appreciably)

- **INTERACTIONS** → Appendix 1 (flecainide).

- **SIDE-EFFECTS**
  - Common or very common A thrombocytopeia • tinnitus • tremor • urticaria • vertigo
  - Rare Anemia • anorexia • anxiety • ataxia • concomitant antidepressants • fatigue • fever • oedema • pro-arrhythmic effects • visual disturbances
  - Frequency not known Anaemia • anorexia • anxiety • ataxia • concomitant antidepressants • drowsiness • flushing • gastrointestinal disturbances • headache • hepatic dysfunction • hypersensitivity reactions • increased antimalarial • increased sweating • insomnia • leucopenia • paraesthesia • photosensitivity • rash • syncope • thrombocytopeia • tremor • urticaria • vertigo

- **PREGNANCY** Used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in animal studies; infant hyperbilirubinemia also reported.

- **BREAST FEEDING** Significant amount present in milk but not known to be harmful.

- **HEPATIC IMPAIRMENT** Avoid or reduce dose in severe impairment.

- **RENAL IMPAIRMENT** Reduce initial oral dose to max. 100 mg daily or reduce intravenous dose by 50%, if eGFR less than 35 ml/minute/1.73 m².

- **MONITORING REQUIREMENTS** With intravenous use ECG monitoring and resuscitation facilities must be available.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Tambocor®), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%. Minimum volume in infusion fluids containing chlorides 500 ml.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Tablet**
  - **Flecainide acetate (Non-proprietary)**
    - Flecainide acetate 50 mg Flecainide 50mg tablets [60 tablet POM] £13.50 DT price = £6.82
    - Flecainide acetate 100 mg Flecainide 100mg tablets [60 tablet POM] £17.65 DT price = £7.23
  - **Tambocor** (Meda Pharmaceuticals Ltd)
    - Flecainide acetate 50 mg Tambocor 50mg tablets [60 tablet POM] £11.57 DT price = £5.82
    - Flecainide acetate 100 mg Tambocor 100mg tablets [60 tablet POM] £16.53 DT price = £7.23

  **Modified-release capsule**
  CAUTIONARY AND ADVISORY LABELS 25
  - **Tambocor XL** (Meda Pharmaceuticals Ltd)
    - Flecainide acetate 200 mg Tambocor XL 200mg capsules [30 capsule POM] £14.77

  **Solution for injection**
  - **Tambocor** (Meda Pharmaceuticals Ltd)
    - Flecainide acetate 10 mg per 1 ml Tambocor 150mg/15ml solution for injection ampoules [5 ampoule POM] £21.99

**Propafenone hydrochloride**

- **INDICATIONS AND DOSE**
  Ventricular arrhythmias (specialist supervision in hospital) Paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter or fibrillation and paroxysmal re-entrant tachycardias involving the AV node or accessory pathway, where standard therapy ineffective or contra-indicated (specialist supervision in hospital)
  - **BY MOUTH**
    - Adult: Initially 150 mg 3 times a day, dose to be taken after food, monitor ECG and blood pressure, if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits; increased if necessary to 300 mg twice daily (max. per dose 300 mg 3 times a day), dose to be increased at intervals of at least 3 days, reduce total daily dose for patients under 70 kg
    - Elderly: Initially 150 mg 3 times a day, dose to be taken after food, monitor ECG and blood pressure, if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits; increased if necessary to 300 mg twice daily (max. per dose 300 mg 3 times a day), dose to be increased at intervals of at least 5 days, reduce total daily dose for patients under 70 kg

- **CONTRA-INDICATIONS** Atrial conduction defects (unless adequately paced) • Brugada syndrome • bundle branch block (unless adequately paced) • cardiogenic shock (except arrhythmia induced) • distal block (unless adequately paced) • electrolyte disturbances • marked hypotension • myasthenia gravis • myocardial infarction within last 3 months • second degree or greater AV block (unless adequately paced) • severe bradycardia • severe obstructive pulmonary disease (due to weak beta-blocking activity) • sinus node dysfunction (unless adequately paced) • uncontrolled congestive heart failure with left ventricular ejection fraction less than 35%

- **CAUTIONS** Elderly • great caution in mild to moderate obstructive airways disease owing to beta-blocking activity • heart failure • pacemaker patients • potential for conversion of paroxysmal atrial fibrillation to atrial flutter with 2:1 or 1:1 conduction block.

- **INTERACTIONS** → Appendix 1 (propafenone).
ANTIARRHYTHMICS 》 CLASS III

Amiodarone hydrochloride

● INDICATIONS AND DOSE

Treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated (including paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, ventricular fibrillation, and tachyarrhythmias associated with Wolff-Parkinson-White syndrome) (initiated in hospital or under specialist supervision)

► BY MOUTH
► Adult: 200 mg 3 times a day for 1 week, then reduced to 200 mg twice daily for a further week, followed by maintenance dose, usually 200 mg daily or the minimum dose required to control arrhythmia
► BY INTRAVENOUS INFUSION
► Adult: Initially 5 mg/kg, to be given over 20–120 minutes with ECG monitoring, subsequent infusions given if necessary according to response; maximum 1.2 g per day

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation (for cardiopulmonary resuscitation)

► INITIALLY BY INTRAVENOUS INJECTION
► Adult: Initially 300 mg, dose to be considered after administration of adrenaline, dose should be given from a pre-filled syringe or diluted in 20 mL glucose 5%, then (by intravenous injection) 150 mg if required, followed by (by intravenous infusion) 900 mg/24 hours

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVISE: SOFOSBUVIR WITH DACLATASVIR; SOFOSBUVIR AND LEDIPASVIR (MAY 2015); SIMEPREVIR WITH SOFOSBUVIR (AUGUST 2015): RISK OF SEVERE BRADYCARDIA AND HEART BLOCK WHEN TAKEN WITH AMIODARONE

Avoid concomitant use unless other antiarrhythmics cannot be given.

● CONTRA-INDICATIONS

GENERAL CONTRA-INDICATIONS

Avoid in severe conduction disturbances (unless pacemaker fitted) - avoid in sinus node disease (unless pacemaker fitted) - iodine sensitivity - sino-atrial heart block (except in cardiac arrest) - sinus bradycardia (except in cardiac arrest) - thyroid dysfunction

SPECIFIC CONTRA-INDICATIONS

► With intravenous use

Avoid bolus injection in cardiomyopathy - avoid bolus injection in congestive heart failure - avoid in circulatory collapse - avoid in severe arterial hypotension - avoid in severe respiratory failure

● CAUTIONS

GENERAL CAUTIONS

Acute porphyrias p.930 - conduction disturbances (in excessive dosage) - elderly - heart failure - hypokalaemia - severe bradycardia (in excessive dosage)

SPECIFIC CAUTIONS

► With intravenous use

Moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) - severe hepatocellular toxicity

● INTERACTIONS

Appendix 1 (amiodarone).

Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped. Use extreme caution or avoid concomitant use of drugs that prolong QT interval.

● SIDE-EFFECTS

GENERAL SIDE-EFFECTS

► Common or very common

Bradycardia - hyperthyroidism - hypothyroidism - jaundice - nausea - persistent slate grey skin discoloration - phototoxicity - pulmonary toxicity (including pneumonitis and fibrosis) - raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders) - reversible corneal microdeposits (sometimes with night glare) - sleep disorders - taste disturbances - tremor - vomiting
► Very rare

Alopecia - aplastic anaemia - ataxia - benign intracranial hypertension - bronchospasm (in patients with severe respiratory failure) - chronic liver disease - cirrhosis - epiderdymo-orchitis - exfoliative dermatitis - haemolytic anaemia - headache - hypersensitivity - impairement of vision due to optic neuritis or optic neuropathy (including blindness) - impotence - rash - sinus arrest - thrombocytopenia - vasculitis - vertigo
► Frequency not known

Hot flushes - hypotension - respiratory distress syndrome - sweating

SPECIFIC SIDE-EFFECTS

► Common or very common

With intravenous use

Injection-site reactions
► Very rare

With intravenous use

Anaphylaxis on rapid injection
**SIDE-EFFECTS, FURTHER INFORMATION**

- **Corneal microdeposits** Most patients taking amiodarone develop corneal microdeposits (reversible on withdrawal of treatment); these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought.
- **Thyroid function** Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can occur. Thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.
- **Hepatotoxicity** Amiodarone is also associated with hepatotoxicity and treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop.
- **Pulmonary toxicity** Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone.
- **Peripheral neuropathy** Fresh neurological symptoms should raise the possibility of peripheral neuropathy.
- **PREGNANCY** Possible risk of neonatal goitre; use only if no alternative.
- **BREAST FEEDING** Avoid; present in milk in significant amounts; theoretical risk of neonatal hypothyroidism from release of iodine.

**MONITORING REQUIREMENTS**

- **Thyroid function tests** should be performed before treatment and then every 6 months. Clinical assessment of thyroid function alone is unreliable. Thyroxine (T4) may be raised in the absence of hyperthyroidism; therefore triiodothyronine (T3), T4, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis.
- **Liver function tests** required before treatment and then every 6 months.
- **Serum potassium concentration** should be measured before treatment.
- **Chest X-ray** required before treatment.
- **With intravenous use** ECG monitoring and resuscitation facilities must be available. Monitor liver transaminases closely.

If concomitant use of amiodarone with sofosbuvir and daclatasvir, simprevir and sofosbuvir, or sofosbuvir and ledipasvir, patients and their carers should be told how to recognise signs and symptoms of bradycardia and heart block and advised to seek immediate medical attention if symptoms such as shortness of breath, light-headedness, palpitations, fainting, unusual tiredness or chest pain develop.

**MEDIcINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug.

**Tablet CAUTIONARY AND ADVISORY LABELS 11**

- **Amiodarone hydrochloride (Non-proprietary)**
  - **Amiodarone hydrochloride 100 mg** Amiodarone 100mg tablets | 28 tablet (£8.15) 0.45 mg/0.375 mg liquid | £4.25 per 1 ml price = £1.64
  - **Amiodarone hydrochloride 200 mg** Amiodarone 200mg tablets | 28 tablet (£8.15) 0.78 mg/0.75 mg liquid | £7.80 OT price = £2.00
  - **Cordarone X (Sanofi)**
    - **Amiodarone hydrochloride 100 mg** Cordarone X 100 tablets | 28 tablet (£8.15) 0.48 mg/0.45 mg liquid | £4.28 OT price = £1.64
    - **Amiodarone hydrochloride 200 mg** Cordarone X 200 tablets | 28 tablet (£8.15) 0.96 mg/0.90 mg liquid | £8.09 OT price = £2.00

**Solution for injection EXCIPIENTS:** May contain Benzyl alcohol.

- **Amiodarone hydrochloride (Non-proprietary)**
  - **Amiodarone hydrochloride 30 mg per 1 ml** Amiodarone 300mg/10ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£8.15) 0.3 mg/0.25 ml liquid | £13.80
  - **Amiodarone hydrochloride 50 mg per 1 ml** Amiodarone 150mg/3ml concentrate for solution for injection ampoules | 10 ampoule (£8.15) 0.5 mg/0.45 ml liquid | £15.00
  - **Cordarone X (Sanofi)**
    - **Amiodarone hydrochloride 50 mg per 1 ml** Cordarone X 150mg/3ml solution for injection ampoules | 6 ampoule (£8.15) 0.9 mg/0.8 ml liquid | £9.60

**Dronedarone**

- **DRUG ACTION** Dronedarone is a multi-channel blocking anti-arrhythmic drug.

- **INDICATIONS AND DOSE** Maintenance of sinus rhythm after cardioversion in clinically stable patients with paroxysmal or persistent atrial fibrillation, when alternative treatments are unsuitable (initiated under specialist supervision)
  - **BY MOUTH**
    - **Adult:** 400 mg twice daily

- **CONTRA-INDICATIONS** Atrial conduction defects - bradycardia - complete bundle branch block - distal block - existing or previous heart failure or left ventricular systolic dysfunction - haemodynamically unstable patients - liver toxicity associated with previous amiodarone use - lung toxicity associated with previous amiodarone use - permanent atrial fibrillation - prolonged QT interval - second- or third- degree AV block - sick sinus syndrome (unless pacemaker fitted) - sinus node dysfunction

- **CAUTIONS** Coronary artery disease - correct hypokalaemia and hypomagnesaemia before starting and during treatment

- **INTERACTIONS** → Appendix 1 (dronedarone).
Patients who do not meet the above criteria who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

www.nice.org.uk/TA197

**ANTIARRHYTHMICS > OTHER**

### Adenosine

#### INDICATIONS AND DOSE

**Rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome)** | **Used to aid to diagnosis of broad or narrow complex supraventricular tachycardias**

- **By rapid intravenous injection**
  - Adult: Initially 6 mg, administer into central or large peripheral vein and give over 2 seconds, cardiac monitoring required, followed by 12 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required, increments should not be given if high level AV block develops at any particular dose

**Rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) in patients with a heart transplant | Aid to diagnosis of broad or narrow complex supraventricular tachycardias in patients with a heart transplant**

- **By rapid intravenous injection**
  - Adult: Initially 3 mg, administer into a central or large peripheral vein and give over 2 seconds, followed by 6 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required, patients with a heart transplant are very sensitive to the effects of adenosine

**Used in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate**

- **By intravenous infusion**
- Adult: (consult product literature)

#### DOSE ADJUSTMENTS DUE TO INTERACTIONS

If essential to give with diprydimal reduce adenosine dose to a quarter of the usual dose.

#### UNLICENSED USE

Adenosine doses in the BNF may differ from those in the product literature.

#### CONTRA-INDICATIONS

- Asthma · chronic obstructive lung disease · decompensated heart failure · long QT syndrome · second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted) · severe hypotension

#### CAUTIONS

- Atrial fibrillation with accessory pathway (conduction down anomalous pathway may increase) · atrial flutter with accessory pathway (conduction down anomalous pathway may increase) · autonomic dysfunction · bundle branch block · first-degree AV block · heart transplant · left main coronary artery stenosis · left to
right shunt • pericardial effusion • pericarditis • QT-interval prolongation • recent myocardial infarction • severe heart failure • stenotic carotid artery disease with cerebrovascular insufficiency • stenotic valvular heart disease • uncorrected hypovolaemia

- INTERACTIONS → Appendix 1 (adenosine); also possibility of interaction with drugs tending to impair myocardial conduction.

- SIDE-EFFECTS
  - Common or very common Angina (discontinue) • apprehension • arrhythmia (discontinue if asystole or severe bradycardia occur) • AV block • dizziness • dyspnoea • flushing • headache • nausea • sinus pause
  - Uncommon Blurred vision • hyperventilation • metallic taste • palpitation • sweating • weakness
  - Very rare Bronchospasm • injection-site reactions • transient worsening of intracranial hypertension
  - Frequency not known Cardiac arrest • convulsions • hypotension (discontinue if severe) • respiratory failure (discontinue) • syncope • vomiting

- PREGNANCY Large doses may produce fetal toxicity; manufacturer advises use only if potential benefit outweighs risk.

- BREAST FEEDING No information available—unlikely to be present in milk owing to short half-life.

- MONITORING REQUIREMENTS Monitor ECG and have resuscitation facilities available.

- DIRECTIONS FOR ADMINISTRATION For rapid intravenous injection give over 2 seconds into central or large peripheral vein followed by rapid Sodium Chloride 0.9% flush; injection solution may be diluted with Sodium Chloride 0.9% if required.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion, solution for infusion

Solution for injection
ELECTROLYTES: May contain Sodium
  - Adenosine 3 mg per 1 ml Adenosine 6mg/2ml solution for injection vials | 6 vial £26.70–£29.24 (Hospital only)
  - Adenocor (Sanofi) Adenosine 3 mg per 1 ml Adenocor 6mg/2ml solution for injection vials | 6 vial £29.94 (Hospital only)

Solution for infusion
ELECTROLYTES: May contain Sodium
  - Adenosine (Non-proprietary) Adenosine 3 mg per 1 ml Adenosine 30mg/10ml solution for infusion vials | 6 vial £70.00–£85.57 (Hospital only)
  - Adenoscan (Sanofi) Adenosine 3 mg per 1 ml Adenoscan 30mg/10ml solution for infusion vials | 6 vial £85.57

BETA-ADRENOCEPTOR BLOCKERS → NON-SELECTIVE

Sotalol hydrochloride

- INDICATIONS AND DOSE
  - Symptomatic non-sustained ventricular tachyarrhythmias • Prophylaxis of paroxysmal atrial tachycardia or fibrillation, paroxysmal AV re-entrant tachycardias (both nodal and involving accessory pathways), and paroxysmal supraventricular tachycardia after cardiac surgery • Maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter
  - BY MOUTH
  - Adult: Initially 80 mg daily in 1–2 divided doses, then increased to 160–320 mg daily in 2 divided doses, dose to be increased gradually at intervals of 2–3 days

Life-threatening arrhythmias including ventricular tachyarrhythmias

- BY MOUTH
  - Adult: Initially 80 mg daily in 1–2 divided doses, then increased to 160–320 mg daily in 2 divided doses, dose to be increased gradually at intervals of 2–3 days, higher doses of 480–640 mg daily may be required for life-threatening ventricular arrhythmias (under specialist supervision)

- CONTRA-INDICATIONS Long QT syndrome (congenital or acquired) • torsade de pointes

- CAUTIONS Diarrhoea (severe or prolonged)

- INTERACTIONS Extreme caution or avoid concomitant use of drugs that prolong QT interval.

- SIDE-EFFECTS Arrhythmogenic (pro-arrhythmic) effect (torsade de pointes—increased risk in females)

- BREAST FEEDING Arrhythmogenic (pro-arrhythmic) effect (torsade de pointes—increased risk in females)

- RENAL IMPAIRMENT Use half normal dose if eGFR 30–60 mL/minute/1.73 m²; use one-quarter normal dose if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².

- MONITORING REQUIREMENTS Measurement of corrected QT interval, and monitoring of ECG and electrolytes required; correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Table
  - **Sotalol hydrochloride (Non-proprietary)**
    - Sotalol hydrochloride 40 mg Sotalol 40mg tablets | 28 tablet £1.11 DT price = £1.01
    - Sotalol hydrochloride 80 mg Sotalol 80mg tablets | 28 tablet £1.75 DT price = £1.29 | 56 tablet no price available
    - Sotalol hydrochloride 160 mg Sotalol 160mg tablets | 28 tablet £6.25 DT price = £5.93
  - **Beta-Cardone (Focus Pharmaceuticals Ltd)**
    - Sotalol hydrochloride 200 mg Beta-Cardone 200mg tablets | 28 tablet £2.40 DT price = £2.40
  - **Sotacor (Bristol-Myers Squibb Pharmaceuticals Ltd)**
    - Sotalol hydrochloride 80 mg Sotacor 80mg tablets | 30 tablet £3.28

CARDIAC GLYCOSIDES

Cardiac glycosides

Digoxin-specific antibody

Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service (see further information, under Emergency treatment of poisoning p. 1204). Digoxin-specific antibody p. 1213 fragments are indicated for the treatment of known or strongly suspected life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine
sulfate p. 1022 and when measures beyond the withdrawal of digoxin below and correction of any electrolyte abnormalities are considered necessary.

Digoxin

Digoxin is most useful for controlling ventricular response in persistent and permanent atrial fibrillation and atrial flutter. Digoxin also has a role in heart failure.

For management of atrial fibrillation, the maintenance dose of digoxin can usually be determined by the ventricular rate at rest, which should not usually be allowed to fall persistently below 60 beats per minute.

Digoxin is now rarely used for rapid control of heart rate (see management of supraventricular arrhythmias). Even with intravenous administration, response may take many hours; persistence of tachycardia is therefore not an indication for exceeding the recommended dose. The intramuscular route is not recommended.

In patients with heart failure who are in sinus rhythm, a loading dose is not required, and a satisfactory plasma-digoxin concentration can be achieved over a period of about a week.

Digoxin has a long half-life and maintenance doses need to be given only once daily (although higher doses may be divided to avoid nausea); renal function is the most important determinant of digoxin dosage.

Unwanted effects depend both on the concentration of digoxin in the plasma and on the sensitivity of the conducting system or of the myocardium, which is often increased in heart disease. It can sometimes be difficult to distinguish between toxic effects and clinical deterioration because symptoms of both are similar. The plasma concentration alone cannot indicate toxicity reliably, but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/litre for digoxin. Digoxin should be used with special care in the elderly, who may be particularly susceptible to digitalis toxicity.

Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected. Hypokalaemia predisposes the patient to digitalis toxicity; it is managed by giving a potassium-sparing diuretic or, if necessary, potassium supplement.

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management. Digoxin-specific antibody fragments are available for reversal of life-threatening overdosage.

Digoxin

**DRUG ACTION**  
Digoxin is a cardiac glycoside that increases conductivity within the atrioventricular (AV) node.

**INDICATIONS AND DOSE**

- **Rapid digitalisation, for atrial fibrillation or flutter**
  - **BY MOUTH**
  - Adult: 0.75—1.5 mg in divided doses, dose to be given over 24 hours, reduce dose in the elderly

- **Maintenance, for atrial fibrillation or flutter**
  - **BY MOUTH**
  - Adult: Maintenance 125—250 micrograms daily, dose according to renal function and initial loading dose, reduce dose in the elderly

- **Heart failure (for patients in sinus rhythm)**
  - **BY MOUTH**
  - Adult: 62.5—125 micrograms once daily, reduce dose in the elderly

**Emergency loading dose, for atrial fibrillation or flutter**

- **INITIALLY BY INTRAVENOUS INFUSION**
  - Adult: Loading dose 0.75—1 mg, to be given over at least 2 hours, then (by mouth) maintenance, loading dose is rarely necessary, maintenance dose to be started on the day following the loading dose, reduce dose in the elderly

**DOSE EQUIVALENCE AND CONVERSION**

- Dose may need to be reduced if digoxin (or another cardiac glycoside) has been given in the preceding 2 weeks.
- When switching from intravenous to oral route may need to increase dose by 20—33% to maintain the same plasma-digoxin concentration.

**UNLICENSED USE**  
Digoxin doses in the BNF may differ from those in product literature.

**CONTRA-INDICATIONS**

- Constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction—but use with caution)
- Hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—but use with caution)
- Intermittent complete heart block
- Myocarditis
- Second degree AV block
- Supraventricular arrhythmias associated with accessory conducting pathways e.g. Wolff-Parkinson-White syndrome (although can be used in infancy), ventricular tachycardia or fibrillation

**CAUTIONS**

- Hypercalcaemia (risk of digitalis toxicity)
- Hypokalaemia (risk of digitalis toxicity)
- Hypomagnesaemia (risk of digitalis toxicity)
- Hypoxia (risk of digitalis toxicity)
- Recent myocardial infarction
- Severe respiratory disease
- Sick sinus syndrome
- Thyroid disease

**SIDE-EFFECTS**

- **Common or very common** 
  - Arrhythmias
  - Blurred vision
  - Conduction disturbances
  - Diarrhoea
  - Dizziness
  - Eosinophilia
  - Nausea
  - Rash
  - Vomiting
  - Yellow vision

- **Uncommon**
  - Depression

- **Very rare**
  - Anorexia
  - Apathy
  - Confusion
  - Fatigue
  - Gynaecomastia
  - Intestinal ischaemia and necrosis
  - Psychosis
  - Thrombocytopenia
  - Weakness

**Overdose**

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management.

**PREGNANCY**

May need dosage adjustment.

**BREAST FEEDING**

Amount too small to be harmful.

**RENAL IMPAIRMENT**

Reduce dose. Monitor plasma-digoxin concentration in renal impairment.

**MONITORING REQUIREMENTS**

- For plasma-digoxin concentration assay, blood should be taken at least 6 hours after a dose.
- Monitor serum electrolytes and renal function. Toxicity increased by electrolyte disturbances.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use Avoid rapid intravenous administration (risk of hypertension and reduced coronary flow). For intravenous infusion (Lanoxin®), give intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to a concentration of not more than 62.5 micrograms/mL. To be given over at least 2 hours.
- With oral use For oral administration, oral solution must not be diluted.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for digoxin elixir (use pipette).
MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection.

Tablet
- **Digoxin (Non-proprietary)**
  - Digoxin 62.5 microgram: 28 tablet (Pom) £9.99 DT price = £2.03 | 500 tablet (Pom) no price available
  - Digoxin 125 microgram: 28 tablet (Pom) £4.99 DT price = £2.10
  - Digoxin 250 microgram: 28 tablet (Pom) £4.99 DT price = £2.04 | 500 tablet (Pom) no price available
- **Lanoxin** (Aspen Pharma Trading Ltd)
  - Digoxin 62.5 microgram: Lanoxin PG 62.5microgram tablets | 500 tablet (Pom) £8.09
  - Digoxin 125 microgram: Lanoxin 125 tablets | 500 tablet (Pom) £8.09
  - Digoxin 250 microgram: Lanoxin 250microgram tablets | 500 tablet (Pom) £8.09

Oral solution
- **Lanoxin** (Aspen Pharma Trading Ltd)
  - Digoxin 50 microgram per 1 ml: Lanoxin PG 50micrograms/ml elixir | 50 ml (Pom) £5.35 DT price = £5.35

Solution for injection
EXCIPIENTS: May contain Alcohol, propylene glycol
- **Digoxin (Non-proprietary)**
  - Digoxin 100 microgram per 1 ml: Lanoxin Injection Pediatric 100micrograms/1ml solution for injection ampoules | 10 ampoule (Pom) no price available

Solution for infusion
- **Digoxin (Non-proprietary)**
  - Digoxin 250 microgram per 1 ml: Digoxin 500micrograms/2ml solution for infusion ampoules | 10 ampoule (Pom) £7.00
  - **Lanoxin** (Aspen Pharma Trading Ltd)
    - Digoxin 250 microgram per 1 ml: Lanoxin 500micrograms/2ml solution for infusion ampoules | 5 ampoule (Pom) £3.30

2 Bleeding disorders

Antifibrinolytic drugs and haemostatics

Overview
Fibrin dissolution can be impaired by the administration of tranexamic acid below, which inhibits fibrinolysis. It can be used to prevent bleeding or to treat bleeding associated with excessive fibrinolysis (e.g., in surgery, dental extraction, obstetric disorders, and traumatic haemorhama) and in the management of menorrhagia. Tranexamic acid may also be used in hereditary angioedema, epistaxis, and in thrombolytic overdose.

Desmopressin p. 611 is used in the management of mild to moderate haemophilia and von Willebrand's disease. It is also used for fibrinolytic response testing.

Etamsylate p. 105 reduces capillary bleeding in the presence of a normal number of platelets; it does not act by fibrin stabilisation, but probably by correcting abnormal adhesion. Etamsylate is less effective than other treatments in the management of heavy menstrual bleeding and its use is no longer recommended.

ANTIHAEMORRHAGICS > ANTIFIBRINOLYTICS

Tranexamic acid

INDICATIONS AND DOSE

Local fibrinolysis
- **BY MOUTH**
  - Adult: 1–1.5 g 2–3 times a day, alternatively 15–25 mg/kg 2–3 times a day
- **INITIALLY BY SLOW INTRAVENOUS INJECTION**
  - Adult: 0.5–1 g 2–3 times a day, to be administered at a rate not exceeding 100 mg/minute, dose may be followed by continuous infusion; (by continuous intravenous infusion) 25–50 mg/kg, dose to be given over 24 hours

Menorrhagia
- **BY MOUTH**
  - Adult: 1 g 3 times a day for up to 4 days, to be initiated when menstruation has started; maximum 4 g per day

Hereditary angioedema
- **BY MOUTH**
  - Adult: 1–1.5 g 2–3 times a day, for short-term prophylaxis of hereditary angioedema, tranexamic acid is started several days before planned procedures which may trigger an acute attack of hereditary angioedema (e.g., dental work) and continued for 2–5 days afterwards

Epistaxis
- **BY MOUTH**
  - Adult: 1 g 3 times a day for 7 days

General fibrinolysis
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 1 g every 6–8 hours, alternatively 15 mg/kg every 6–8 hours, dose to be given at a rate not exceeding 100 mg/minute

UNLICENSED USE
Use of tranexamic acid by continuous intravenous infusion for treatment of local fibrinolysis is an unlicensed route of administration.

CONTRA-INDICATIONS
Fibrinolytic conditions following disseminated intravascular coagulation (unless predominant activation of fibrinolytic system with severe bleeding) · history of convulsions · thromboembolic disease

CAUTIONS
Irregular menstrual bleeding (establish cause before initiating therapy) · massive haematuria (avoid if risk of ureteric obstruction) · patients receiving oral contraceptives (increased risk of thrombosis)

CAUTIONS, FURTHER INFORMATION
Menorrhagia Before initiating treatment for menorrhagia, exclude structural or histological causes or fibroids causing distortion of uterine cavity.

SIDE-EFFECTS
- **Common or very common** Diarrhoea (reduce dose) · nausea · vomiting
- **Uncommon** Dermatitis
- **Rare** Impairment of colour vision (discontinue) · thromboembolic events · visual disturbances (discontinue)
- **Frequency not known** Convulsions (usually with high doses) · hypotension (on rapid intravenous injection) · malaise (on rapid intravenous injection)

PREGNANCY
No evidence of teratogenicity in animal studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta.

BREAST FEEDING
Small amount present in milk—antifibrinolytic effect in infant unlikely.

RENAI IMPAIRMENT Reduce dose—consult product literature for details.

MONITORING Requirements Regular liver function tests in long-term treatment of hereditary angioedema.
Coagulation factor deficiencies

2.1 Coagulation factor deficiencies

BLOOD AND RELATED PRODUCTS

Dried prothrombin complex

(Human prothrombin complex)

- **INDICATIONS AND DOSE**
  Treatment and peri-operative prophylaxis of haemorrhage in patients with congenital deficiency of factors II, VII, IX, or X if purified specific coagulation factors not available | Treatment and peri-operative prophylaxis of haemorrhage in patients with acquired deficiency of factors II, VII, IX, or X (e.g. during warfarin treatment)
  - BY INTRAVENOUS INFUSION
  - Adult: (consult haematologist)

Major bleeding in patients on warfarin following phytomenadione (initiated under specialist supervision)
  - BY INTRAVENOUS INFUSION
  - Adult: 25–50 units/kg

- **CONTRA-INDICATIONS**
  - Angina | History of heparin induced thrombocytopenia | Recent myocardial infarction (except in life-threatening haemorrhage following overdosage of oral anticoagulants, and before induction of fibrinolytic therapy)
  - CAUTIONS
    - Disseminated intravascular coagulation | History of myocardial infarction or coronary heart disease | Postoperative use | Risk of thrombosis
  - SIDE-EFFECTS
    - Rare: Headache | Very rare: Anaphylaxis | Antibody formation | Hypersensitivity reactions | Pyrexia
    - Frequency not known: Disseminated intravascular coagulation | Nephrotic syndrome | Thrombotic events
  - PRESCRIBING AND DISPENSING INFORMATION
    - Dried prothrombin complex is prepared from human plasma by a suitable fractionation technique, and contains factor IX, together with variable amounts of factors II, VII, and X.
    - Available from CSL Behring (Beriplex® P/N), Octapharma (Octaplex®).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

2.1 Coagulation factor deficiencies

BLOOD AND RELATED PRODUCTS

Dried prothrombin complex

(Human prothrombin complex)

- **INDICATIONS AND DOSE**
  Treatment and peri-operative prophylaxis of haemorrhage in patients with congenital deficiency of factors II, VII, IX, or X if purified specific coagulation factors not available | Treatment and peri-operative prophylaxis of haemorrhage in patients with acquired deficiency of factors II, VII, IX, or X (e.g. during warfarin treatment)
  - BY INTRAVENOUS INFUSION
  - Adult: (consult haematologist)

**ANTIHAEMORRHAGICS**

Etamsylate

(Ethamsylate)

- **INDICATIONS AND DOSE**
  - Short-term blood loss in menorrhagia
    - BY MOUTH
    - Adult: 500 mg 4 times a day during menstruation

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 930

- **CAUTIONS**
  - Exclude structural or histological causes of menorrhagia, or fibroids causing distortion of the uterine cavity, before initiating treatment

- **SIDE-EFFECTS**
  - Diarrhoea | Fever (discontinue treatment) | Headache | Nausea | Rash | Vomiting

- **BREAST FEEDING**
  - Present in milk—manufacturer advises avoidance

- **LESS SUITABLE FOR PRESCRIBING**
  - Less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**ANTIHAEMORRHAGICS**

Haemostatics

**ANTIHAEMORRHAGICS**

Etamsylate

(Ethamsylate)

- **INDICATIONS AND DOSE**
  - Short-term blood loss in menorrhagia
    - BY MOUTH
    - Adult: 500 mg 4 times a day during menstruation

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 930

- **CAUTIONS**
  - Exclude structural or histological causes of menorrhagia, or fibroids causing distortion of the uterine cavity, before initiating treatment

- **SIDE-EFFECTS**
  - Diarrhoea | Fever (discontinue treatment) | Headache | Nausea | Rash | Vomiting

- **BREAST FEEDING**
  - Present in milk—manufacturer advises avoidance

- **LESS SUITABLE FOR PRESCRIBING**
  - Less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution
**Factor VIII fraction, dried**  
*(Human coagulation factor VIII, dried)*

- **INDICATIONS AND DOSE**  
  Treatment and prophylaxis of haemorrhage in congenital factor VIII deficiency (haemophilia A), acquired factor VIII deficiency | Von Willebrand's disease
  - BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY CONTINUOUS INTRAVENOUS INFUSION
  - Adult: (consult haematologist)

- **CAUTIONS**  
  Intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB—less likely with high potency concentrates

- **SIDE-EFFECTS**  

- **MONITORING REQUIREMENTS**  
  Monitor for development of factor VIII inhibitors.

- **PRESCRIBING AND DISPENSING INFORMATION**  
  Dried factor VIII fraction is prepared from human plasma by a suitable fractionation technique; it may also contain varying amounts of Von Willebrand factor. **Optivate®**, **Fanbdhi®**, and **Octanate®** are not indicated for use in Von Willebrand’s disease.

  Recombinant human coagulation factor VIII including octocog alfa, morocotocog alfa, and simoctocog alfa are not indicated for use in Von Willebrand’s disease.

**Factor VIIa (recombinant)**  
*(Eptacog alfa (activated))*

- **INDICATIONS AND DOSE**  
  Treatment and prophylaxis of haemorrhage in patients with haemophilia A or B with inhibitors to factors VIII or IX, acquired haemophilia, factor VII deficiency, or Glanzmann’s thrombasthenia
  - BY INTRAVENOUS INJECTION
  - Adult: (consult haematologist)

- **CAUTIONS**  
  Disseminated intravascular coagulation - risk of thrombosis

- **SIDE-EFFECTS**  
  Uncommon Deep vein thrombosis - fever - pulmonary embolism - rash - venous thromboembolic events
  - Rare Angina - arterial thrombotic events - cerebrovascular accident - coagulation disorders - headache - myocardial infarction - nausea
  - Frequency not known Anaphylaxis - angioedema - flushing

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder and solvent for solution for injection**
    - **NovoSeven** (Novo Nordisk Ltd)
      - Eptacog alfa activated 50000 unit  
        NovoSeven 1mg (50,000 units) powder and solvent for solution for injection pre-filled syringes | 1 vial (Pom) £525.20 (Hospital only)
      - Eptacog alfa activated 100000 unit  
        NovoSeven 2mg (100,000 units) powder and solvent for solution for injection vials | 1 vial (Pom) £1,050.40 (Hospital only)
      - Eptacog alfa activated 250000 unit  
        NovoSeven 5mg (250,000 units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pom) £2,626.00 (Hospital only)
      - Eptacog alfa activated 400000 unit  
        NovoSeven 8mg (400,000 units) powder and solvent for solution for injection vials | 1 vial (Pom) £4,201.60 (Hospital only)
  - **Elocta** (Swedish Orphan Biovitrum Ltd)
    - Efmonoctocog alfa 250 unit  
      Elocta 250unit powder and solvent for solution for injection vials | 1 vial (Pom) £151.80 (Hospital only)
    - Efmonoctocog alfa 500 unit  
      Elocta 500unit powder and solvent for solution for injection vials | 1 vial (Pom) £525.20 (Hospital only)
    - Efmonoctocog alfa 1000 unit  
      Elocta 1,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £1,050.40 (Hospital only)
    - Efmonoctocog alfa 2000 unit  
      Elocta 2,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £2,626.00 (Hospital only)
  - **Fanbdhi** (Grifols UK Ltd)
    - Factor VII high purity 500 unit  
      Fanbdhi 500unit powder and solvent for solution for injection vials | 1 vial (Pom) £165.00 (Hospital only)
    - Factor VII high purity 1000 unit  
      Fanbdhi 1,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £330.00 (Hospital only)
    - Factor VII high purity 1500 unit  
      Fanbdhi 1,500unit powder and solvent for solution for injection vials | 1 vial (Pom) £495.00

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**Repleine-VF** (Bio Products Laboratory Ltd)
- Factor IX high purity 500 unit  
  Repleine-VF 500unit powder and solvent for solution for injection vials | 1 vial (Pom) £180.00 | 10 vial (Pom) no price available
- Factor IX high purity 1000 unit  
  Repleine-VF 1,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £360.00 | 10 vial (Pom) no price available

**BeneFIX** (Pfizer Ltd)
- Nonacog alfa 250 unit  
  BeneFIX 250unit powder and solvent for solution for injection vials | 1 vial (Pom) £151.80 (Hospital only)
- Nonacog alfa 500 unit  
  BeneFIX 500unit powder and solvent for solution for injection vials | 1 vial (Pom) £303.60 (Hospital only)
- Nonacog alfa 1000 unit  
  BeneFIX 1,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £607.20 (Hospital only)
- Nonacog alfa 2000 unit  
  BeneFIX 2,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £1,214.40 (Hospital only)
- Nonacog alfa 3000 unit  
  BeneFIX 3,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £1,821.60 (Hospital only)

**Pentasage-VF** (Repligen)
- Octocog alfa 250 unit  
  Octocog alfa 250unit (Hospital only)
- Octocog alfa 500 unit  
  Octocog alfa 500unit (Hospital only)
- Octocog alfa 1000 unit  
  Octocog alfa 1,000unit (Hospital only)
- Octocog alfa 2000 unit  
  Octocog alfa 2,000unit (Hospital only)
- Efmoroctocog alfa 250 unit  
  Efmoroctocog alfa 250unit (Hospital only)
- Efmoroctocog alfa 1500 unit  
  Efmoroctocog alfa 1,500unit (Hospital only)
- Efmoroctocog alfa 2000 unit  
  Efmoroctocog alfa 2,000unit (Hospital only)

**Factor VIII fraction**
- Factor VIII high purity 500 unit  
  Fanbdhi 500unit powder and solvent for solution for injection vials | 1 vial (Pom) £165.00 (Hospital only)
- Factor VIII high purity 1000 unit  
  Fanbdhi 1,000unit powder and solvent for solution for injection vials | 1 vial (Pom) £330.00 (Hospital only)
- Factor VIII high purity 1500 unit  
  Fanbdhi 1,500unit powder and solvent for solution for injection vials | 1 vial (Pom) £495.00

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**BNF 73**

**Cardiovascular system**

**106 Bleeding disorders**

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**No price available** (Hospital only)
Fibrinogen, dried
(Human fibrinogen)

- INDICATIONS AND DOSE
  Treatment of haemorrhage in congenital hypofibrinogenaeamia or afibrinogenaeamia
  - BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
  - Adult: (consult haematologist)

- CAUTIONS
  - Risk of thrombosis

- SIDE-EFFECTS
  - Rare: Allergic reactions - fever
  - Very rare: Myocardial infarction - pulmonary embolism - thromboembolic events

- PREGNANCY
  Manufacturer advises not known to be harmful — no information available.

- BREAST FEEDING
  Manufacturer advises avoid — no information available.

- PRESCRIBING AND DISPENSING INFORMATION
  Fibrinogen is prepared from human plasma.

Protein C concentrate

- INDICATIONS AND DOSE
  Congenital protein C deficiency
  - BY INTRAVENOUS INJECTION
  - Adult: (consult haematologist)

- CAUTIONS
  - Hypersensitivity to heparins

- SIDE-EFFECTS
  - Very rare: Bleeding - dizziness - fever - hypersensitivity reactions

- PRESCRIBING AND DISPENSING INFORMATION
  Protein C is prepared from human plasma.

Factor XIII fraction, dried
(Human fibrin-stabilising factor, dried)

- INDICATIONS AND DOSE
  Congenital factor XIII deficiency
  - BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
  - Adult: (consult haematologist)

- SIDE-EFFECTS
  - Rare: Allergic reactions - fever

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
  - Advate (Baxalta UK Ltd)
    Octocog alfa 1500 unit Advate 1,500 unit powder and solvent for solution for infusion vials | 1 vial (POD) no price available
  - Kogenate (Bayer Plc)
    Octocog alfa 3000 unit Kogenate Bayer 3,000 unit powder and solvent for solution for infusion vials | 1 vial (POD) no price available

BLOOD AND RELATED PRODUCTS
HAEMOSTATIC PRODUCTS

Factor VIII inhibitor bypassing fraction

- INDICATIONS AND DOSE
  Treatment and prophylaxis of haemorrhage in patients with congenital factor VIII deficiency (haemophilia A) and factor VIII inhibitors | Treatment of haemorrhage in non-haemophilia patients with acquired factor VIII inhibitors
  - BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION
  - Adult: (consult haematologist)

- CONTRA-INDICATIONS
  Disseminated intravascular coagulation
Bleeding disorders

2.2 Subarachnoid haemorrhage

CALCIUM-CHANNEL BLOCKERS

Nimodipine

- **DRUG ACTION** Nimodipine is a dihydropyridine calcium-channel blocker.

- **INDICATIONS AND DOSE**
  - Prevention of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage
    - **BY MOUTH**
      - Adult: 60 mg every 4 hours, to be started within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days.
    - Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage
      - **BY INTRAVENOUS INFUSION**
        - Adult (body-weight up to 70 kg): Initially up to 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.
        - Adult (body-weight 70 kg and above): Initially 1 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.

  - Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage in patients with unstable blood pressure
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially up to 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 - unstable angina - within 1 month of myocardial infarction
- **CAUTIONS** Cerebral oedema - hypotension - severely raised intracranial pressure
- **INTERACTIONS** → Appendix 1 (calcium-channel blockers, alcohol (infusion only)). Avoid concomitant administration with other calcium-channel blockers, beta blocker and nephrotoxic drugs.
- **SIDE-EFFECTS** Flushing - gaster - intestinal disorders - headache - hypotension - ileus - nausea - sweating and feeling of warmth - thrombocytopenia - variation in heart-rate
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk.
- **HEPATIC IMPAIRMENT** Elimination reduced in cirrhosis—monitor blood pressure.
- **RENAL IMPAIRMENT** With intravenous use Manufacturer advises monitor renal function closely in renal impairment.
- **DIRECTIONS FOR ADMINISTRATION** Avoid concomitant administration of nimodipine infusion and tablets.

### Fresh frozen plasma

- **INDICATIONS AND DOSE**
  - Replacement of coagulation factors or other plasma proteins where their concentration or functional activity is critically reduced
    - **BY INTRAVENOUS INFUSION**
      - Adult: (consult haematologist)
    - Major bleeding in patients on warfarin following prophylamendine (if dried prothrombin complex is unavailable)
      - Adult: 15 mL/kilogram

- **CONTRA-INDICATIONS** Avoid use as a volume expander· IgA deficiency with confirmed antibodies to IgA
- **CAUTIONS** Cardiac decompensation · need for compatibility · pulmonary oedema · severe protein S deficiency (avoid products with low protein S activity e.g. OctaplasLG®)
- **SIDE-EFFECTS**
  - Common or very common Nausea · pruritus · rash
  - Uncommon Oedema · vomiting
  - Rare Agitation · allergic reactions · bronchospasm · cardiorespiratory collapse · chills · fever · tachycardia
  - Very rare Arrhythmia · hypertension · thromboembolism
- **PRESCRIBING AND DISPENSING INFORMATION** Fresh frozen plasma is prepared from the supernatant liquid obtained by centrifugation of one donation of whole blood. A preparation of solvent/detergent treated human plasma (frozen) from pooled donors is available from Octapharma (OctaplasLG®).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

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### Plasma products

- **INDICATIONS AND DOSE**
  - Prevention of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage
  - **BY INTRAVENOUS INFUSION**
    - Adult: 60 mg every 4 hours, to be started within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days.
  - Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage
    - **BY INTRAVENOUS INFUSION**
      - Adult (body-weight up to 70 kg): Initially up to 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.
      - Adult (body-weight 70 kg and above): Initially 1 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 - unstable angina - within 1 month of myocardial infarction
- **CAUTIONS** Cerebral oedema - hypotension - severely raised intracranial pressure
- **INTERACTIONS** → Appendix 1 (calcium-channel blockers, alcohol (infusion only)). Avoid concomitant administration with other calcium-channel blockers, beta blocker and nephrotoxic drugs.
- **SIDE-EFFECTS** Flushing - gaster - intestinal disorders - headache - hypotension - ileus - nausea - sweating and feeling of warmth - thrombocytopenia - variation in heart-rate
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk.
- **HEPATIC IMPAIRMENT** Elimination reduced in cirrhosis—monitor blood pressure.
- **RENAL IMPAIRMENT** With intravenous use Manufacturer advises monitor renal function closely in renal impairment.
- **DIRECTIONS FOR ADMINISTRATION** Avoid concomitant administration of nimodipine infusion and tablets.
With oral use For administration by mouth, tablets may be crushed or halved but are light sensitive—administer immediately.

With intravenous use For intravenous infusion, give via drip tubing in Glucose 5% or Sodium chloride 0.9%. Not to be added to infusion container; administer via an infusion pump through a Y-piece into a central catheter; incompatible with polyvinyl chloride giving sets or containers; protect infusion from light.

With intravenous use Polyethylene, polypropylene, or glass apparatus should be used. PVC should be avoided.

## MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **Nimotop** (Bayer Plc)
  - Nimodipine 30 mg Nimotop 30 mg tablets | 100 tablet £40.00

**Solution for infusion**
- **Nimotop** (Bayer Plc)
  - Nimodipine 200 microgram per 1 ml Nimotop 0.02% solution for infusion 50 ml vials | 5 vial £68.00 (Hospital only)

3 Blood clots

### Blocked catheters and lines

Other drugs used for Blocked catheters and lines Heparin (unfractionated), p. 125 - Urokinase, p. 129

### ANTITHROMBOTIC DRUGS > PROSTAGLANDINS, CARDIOVASCULAR

**Epoprostenol**

*(Prostacyclin)*

**DRUG ACTION** Epoprostenol is a prostaglandin and a potent vasodilator. It is also a powerful inhibitor of platelet aggregation.

**INDICATIONS AND DOSE**

Inhibition of platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated

Treatment of primary pulmonary hypertension resistant to other treatments, usually with oral anti-coagulation (initiated by a specialist)

- **BY CONTINUOUS INTRAVENOUS INFUSION**
- **Adult:** (consult product literature)

**PHARMACOKINETICS**

Short half-life of approximately 3 minutes, therefore it must be administered by continuous intravenous infusion.

**CONTRA-INDICATIONS** Severe left ventricular dysfunction

**CAUTIONS** Avoid abrupt withdrawal when used for primary pulmonary hypertension (risk of rebound pulmonary hypertension) - extreme caution in coronary artery disease - haemorrhagic diathesis - pulmonary veno-occlusive disease - reconstituted solution highly alkaline - avoid extravasation (irritant to tissues) - risk of pulmonary oedema (dose titration for pulmonary hypertension should be in hospital)

**INTERACTIONS** Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - anxiety - arthralgia - bleeding - bradycardia - chest pain - diarrhoea - flushing - headache - hypotension - jaw pain - nausea - rash - sepsis - tachycardia - thrombocytopenia - vomiting

- **Uncommon** Dry mouth - sweating

- **Very rare** Agitation - hyperthyroidism - malaise - pallor

- **Frequency not known** Hyperglycaemia - pulmonary oedema (avoid chronic use if occurs during dose titration)

**PREGNANCY** Use if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises avoid — no information available.

**MONITORING REQUIREMENTS** Anticoagulant monitoring required when given with anticoagulants.

**TREATMENT CESSION** Avoid abrupt withdrawal when used for primary pulmonary hypertension (risk of rebound pulmonary hypertension).

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion *(Flolan)*, give continuously in Sodium chloride 0.9%; reconstitute using the filter and solvent (glycine buffer diluent) provided to make a concentrate; may be diluted further (consult product literature); for pulmonary hypertension dilute further with glycine buffer diluent only and administer via a central venous catheter (can give via peripheral vein until central venous access established); for renal dialysis may be diluted further with sodium chloride 0.9%; protect infusion from light. For intravenous infusion *(Veletri)*, give continuously in Sodium chloride 0.9%; reconstitute each vial with 5 ml Sodium chloride 0.9% then dilute to required concentration with sodium chloride 0.9% (consult product literature); administer through an in-line 0.22 micron filter; for pulmonary hypertension, administer via a central venous catheter (can give via peripheral vein until central venous access established); protect infusion from direct sunlight.

3.2 Thromboembolism

**Venous thromboembolism**

**Overview** Venous thromboembolism includes deep-vein thrombosis and pulmonary embolism, and occurs as a result of thrombus formation in a vein.
Prophylaxis of venous thromboembolism

All patients admitted to hospital should undergo a risk assessment for venous thromboembolism on admission. Patients considered to be at high risk include those who have a substantial reduction in mobility, those with obesity, malignant disease, history of venous thromboembolism, thrombophilic disorder, or patients over 60 years. Patients with risk factors for bleeding (e.g. acute stroke, thrombocytopenia, acquired or untreated inherited bleeding disorders) should only receive pharmacological prophylaxis when the risk of bleeding does not outweigh the risk of venous thromboembolism. NICE clinical guideline 92 (January 2010) provides a full list of risk factors, and gives recommendations for prophylaxis. A venous thromboembolism risk assessment checklist is also available from the Department of Health (www.gov.uk/dh).

Patients scheduled for surgery should be offered mechanical prophylaxis (e.g. anti-embolism stockings) on admission if appropriate; prophylaxis should continue until the patient is sufficiently mobile. Choice of mechanical prophylaxis will depend on factors such as the type of surgery, suitability for the patient, and their condition.

Patients undergoing general or orthopaedic surgery, who are considered to be at high risk of venous thromboembolism, should be offered pharmacological prophylaxis. Choice of prophylaxis will depend on the type of surgery, suitability for the patient, and local policy. A low molecular weight heparin is suitable in all types of general and orthopaedic surgery. Heparin (unfractionated) p. 125 is preferred for patients in renal failure. Fondaparinux sodium p. 119 is an option for patients undergoing hip or knee replacement surgery, hip fracture surgery, gastro-intestinal, bariatric, or day surgery procedures. The oral anticoagulants apixaban p. 117, dabigatran etexilate p. 128, and rivaroxaban p. 120 are indicated for thromboprophylaxis following hip or knee replacement surgery.

Pharmacological prophylaxis in general surgery should usually continue for 5–7 days, or until sufficient mobility has been re-established. Pharmacological prophylaxis should be extended to 28 days after major cancer surgery in the abdomen or pelvis. Hip or knee replacement surgery, and hip fracture surgery, require an extended duration of pharmacological prophylaxis, depending on the preparation used (consult product literature).

General medical patients who are considered to be at high risk of venous thromboembolism should be offered pharmacological prophylaxis on admission. Choice of prophylaxis will depend on the medical condition, suitability for the patient, and local policy. Patients should receive either a low molecular weight heparin, heparin (unfractionated) (if patient in renal failure), or fondaparinux sodium. Prophylaxis should continue until the patient is no longer considered to be at significant risk of venous thromboembolism. Mechanical prophylaxis (e.g. anti-embolism stockings) can be offered to medical patients in whom pharmacological prophylaxis is contra-indicated, and continued until the patient is sufficiently mobile.

Edoxaban p. 118, an inhibitor of factor Xa, is given orally for the treatment and prophylaxis of venous thromboembolism, although, it should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy. Duration of therapy should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e. recent surgery, trauma, immobilisation, and longer durations should be based on permanent risk factors or idiopathic deep-vein thrombosis or pulmonary embolism. Edoxaban is also licensed for the prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one other risk factor.

Treatment of venous thromboembolism

For the initial treatment of deep-vein thrombosis and pulmonary embolism a low molecular weight heparin is used; alternatively, heparin (unfractionated) is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or (for deep-vein thrombosis only) by intermittent subcutaneous injection. Intermittent intravenous injection of heparin (unfractionated) is no longer recommended. An oral anticoagulant (usually warfarin sodium p. 131 is started at the same time as unfractionated or low molecular weight heparin (the heparin needs to be continued for at least 5 days and until the INR is ≥2 for at least 24 hours). Laboratory monitoring for heparin (unfractionated), preferably on a daily basis, is essential; determination of the activated partial thromboplastin time (APTT) is the most widely used measure (for heparin (unfractionated). A low molecular weight heparin or, in some circumstances, heparin (unfractionated) is also used in regimens for the management of myocardial infarction and unstable angina.

Management of venous thromboembolism in pregnancy

Heparins are used for the management of venous thromboembolism in pregnancy because they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen for drugs such as dalteparin sodium p. 123, enoxaparin sodium p. 124, and tinzaparin sodium p. 126. Treatment should be stopped at the onset of labour and advice sought from a specialist on continuing therapy after birth.

Extracorporeal circuits

Heparin (unfractionated) is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Haemorrhage

If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate p. 1213 is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

Management of stroke

Overview

Stroke is associated with a significant risk of morbidity and mortality. Patients presenting with acute symptoms should be immediately transferred to hospital for accurate diagnosis of stroke type, and urgent initiation of appropriate treatment; patients should be managed by a specialist multidisciplinary stroke team.

The following notes give an overview of the initial and long-term management of transient ischaemic attack, ischaemic stroke, and intracerebral haemorrhage.

Transient ischaemic attack

Patients suspected of having a transient ischaemic attack should immediately receive aspirin p. 114 (patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel p. 115 [unlicensed use] as an alternative). Following a confirmed diagnosis, patients should receive treatment for secondary prevention (see Long-term Management, under Ischaemic Stroke).
Ischaemic stroke

Initial management

Altiplase p. 205 is recommended in the treatment of acute ischaemic stroke if it can be administered within 4.5 hours of symptom onset; it should be given by medical staff experienced in the administration of thrombolytics and the treatment of acute stroke, preferably within a specialist stroke centre. Treatment with aspirin should be initiated 24 hours after thrombolysis (or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis); patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel [unlicensed use] as an alternative.

Anticoagulants are not recommended as an alternative to antiplatelet drugs in acute ischaemic stroke in patients who are in sinus rhythm. However, parenteral anticoagulants may be indicated in patients who are symptomatic of, or at high risk of developing, deep vein thrombosis or pulmonary embolism; warfarin sodium p. 131 should not be commenced in the acute phase of ischaemic stroke.

Anticoagulants should be considered after cardio-embolic ischaemic stroke in patients with atrial fibrillation, however patients presenting with atrial fibrillation following a disabling ischaemic stroke should receive aspirin before being considered for anticoagulant treatment. Patients already receiving anticoagulation for a prosthetic heart valve who experience a disabling ischaemic stroke and are at significant risk of haemorrhagic transformation, should have their anticoagulant treatment stopped for 7 days and substituted with aspirin.

Treatment of hypertension in the acute phase of ischaemic stroke can result in reduced cerebral perfusion, and should therefore only be instituted in the event of a hypertensive emergency, or in those patients considered for thrombolysis.

Long-term management

Patients should receive long-term treatment following a transient ischaemic attack or an ischaemic stroke to reduce the risk of further cardiovascular events.

Following a transient ischaemic attack, long-term treatment with modified-release dipyridamole in combination with aspirin is recommended. If patients are intolerant of aspirin, or it is contra-indicated, then modified-release dipyridamole p. 116 alone is recommended; if patients are intolerant of dipyridamole, or it is contra-indicated, then aspirin alone is recommended. Patients who are intolerant of both aspirin and dipyridamole should receive clopidogrel alone [unlicensed use].

Following an ischaemic stroke (not associated with atrial fibrillation), clopidogrel is recommended as long-term treatment. If clopidogrel is contra-indicated or not tolerated, patients should receive modified-release dipyridamole in combination with aspirin; if both aspirin and clopidogrel are contra-indicated or not tolerated, then modified-release dipyridamole alone is recommended; if both dipyridamole and clopidogrel are contra-indicated or not tolerated, then aspirin alone is recommended.

Patients with stroke associated with atrial fibrillation should be reviewed for long-term treatment with warfarin sodium or an alternative anticoagulant (see Initial Management under Ischaemic Stroke).

Anticoagulants are not routinely recommended in the long-term prevention of recurrent stroke, except in patients with atrial fibrillation.

A statin should be initiated 48 hours after stroke symptom onset, irrespective of the patient’s serum-cholesterol concentration.

Following the acute phase of ischaemic stroke, blood pressure should be measured and treatment initiated to achieve a target blood pressure of <130/80 mmHg. Beta-blockers should not be used in the management of hypertension following a stroke, unless they are indicated for a co-existing condition.

All patients should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight, alcohol intake, and smoking.

Intracerebral haemorrhage

Initial Management

Surgical intervention may be required following intracerebral haemorrhage to remove the haematoma and relieve intracranial pressure. Patients taking anticoagulants should have this treatment stopped and reversed; anticoagulant therapy has, however, been used in patients with intracerebral haemorrhage who are symptomatic of deep vein thrombosis or pulmonary embolism; placement of a caval filter is an alternative in this situation.

Long-term management

Aspirin therapy should only be given to patients at a high risk of a cardiac ischaemic event. Anticoagulant therapy is not recommended following an intracerebral haemorrhage, even in those with atrial fibrillation, unless the patient is at very high risk of an ischaemic stroke or cardiac ischaemic events; advice from a specialist should be sought in this situation. Blood pressure should be measured and treatment initiated where appropriate, taking care to avoid hypoperfusion. Statins should be avoided following intracerebral haemorrhage, however they can be used with caution when the risk of a vascular event outweighs the risk of further haemorrhage.

Oral anticoagulants

Overview

The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.

Coumarins and phenindione

The oral anticoagulants warfarin sodium p. 131, acenocoumarol p. 131 and phenindione p. 131, antagonise the effects of vitamin K, and take at least 48 to 72 hours for the anticoagulant effect to develop fully; warfarin sodium is the drug of choice. If an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly.

These oral anticoagulants should not be used in cerebral artery thrombosis or peripheral artery occlusion as first-line therapy; aspirin p. 114 is more appropriate for reduction of risk in transient ischaemic attacks. Unfractionated or a low molecular weight heparin (see under Parenteral anticoagulants p. 113) is usually preferred for the prophylaxis of venous thromboembolism in patients undergoing surgery; alternatively, warfarin sodium can be continued in selected patients currently taking long-term warfarin sodium and who are at high risk of thromboembolism (seek expert advice).

Dose

The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.

Target INR

The following indications and target INRs for adults for warfarin take into account recommendations of the British Society for Haematology guidelines on

An INR which is within 0.5 units of the target value is generally satisfactory; larger deviations require dosage adjustment. Target values (rather than ranges) are now recommended. INR 2.5 for:

- treatment of deep-vein thrombosis or pulmonary embolism (including those associated with antiphospholipid syndrome or for recurrence in patients no longer receiving warfarin sodium)
- atrial fibrillation
- cardioversion—target INR should be achieved at least 3 weeks before cardioversion and anticoagulation should continue for at least 4 weeks after the procedure (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR)
- dilated cardiomyopathy
- mitral stenosis or regurgitation in patients with either atrial fibrillation, a history of systemic embolism, a left atrial thrombus, or an enlarged left atrium
- bioprosthetic heart valves in the mitral position (treat for 3 months), or in patients with a history of systemic embolism (treat for at least 3 months), or with a left atrial thrombus with surgery (treat until clot resolves), or with other risk factors (e.g. atrial fibrillation or a low ventricular ejection fraction)
- acute arterial embolism requiring embolectomy (consider long-term treatment)
- myocardial infarction
- INR 3.5 for:
- recurrent deep-vein thrombosis or pulmonary embolism in patients currently receiving anticoagulation and with an INR above 2;
- Mechanical prosthetic heart valves:
  - the recommended target INR depends on the type and location of the valve, and patient-related risk factors
  - consider increasing the INR target or adding an antiplatelet drug, if an embolic event occurs whilst anticoagulated at the target INR.

Duration

The risks of thromboembolism recurrence and anticoagulant-related bleeding should be considered when deciding the duration of anticoagulation.


- 6 weeks for isolated calf-vein deep-vein thrombosis
- 3 months for venous thromboembolism provoked by surgery or other transient risk factor (e.g. combined oral contraceptive use, pregnancy, plaster cast)
- at least 3 months for unprovoked proximal deep-vein thrombosis or pulmonary embolism; long-term anticoagulation may be required.

Haemorrhage

The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential; if the anticoagulant is stopped but not reversed, the INR should be measured 2–3 days later to ensure that it is falling. The cause of an elevated INR should be investigated. The following recommendations (which take into account the recommendations of the British Society for Haematology Guidelines on Oral Anticoagulation with Warfarin—fourth edition. Br J Haematol 2011; 154: 311–324) are based on the result of the INR and whether there is major or minor bleeding; the recommendations apply to adults taking warfarin:

- Major bleeding—stop warfarin sodium; give phytomenadione p. 958 (vitamin K) by slow intravenous injection; give dried prothrombin complex p. 105 (factors II, VII, IX, and X); if dried prothrombin complex unavailable, fresh frozen plasma can be given but is less effective; recombinant factor VIIa is not recommended for emergency anticoagulation reversal
- INR >8.0, minor bleeding—stop warfarin sodium; give phytomenadione (vitamin K) by slow intravenous injection; repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin sodium when INR <5.0
- INR >8.0, no bleeding—stop warfarin sodium; give phytomenadione (vitamin K) by mouth using the intravenous preparation orally [unlicensed use]; repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin when INR <5.0
- INR 5.0–8.0, minor bleeding—stop warfarin sodium; give phytomenadione (vitamin K) by slow intravenous injection; restart warfarin sodium when INR <5.0
- INR 5.0–8.0, no bleeding—hold 1 or 2 doses of warfarin sodium and reduce subsequent maintenance dose
- Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

Peri-operative anticoagulation

Warfarin sodium should usually be stopped 5 days before elective surgery; phytomenadione (vitamin K) by mouth (using the intravenous preparation orally [unlicensed use]) should be given the day before surgery if the INR is >1.5. If haemostasis is adequate, warfarin sodium can be resumed at the normal maintenance dose on the evening of surgery or the next day.

Patients stopping warfarin sodium prior to surgery who are considered to be at high risk of thromboembolism (e.g. those with a venous thromboembolic event within the last 3 months, atrial fibrillation with previous stroke or transient ischaemic attack, or mitral mechanical heart valve) may require interim therapy ('bridging') with a low molecular weight heparin (using treatment dose). The low molecular weight heparin should be stopped at least 24 hours before surgery; if the surgery carries a high risk of bleeding, the low molecular weight heparin should not be restarted until at least 48 hours after surgery.

Patients on warfarin sodium p. 131 who require emergency surgery that can be delayed for 6–12 hours can be given intravenous phytomenadione p. 958 (vitamin K) to reverse the anticoagulant effect. If surgery cannot be delayed, dried prothrombin complex p. 105 can be given in addition to intravenous phytomenadione (vitamin K) and the INR checked before surgery.

Combined anticoagulant and antiplatelet therapy

Existing antiplatelet therapy following an acute coronary syndrome or percutaneous coronary intervention should be continued for the necessary duration according to the indication being treated. The addition of warfarin sodium, when indicated (e.g. for venous thromboembolism or atrial fibrillation) should be considered following an assessment of the patient’s risk of bleeding and discussion with a cardiologist. The duration of treatment with dual therapy (e.g. aspirin p. 114 and warfarin sodium) or triple therapy (e.g. aspirin with clopidogrel p. 115 and warfarin sodium) should be kept to a minimum where possible. The risk of bleeding with aspirin and warfarin sodium dual therapy is lower than with clopidogrel and warfarin sodium. Depending on the indications being treated and the patient’s risk of thromboembolism, it may be possible to withhold antiplatelet therapy until warfarin sodium therapy is continued for:
complete, or vice versa (on specialist advice) in order to reduce the length of time on dual or triple therapy.

Parenteral anticoagulants

Overview

The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-moving vessels thrombi are composed mainly of platelets with little fibrin.

Heparin

Heparin initiates anticoagulation rapidly but has a short duration of action. It is often referred to as ‘standard’ or heparin (unfractionated). p. 125 to distinguish it from the low molecular weight heparins, which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, heparin (unfractionated) can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.

Low molecular weight heparins

Low molecular weight heparins (dalteparin sodium p. 123, enoxaparin sodium p. 124, and tinzaparin sodium p. 126) are usually preferred over heparin (unfractionated) in the prevention of Venous thromboembolism p. 109 because they are as effective and they have a lower risk of heparin-induced thrombocytopenia. The standard prophylactic regimen does not require anticoagulant monitoring. The duration of action of low molecular weight heparins is longer than that of heparin (unfractionated) and once-daily subcutaneous administration is possible for some indications, making them convenient to use.

Low molecular weight heparins are generally preferred over heparin (unfractionated) in the treatment of deep vein thrombosis and pulmonary embolism, and are also used in the treatment of myocardial infarction, unstable coronary artery disease (see under Acute coronary syndromes p. 201) and for the prevention of clotting in extracorporeal circuits.

Dalteparin sodium and tinzaparin sodium (only 20 000 unit/mL syringe) are also licensed for the extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours; treatment is recommended for a duration of 6 months. Treatment should be initiated by healthcare professionals experienced in the treatment of venous thromboembolism.

Heparinoids

Danaparoid sodium p. 122 is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopaedic surgery. Providing there is no evidence of cross-reactivity, it also has a role in patients who develop heparin-induced thrombocytopenia.

Argatroban

An oral anticoagulant can be given with argatroban monohydrate p. 126, but it should only be started once thrombocytopenia has substantially resolved.

Hirudins

Bivalirudin, a hirudin analogue, is a thrombin inhibitor which is licensed for unstable angina or non-ST-segment elevation myocardial infarction in patients planned for urgent or early intervention, and as an anticoagulant for patients undergoing percutaneous coronary intervention (including patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention—see also Management of ST-segment elevation myocardial infarction in Acute coronary syndromes p. 201).

Heparin flushes

The use of heparin flushes should be kept to a minimum. For maintaining patency of peripheral venous catheters, sodium chloride injection 0.9% is as effective as heparin flushes. The role of heparin flushes in maintaining patency of arterial and central venous catheters is unclear.

Epoprostenol

Epoprostenol (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated. It is also licensed for the treatment of primary pulmonary hypertension resistant to other treatment, usually with oral anticoagulation; it should be initiated by specialists in pulmonary hypertension. Epoprostenol is a potent vasodilator. It has a short half-life of approximately 3 minutes and therefore it must be administered by continuous intravenous infusion.

Fondaparinux

Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

Other drugs used for Thromboembolism Streptokinase, p. 206

ANTITHROMBOTIC DRUGS \(\rightarrow\) ANTIPLATELET DRUGS

Antiplatelet drugs

Overview

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation, because in faster-moving vessels, thrombi are composed mainly of platelets with little fibrin.

Use of aspirin p. 114 in primary prevention of cardiovascular events, in patients with or without diabetes, is of unproven benefit. Long-term use of aspirin is of benefit in established cardiovascular disease (secondary prevention); unduly high blood pressure must be controlled before aspirin is given. If the patient is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor can be added.

Aspirin is given following coronary bypass surgery. It is also used in atrial fibrillation, for intermittent claudication, for stable angina and acute coronary syndromes, for use following placement of coronary stents and for use in stroke.

Clopidogrel p. 115 is licensed for the prevention of atherothrombotic events in patients with a history of symptomatic ischaemic disease. Clopidogrel, in combination with low-dose aspirin, is also licensed for acute coronary syndrome without ST-segment elevation; in these circumstances the combination is given for up to 12 months (most benefit occurs during the first 3 months; there is no evidence of benefit beyond 12 months). Clopidogrel, in combination with low-dose aspirin, is also licensed for acute myocardial infarction with ST-segment elevation; the combination is licensed for at least 4 weeks, but the optimum treatment duration has not been established. In patients undergoing percutaneous coronary intervention, clopidogrel is used as an adjunct with aspirin. Patients who are not already taking clopidogrel should receive a loading dose prior to procedure.

Clopidogrel is also licensed, in combination with low-dose aspirin, for the prevention of atherothrombotic and thromboembolic events in patients with
atrial fibrillation (and at least one risk factor for a vascular event), and for whom warfarin sodium p. 131 is unsuitable.

Use of clopidogrel with aspirin increases the risk of bleeding. Clopidogrel monotherapy may be an alternative when aspirin is contra-indicated, for example in those with aspirin hypersensitivity, or when aspirin is not tolerated despite the addition of a proton pump inhibitor (see also NICE guidance).

Clopidogrel also has uses in stroke. Dipyridamole p. 116 is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified-release preparations are licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.

Prasugrel p. 203, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention; the combination is usually given for up to 12 months.

Ticagrelor p. 204, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome; the combination is usually given for up to 12 months.

Cangrelor p. 197, in combination with aspirin, is licensed for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received treatment with oral clopidogrel, prasugrel or ticagrelor prior to the procedure and in whom oral therapy with these drugs is not suitable. Cangrelor is to be used under expert supervision only.

Antiplatelet drugs and coronary stents
Patients selected for percutaneous coronary intervention, with the placement of a coronary stent, will require dual antiplatelet therapy with aspirin and either cangrelor, clopidogrel, prasugrel, or ticagrelor. Aspirin therapy should continue indefinitely. Clopidogrel is recommended for 1 month following elective percutaneous coronary intervention with placement of a bare-metal stent, and for 12 months if percutaneous coronary intervention with placement of a bare-metal stent was for an acute coronary syndrome; the combination is usually given for up to 12 months.

Cangrelor p. 197, in combination with aspirin, is licensed for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received treatment with oral clopidogrel, prasugrel or ticagrelor prior to the procedure and in whom oral therapy with these drugs is not suitable. Cangrelor is to be used under expert supervision only.

Antiplatelet drugs and coronary stents
Patients selected for percutaneous coronary intervention, with the placement of a coronary stent, will require dual antiplatelet therapy with aspirin and either cangrelor, clopidogrel, prasugrel, or ticagrelor. Aspirin therapy should continue indefinitely. Clopidogrel is recommended for 1 month following elective percutaneous coronary intervention with placement of a bare-metal stent, and for 12 months if percutaneous coronary intervention with placement of a bare-metal stent was for an acute coronary syndrome; the combination is usually given for up to 12 months.

Cangrelor p. 197, in combination with aspirin, is licensed for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received treatment with oral clopidogrel, prasugrel or ticagrelor prior to the procedure and in whom oral therapy with these drugs is not suitable. Cangrelor is to be used under expert supervision only.

Glycoprotein IIb/IIIa inhibitors
Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets. Abciximab p. 198 is a monoclonal antibody which binds to glycoprotein IIb/IIIa receptors and to other related sites; it is licensed as an adjunct to heparin (unfractionated) p. 125 and aspirin for the prevention of ischaemic complications in high-risk patients undergoing percutaneous transluminal coronary intervention. Abciximab should be used once only (to avoid additional risk of thrombocytopenia). Eptifibatide p. 198 (in combination with heparin (unfractionated) and aspirin) and tirofiban p. 199 (in combination with heparin (unfractionated), aspirin, and clopidogrel) also inhibit glycoprotein IIb/IIIa receptors; they are licensed for use to prevent early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction. Tirofiban is also licensed for use in combination with heparin (unfractionated), aspirin, and clopidogrel, for the reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention. Abciximab, eptifibatide and tirofiban should be used by specialists only.

Epoprostenol p. 109 is also used to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated.

Aspirin
(Acetylsalicylic Acid)

- **INDICATIONS AND DOSE**
  - **Cardiovascular disease (secondary prevention)**
    - **BY MOUTH**
      - Adult: 75 mg daily
  - **Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) / Management of ST-segment elevation myocardial infarction (STEMI)**
    - **BY MOUTH**
      - Adult: 300 mg, chewed or dispersed in water
  - **Suspected transient ischaemic attack**
    - **BY MOUTH**
      - Adult: 75 mg once daily
  - **Acute ischaemic stroke**
    - **BY MOUTH**
      - Adult: 300 mg once daily for 14 days, to be initiated 24 hours after thrombolysis or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis
  - **Atrial fibrillation following a disabling ischaemic stroke (before being considered for anticoagulant treatment)**
    - **BY MOUTH**
      - Adult: 300 mg once daily for 14 days
  - **Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve and who are at significant risk of haemorrhagic transformation**
    - **BY MOUTH**
      - Adult: 300 mg once daily, anticoagulant treatment stopped for 7 days and to be substituted with aspirin
  - **Following coronary by-pass surgery**
    - **BY MOUTH**
      - Adult: 75–300 mg daily
  - **Mild to moderate pain / Pyrexia**
    - **BY MOUTH**
      - Adult: 300–900 mg every 4–6 hours as required; maximum 4 g per day
      - **BY RECTUM**
        - Adult: 450–900 mg every 4 hours; maximum 3.6 g per day

- **CONTRA-INDICATIONS**
  - Active peptic ulceration
  - bleeding disorders (platelet dose) - children under 16 years (risk of Reye’s syndrome) - haemophilia - previous peptic ulceration (analgesic dose) - severe cardiac failure (analgesic dose)

**CONTRA-INDICATIONS, FURTHER INFORMATION**
- **Reye’s syndrome** Owing to an association with Reye’s syndrome, aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, e.g. for Kawasaki disease.
Aspirin Dispersible Tablets

▶ Aspirin (Non-proprietary)
- Aspirin 75 mg: Aspirin 75mg dispersible tablets
- Aspirin 300 mg: Aspirin 300mg dispersible tablets

Gastro-resistant tablet

▶ Aspirin (Non-proprietary)
- Aspirin 75 mg: Aspirin 75mg gastro-resistant tablets
- Aspirin 300 mg: Aspirin 300mg gastro-resistant tablets

Suppository

▶ Aspirin (Non-proprietary)
- Aspirin 150 mg: Aspirin 150mg suppositories
- Aspirin 300 mg: Aspirin 300mg suppositories

Clopidogrel

▶ INDICATIONS AND DOSE
Prevention of atherothrombotic events in percutaneous coronary intervention (adjunct with aspirin) in patients not already on clopidogrel
- By mouth
  - Adult: Loading dose 300 mg, to be taken prior to the procedure, alternatively loading dose 600 mg, higher dose may produce a greater and more rapid inhibition of platelet aggregation

Transient ischaemic attack for patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor
- By mouth
  - Adult: 75 mg once daily

Prevention of atherothrombotic events in peripheral arterial disease or within 35 days of myocardial infarction, or within 6 months of ischaemic stroke
- By mouth
  - Adult: 75 mg once daily

Prevention of atherothrombotic events in acute coronary syndrome without ST-segment elevation (given with aspirin)
- By mouth
  - Adult: Initially 300 mg, then 75 mg daily for up to 12 months
Prevention of artherothrombotic events in acute myocardial infarction with ST-segment elevation (given with aspirin)

- Adult 18–75 years: Initially 300 mg, then 75 mg for at least 4 weeks
- Adult 76 years and over: 75 mg daily for at least 4 weeks

Prevention of artherothrombotic and thromboembolic events in patients with atrial fibrillation and at least one risk factor for a vascular event (with aspirin) and for whom warfarin is unsuitable

- BY MOUTH
- Adult: 75 mg once daily

- UNLICENSED USE 600 mg loading dose prior to percutaneous coronary intervention is an unlicensed dose. Use in transient ischaemic attack or acute ischaemic stroke, in patients with aspirin hypersensitivity or intolerant of aspirin, is unlicensed.

- CONTRA-INDICATIONS Active bleeding

- CAUTIONS Discontinue 7 days before elective surgery if antiplatelet effect not desirable. Patients at risk of increased bleeding from trauma, surgery, or other pathological conditions

- INTERACTIONS Appendix 1 (clopidogrel).

Caution with concomitant use of drugs that increase risk of bleeding.

- SIDE-EFFECTS
  - Common or very common Abdominal pain; bleeding disorders (including gastro-intestinal and intracranial); diarrhoea; dyspepsia
  - Uncommon Constipation; decreased platelets; dizziness; duodenal ulcers; eosinophilia; flatulence; gastric ulcer; gastritis; headache; leucopenia; nausea; paraesthesia; pruritus; rash; vomiting
  - Rare Vertigo
  - Very rare Acquired haemophilia; acute liver failure; agranulocytosis; arthralgia; blood disorders; bronchospasm; colitis; confusion; eosinophilic pneumonia; fever; glomerulonephritis; hallucinations; hepatitis; hypersensitivity-like reactions; interstitial pneumonitis; lichen planus; pancreatitis; pancytopenia; severe thrombocytopenia; Stevens-Johnson syndrome; stomatitis; taste disturbance; thrombocytopenic purpura; toxic epidermal necrolysis; vasculitis

- ALLERGY AND CROSS-SENSITIVITY Caution with history of hypersensitivity reactions to thienopyridines (e.g. prasugrel).

- PREGNANCY Manufacturer advises avoid—no information available.

- BREAST FEEDING Manufacturer advises avoid.

- HEPATIC IMPAIRMENT Manufacturer advises caution (risk of bleeding). Avoid in severe impairment.

- RENAL IMPAIRMENT Manufacturer advises caution.

- NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (December 2010)

NICE TA210

The guidance applies to patients who have had an occlusive vascular event, or who have established peripheral arterial disease. The guidance does not apply to patients who have had, or are at risk of, stroke associated with atrial fibrillation, or who need prophylaxis for occlusive events following coronary revascularisation or carotid artery procedures.

Clopidogrel monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:

- an ischaemic stroke, or who have peripheral arterial disease or multivascular disease, or
- a myocardial infarction, only if aspirin is contra-indicated or not tolerated.

www.nice.org.uk/TA210

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2004) that clopidogrel be accepted for restricted use for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. Clopidogrel should be initiated in hospital inpatients only.

The Scottish Medicines Consortium has also advised (July 2007) that clopidogrel be accepted for restricted use for patients with ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only.

- MEDICINAL FORMS

There can be variation in the licensing of different medicine containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

- Clopidogrel (Non-proprietary)
  - Clopidogrel 75 mg Clopidogrel 75 mg tablets | 28 tablet £30.53 DT price = £1.44 | 30 tablet £32.71
  - Grepid (Beacon Pharmaceuticals Ltd)
  - Clopidogrel 75 mg Clopidogrel 75 mg tablets | 30 tablet £32.28
  - Plavix (Sanofi)
  - Clopidogrel 75 mg Plavix 75 mg tablets | 30 tablet £35.64
  - Clopidogrel (as Clopidogrel hydrogen sulfate) 300 mg Plavix 300 mg tablets | 30 tablet £142.54 DT price = £142.54

Dipyridamole

- INDICATIONS AND DOSE

Secondary prevention of ischaemic stroke (not associated with atrial fibrillation) and transient ischaemic attacks (used alone or with aspirin) Adjunct to oral antiocoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 200 mg twice daily, to be taken preferably with food

Adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves

- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: 300–600 mg daily in 3–4 divided doses

Myocardial imaging—diagnostic use only

- BY INTRAVENOUS INJECTION
  - Adult: (consult product literature)

- CAUTIONS
  - Aortic stenosis, coagulation disorders, heart failure, hypotension, left ventricular outflow obstruction—may exacerbate migraine, myasthenia gravis (risk of exacerbation), rapidly worsening angina, recent myocardial infarction

- INTERACTIONS Appendix 1 (dipyridamole).

Caution with concomitant use of drugs that increase risk of bleeding.

- SIDE-EFFECTS
  - Angioedema, dizziness, gastro-intestinal effects, hot flushes, hypersensitivity reactions, hypotension, increased bleeding after surgery, increased bleeding during surgery, myalgia, rash, severe bronchospasm, tachycardia, throbbing headache, thrombocytopenia, urticaria, worsening symptoms of coronary heart disease

- PREGNANCY
  - Not known to be harmful.

- BREAST FEEDING
  - Manufacturers advise use only if essential—small amount present in milk.
Dipyridamole with aspirin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dipyridamole p. 116, aspirin p. 114.

**INDICATIONS AND DOSE**

Secondary prevention of ischaemic stroke and transient ischaemic attacks

- **By mouth using modified-release medicines**
  - Adult: 25/200 mg twice daily

**PRESCRIBING AND DISPENSING INFORMATION**

Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>21, 25, 32</th>
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</thead>
<tbody>
<tr>
<td>- <strong>Dipyridamole with aspirin</strong></td>
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<tr>
<td>- <em>Non-proprietary</em></td>
<td></td>
</tr>
<tr>
<td>- <strong>Aspirin 25 mg</strong>, <strong>Dipyridamole 200 mg</strong></td>
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<tr>
<td>- <strong>Modified-release</strong></td>
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<tr>
<td>- <strong>Asasantin Retard</strong> (Boehringer Ingelheim Ltd)</td>
<td></td>
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<tr>
<td>- <strong>Aspirin 25</strong> mg, <strong>Dipyridamole 200 mg</strong></td>
<td></td>
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<tr>
<td>- <strong>Asasantin Retard capsules</strong></td>
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<tr>
<td>- 60 capsule <strong>PoT</strong> £9.84 DT price = £9.84</td>
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<tr>
<td>- <strong>Molita</strong> (Dr Reddy's Laboratories (UK) Ltd)</td>
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<td>- <strong>Aspirin 25 mg</strong>, <strong>Dipyridamole 200 mg</strong></td>
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<tr>
<td>- <strong>Molita 200mg/25mg modified-release capsules</strong></td>
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<td>- 100 capsule <strong>PoT</strong> £9.35</td>
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**ANTITHROMBOTIC DRUGS**

**Factor Xa inhibitors**

**Apixaban**

**Drug action** Apixaban is a direct inhibitor of activated factor X (factor Xa).

**INDICATIONS AND DOSE**

Prophylaxis of venous thromboembolism following knee replacement surgery

- **By mouth**
  - Adult: 2.5 mg twice daily for 10–14 days, to be started 12–24 hours after surgery

Prophylaxis of venous thromboembolism following hip replacement surgery

- **By mouth**
  - Adult: 2.5 mg twice daily for 32–38 days, to be started 12–24 hours after surgery

Treatment of deep-vein thrombosis | Treatment of pulmonary embolism

- **By mouth**
  - Adult: Generally 10 mg twice daily for 7 days, then maintenance 5 mg twice daily

Prophylaxis of recurrent deep-vein thrombosis | Prophylaxis of recurrent pulmonary embolism

- **By mouth**
  - Adult: 2.5 mg twice daily, following completion of 6 months anticoagulant treatment

Prophylaxis of stroke and systemic embolism in non-valvar atrial fibrillation and at least one risk factor such as previous stroke or transient ischaemic attack, symptomatic heart failure, diabetes mellitus, hypertension, or age ≥ 75 years

- **By mouth**
  - Adult 18–79 years: 5 mg twice daily
  - Adult 80 years and over (body-weight up to 61 kg): 2.5 mg twice daily
  - Adult 80 years and over (body-weight 61 kg and above): 5 mg twice daily

**Solution for injection**

- **Persantin** (Boehringer Ingelheim Ltd)
  - **Dipyridamole 5 mg per 1 ml** Persantin 10mg/2ml solution for injection ampoules | 5 ampoule **PoT** £3.82

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (December 2010) NICE TA210

**The guidance applies to patients who have had an occlusive vascular event, or who have established peripheral arterial disease. The guidance does not apply to patients who have had, or are at risk of, stroke associated with atrial fibrillation, or who need prophylaxis for occlusive events following coronary revascularisation or carotid artery procedures.**

**Modified-release dipyridamole, in combination with aspirin, is recommended as an option to prevent occlusive vascular events in patients who have had:**

- a transient ischaemic attack, or
- an ischaemic stroke, only if clopidogrel is contra-indicated or not tolerated.

**Modified-release dipyridamole monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:**

- an ischaemic stroke, only if aspirin and clopidogrel are contra-indicated or not tolerated, or
- a transient ischaemic attack, only if aspirin is contra-indicated or not tolerated.

www.nice.org.uk/TA210

**MEDITICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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</thead>
<tbody>
<tr>
<td>- <strong>Dipyridamole</strong></td>
<td></td>
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<tr>
<td>- <em>Non-proprietary</em></td>
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<td>- <strong>Dipyridamole 25 mg</strong> Dipyridamole 25mg tablets</td>
<td>84 tablet <strong>PoT</strong> £9.40 DT price = £9.40</td>
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<td>- <strong>Dipyridamole 100 mg</strong> Dipyridamole 100mg tablets</td>
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<tr>
<td>- <strong>Persantin</strong> (Boehringer Ingelheim Ltd)</td>
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<tr>
<td>- <strong>Dipyridamole 100 mg</strong> Persantin 100mg tablets</td>
<td>84 tablet <strong>PoT</strong> £6.30 DT price = £4.14</td>
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**Modified-release capsule**

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<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tr>
<td>- <strong>Dipyridamole</strong></td>
<td></td>
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<tr>
<td>- <em>Non-proprietary</em></td>
<td></td>
</tr>
<tr>
<td>- <strong>Dipyridamole 200 mg</strong> Dipyridamole 200mg modified-release capsules</td>
<td>60 capsule <strong>PoT</strong> £10.06 DT price = £10.06</td>
</tr>
<tr>
<td>- <strong>Attila</strong> (Dr Reddy's Laboratories (UK) Ltd)</td>
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<tr>
<td>- <strong>Dipyridamole 200 mg</strong> Attila 200mg modified-release capsules</td>
<td>60 capsule <strong>PoT</strong> £9.56 DT price = £10.06</td>
</tr>
<tr>
<td>- <strong>Ofcram PR</strong> (Focus Pharmaceuticals Ltd)</td>
<td></td>
</tr>
<tr>
<td>- <strong>Dipyridamole 200 mg</strong> Ofcram PR 200mg capsules</td>
<td>60 capsule <strong>PoT</strong> £10.06 DT price = £10.06</td>
</tr>
<tr>
<td>- <strong>Persantin Retard</strong> (Boehringer Ingelheim Ltd, Consilient Health Ltd)</td>
<td></td>
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<tr>
<td>- <strong>Dipyridamole 200 mg</strong> Persantin Retard 200mg capsules</td>
<td>60 capsule <strong>PoT</strong> £8.55–£10.06 DT price = £10.06</td>
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</tbody>
</table>

**Oral suspension**

| - **Dipyridamole** |
|  - *Non-proprietary* |
|  - **Dipyridamole 10 mg per 1 ml** Dipyridamole 50mg/5ml oral suspension sugar free sugar-free | 150 ml **PoT** £41.06 DT price = £41.06 |
|  - **Dipyridamole 40 mg per 1 ml** Dipyridamole 200mg/5ml oral suspension sugar free sugar-free | 150 ml **PoT** £122.78–£134.24 DT price = £133.53 |

**Solution for injection**

| - **Persantin** (Boehringer Ingelheim Ltd) |
|  - **Dipyridamole 5 mg per 1 ml** Persantin 10mg/2ml solution for injection ampoules | 5 ampoule **PoT** £3.82 |
Apixaban for the prevention of stroke and systemic embolism ▶

NATIONAL FUNDING/ACCESS DECISIONS

PRESCRIBING AND DISPENSING INFORMATION

No routine anticoagulant monitoring required (INR tests ▶

MONITORING REQUIREMENTS

Anaesthesia with postoperative indwelling catheter (risk of paralysis—monitor neurological signs and wait 20–30 hours after apixaban dose before removing catheter and do not give next dose until at least 5 hours after catheter removal) — prosthetic heart valve (efficacy not established) — risk of bleeding

INTERACTIONS ▶

Caution in concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS

Common or very common Anaemia — bruising — haemorrhage — nausea

Uncommon Hypotension — rash — thrombocytopenia

PREGNANCY Manufacturer advises avoid — no information available.

BREAST FEEDING Manufacturer advises avoid — present in milk in animal studies.

HEPATIC IMPAIRMENT Avoid in severe impairment and in hepatic disease associated with coagulopathy.

RENAI IMPAIRMENT When used for prophylaxis of stroke and systemic embolism in atrial fibrillation, reduce dose to 2.5 mg twice daily if creatinine clearance 15–29 mL/minute, or if serum-creatinine >133 micromol/litre and age ≥80 years or body-weight ≤60 kg. When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery, prophylaxis of recurrent deep-vein thrombosis or pulmonary embolism, and treatment of deep-vein thrombosis or pulmonary embolism, use with caution if creatinine clearance 15–29 mL/minute. Manufacturer advises avoid if creatinine clearance less than 15 mL/minute — no information available.

MONITORING REQUIREMENTS

Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

No routine anticoagulant monitoring required (INR tests are unreliable).

PRESCRIBING AND DISPENSING INFORMATION Duration of treatment should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e. recent surgery, trauma, immobilisation.

Apixaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (January 2012) NICE TA245

Apixaban is an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery.

www.nice.org.uk/TA245

Apixaban for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (February 2013) NICE TA275

Apixaban is an option for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation in accordance with its licensed indication; with one or more of the following risk factors:

- previous stroke or transient ischaemic attack
- symptomatic heart failure
- age ≥75 years
- diabetes mellitus
- hypertension

The risks and benefits of apixaban compared to warfarin, dabigatran etexilate, and rivaroxaban should be discussed with the patient.

www.nice.org.uk/TA275

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (June 2015) NICE TA341

Apixaban is an option for the treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults.

www.nice.org.uk/TA341

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

Eliquis (Bristol-Myers Squibb Pharmaceuticals Ltd)

Apixaban 2.5 mg Eliquis 2.5mg tablets | 10 tablet | £9.50 | 20 tablet | £19.00 | 60 tablet | £57.00 DT price = £57.00

Apixaban 5 mg Eliquis 5mg tablets | 28 tablet | £26.60 | 56 tablet | £53.20 DT price = £53.20

Edoxaban

25-Apr-2016

DRUG ACTION Edoxaban is a direct and reversible inhibitor of activated factor X (factor Xa), which prevents conversion of prothrombin to thrombin and prolongs clotting time, thereby reducing the risk of thrombus formation.

INDICATIONS AND DOSE

Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation, in patients with at least one risk factor (such as congestive heart failure, hypertension, aged 75 years and over, diabetes mellitus, previous stroke or transient ischaemic attack)

BY MOUTH

Adult (body-weight up to 61 kg): 30 mg once daily

Adult (body-weight 61 kg and above): 60 mg once daily

Treatment of deep-vein thrombosis | Prophylaxis of recurrent deep-vein thrombosis | Treatment of pulmonary embolism | Prophylaxis of recurrent pulmonary embolism

BY MOUTH

Adult (body-weight up to 61 kg): 30 mg once daily, duration of treatment adjusted according to risk factors — consult product literature, treatment should follow initial use of parenteral anticoagulant for at least 5 days

Adult (body-weight 61 kg and above): 60 mg once daily, duration of treatment adjusted according to risk factors — consult product literature, treatment should follow initial use of parenteral anticoagulant for at least 5 days

DOSE ADJUSTMENTS DUE TO INTERACTIONS

Maximum dose of 30 mg once daily with concomitant ciclosporin, dronedarone, erythromycin, or ketoconazole.

DOSE EQUIVALENCE AND CONVERSION

For information on changing from, or to, other anticoagulants, consult product literature.

CONTRA-INDICATIONS

Active bleeding • arteriovenous malformations • current or recent gastro-intestinal ulceration • hepatic disease (associated with coagulopathy
and clinically relevant bleeding risk) - known or suspected oesophageal varices - major intraspinal or intracerebral vascular abnormalities - presence of malignant neoplasms at high risk of bleeding - recent brain or spinal injury - recent brain, spinal or ophthalmic surgery - recent intracranial haemorrhage - uncontrolled severe hypertension - vascular aneurysms

CONTRA-INDICATIONS, FURTHER INFORMATION
- Risk for major bleeding. Edoxaban treatment is contra-indicated in patients with significant risk factors for major bleeding, these include those listed above.
- **CAUTIONS** Moderate to severe mitral stenosis (safety and efficacy not established) - prosthetic heart valve (safety and efficacy not established) - risk of bleeding - surgery

**INTERACTIONS** → Appendix 1 (edoxaban). Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- Common or very common Anaemia - epistaxis - haemorrhage - nausea - pruritus - rash
- Uncommon Urticaria
- Rare Allergic oedema

SIDE-EFFECTS, FURTHER INFORMATION
- Management of bleeding. Should a bleeding complication arise in a patient receiving edoxaban, the manufacturer recommends to delay the next dose or treatment should be discontinued as appropriate.
- **PREGNANCY** Manufacturer advises avoid - toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid - present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment; use with caution in mild to moderate impairment.
- **RENAL IMPAIRMENT** Manufacturer advises reduce dose to 30 mg once daily in moderate to severe impairment; avoid in end-stage renal disease or in patients undergoing dialysis.

**MONITORING REQUIREMENTS**
- Manufacturer advises monitor renal function before treatment and when clinically indicated during treatment; monitor hepatic function before treatment and repeat periodically if treatment duration longer than 1 year.
- Manufacturer advises monitor for signs of mucosal bleeding and anaemia in patients at increased risk; treatment should be stopped if severe bleeding occurs.
- No routine anticoagulant monitoring required (INR tests are unreliable).

**PATIENT AND CARER ADVICE** Patients should be provided with an alert card and advised to keep it with them at all times.

**NATIONAL FUNDING/ACCESS DECISIONS**
- Edoxaban for treating and preventing deep vein thrombosis and pulmonary embolism (August 2015) NICE TA354
- Edoxaban (Lixiana®) is recommended as an option for treating and preventing recurrent deep vein thrombosis and pulmonary embolism.
  - www.nice.org.uk/guidance/ta354
- Edoxaban for preventing stroke and systemic embolism in non-valvular atrial fibrillation (September 2015) NICE TA355
- Edoxaban (Lixiana®) is an option for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation, with one or more of the following risk factors:
  - previous stroke or transient ischaemic attack
  - congestive heart failure
  - age ≥ 75 years
  - diabetes mellitus
  - hypertension

The risks and benefits of edoxaban treatment compared to warfarin, apixaban, dabigatran etexilate, and rivaroxaban should be discussed with the patient.

www.nice.org.uk/TA355

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Lixiana** (Daichi Sankyo UK Ltd) ▼
  - Edoxaban (as Edoxaban tosylate) 15 mg → £18.50 DT price = £18.50
  - Edoxaban (as Edoxaban tosylate) 30 mg → £31.40 DT price = £31.80
  - Edoxaban (as Edoxaban tosylate) 60 mg → £51.80 DT price = £51.80

**CONTRA-INDICATIONS, FURTHER INFORMATION**
- EDOXABAN treatment is contra-indicated in patients with significant risk factors for major bleeding, these include those listed above.
- Caution with concomitant use of drugs that increase risk of bleeding.

**INTERACTIONS**
- **Drug action** Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

**Fondaparinux sodium**
- **INDICATIONS AND DOSE**
  - **Prophylaxis of venous thromboembolism in patients after undergoing major orthopaedic surgery of the hip or leg, or abdominal surgery**
    - By subcutaneous injection
    - Adult: Initially 2.5 mg, dose to be given 6 hours after surgery, then 2.5 mg once daily
  - **Prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness**
    - By subcutaneous injection
    - Adult: 2.5 mg once daily

**Treatment of superficial-vein thrombosis**
- By subcutaneous injection
- Adult (body-weight 50 kg and above): 2.5 mg once daily for at least 30 days (max. 45 days if high risk of thromboembolic complications), treatment should be stopped 24 hours before surgery and restarted at least 6 hours post operatively.

**Treatment of unstable angina and non-ST-segment elevation myocardial infarction**
- By subcutaneous injection
- Adult: 2.5 mg once daily for the first day, then (by subcutaneous injection) 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

**Treatment of ST-segment elevation myocardial infarction**
- Initially by intravenous injection, or by intravenous infusion
- Adult: Initially 2.5 mg daily for 3 days, then (by subcutaneous injection) 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

**Treatment of deep-vein thrombosis and pulmonary embolism**
- By subcutaneous injection
- Adult (body-weight up to 50 kg): 5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours)
- Adult (body-weight 50–100 kg): 7.5 mg every 24 hours, an oral anticoagulant (usually warfarin) is continued →
Cardiovascular system

When used for treatment of acute coronary syndromes or prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis, caution in severe impairment (increased risk of bleeding). Avoid if eGFR less than 120 ml/minute/1.73 m².

When used for prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis, reduce dose to 1.5 mg daily, if eGFR 20–50 ml/minute/1.73 m². When used for treatment of acute coronary syndromes or prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis, avoid if eGFR less than 20 ml/minute/1.73 m². When used for treatment of venous thromboembolism, use with caution if eGFR 30–50 ml/minute/1.73 m², avoid if eGFR less than 30 ml/minute/1.73 m².

For intravenous infusion (Arixtra™), give intermittently in Sodium chloride 0.9%. For ST-segment elevation myocardial infarction, add requisite dose to 25–50 ml infusion fluid and give over 1–2 minutes.

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Fondaparinux sodium (Non-proprietary)
  - Fondaparinux sodium 5 mg per 1 ml Fondaparinux sodium 2.5mg/0.5ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£62.79)
  - Fondaparinux sodium 12.5 mg per 1 ml Fondaparinux sodium 5mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£3.90)

- Arixtra (Aspen Pharma Trading Ltd)
  - Arixtra 2.5mg/0.5ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£62.79)
  - Arixtra 7.5mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£116.53)

Fondaparinux sodium 12.5 mg per 1 ml Arixtra 7.5mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£116.53)

Fondaparinux sodium 10mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£110.70)

Fondaparinux sodium 7.5mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£110.70)

- Arixtra 10mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£116.53)

Rivaroxaban

DRUG ACTION Rivaroxaban is a direct inhibitor of activated factor X (factor Xa).

INDICATIONS AND DOSE

Prophylaxis of venous thromboembolism following knee replacement surgery

- BY MOUTH
  - Adult: 10 mg once daily for 2 weeks, to be started 6–10 hours after surgery

Prophylaxis of venous thromboembolism following hip replacement surgery

- BY MOUTH
  - Adult: 10 mg once daily for 5 weeks, to be started 6–10 hours after surgery

Initial treatment of deep-vein thrombosis | Initial treatment of pulmonary embolism

- BY MOUTH
  - Adult: Initially 15 mg twice daily for 21 days, to be taken with food

Continued treatment of deep-vein thrombosis (following initial treatment) | Continued treatment of pulmonary embolism (following initial treatment) | Prophylaxis of recurrent deep-vein thrombosis | Prophylaxis of recurrent pulmonary embolism

- BY MOUTH
  - Adult: 20 mg once daily, to be taken with food

Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age ≥ 75 years, or diabetes mellitus

- BY MOUTH
  - Adult: 20 mg once daily, to be taken with food

Prophylaxis of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel)

- BY MOUTH
  - Adult: 2.5 mg twice daily usual duration 12 months

DOSE EQUIVALENCE AND CONVERSION

For information on changing from, or to, other anticoagulants—consult product literature.

CONTRA-INDICATIONS Active bleeding | acute coronary syndrome—previous stroke | acute coronary syndrome—transient ischaemic attack | malignant neoplasms | oesophageal varices | recent brain surgery | recent gastrointestinal ulcer | recent intracranial haemorrhage | recent ophthalmic surgery | recent spine surgery | significant risk of major bleeding | vascular aneurysm

CAUTIONS Anaesthesia with postoperative indwelling epidural catheter (risk of paraly—monitor neurological signs and wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal) | bronchiectasis | prosthetic heart valve (efficacy not established) | risk of

CONTRA-INDICATIONS

Active bleeding, bacterial endocarditis

CAUTIONS

Active gastro-intestinal ulcer disease | bleeding disorders | brain surgery | elderly patients | low bodyweight | ophthalmic surgery | recent intracranial haemorrhage | risk of catheter thrombus during percutaneous coronary intervention | spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses) | surgical

INTERACTIONS

Appendix 1 (fondaparinux). Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS

Common or very common
  - Anaemia | bleeding | purpura

Uncommon
  - Chest pain | dyspnoea | gastro-intestinal disturbances | hepatic impairment | oedema | pruritus | rash | thrombocytopenia | thrombocytopenia

Rare
  - Anxiety | confusion | cough | dizziness | drowsiness | flushing | headache | hyperbilirubinaemia | hypokalaemia | hypotension | injection-site reactions | vertigo

Frequency not known
  - Atrial fibrillation | pyrexia | tachycardia

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs possible risk—no information available.

BREAST FEEDING

Present in milk in animal studies—manufacturer advises avoid.

HEPATIC IMPAIRMENT

Caution in severe impairment (increased risk of bleeding).

RENAL IMPAIRMENT

Increased risk of bleeding in renal impairment.

When used for prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis—Reduce dose to 1.5 mg daily if eGFR 20–50 ml/minute/1.73 m².

When used for treatment of acute coronary syndromes or prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis—Avoid if eGFR less than 20 ml/minute/1.73 m².

When used for treatment of venous thromboembolism—Use with caution if eGFR 30–50 ml/minute/1.73 m², avoid if eGFR less than 30 ml/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Arixtra™), give intermittently in Sodium chloride 0.9%. For ST-segment elevation myocardial infarction, add requisite dose to 25–50 ml infusion fluid and give over 1–2 minutes.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
bleeding. Rivaroxaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy. Severe hypertension or vascular retinopathy

**INTERACTIONS** → Appendix 1 (rivaroxaban). Caution in concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain, constipation, diarrhoea, dizziness, dyspepsia, haemorrhage, headache, hypotension, nausea, pain in extremities, pruritus, rash, renal impairment, vomiting
- **Uncommon** Angioedema, dry mouth, malaise, syncope, tachycardia, thrombocythaemia
- **Rare** Jaundice, oedema

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Avoid in liver disease with coagulopathy.

**RENAL IMPAIRMENT** When used for treatment of deep-vein thrombosis or pulmonary embolism and prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism, initially 15 mg twice daily for 21 days, then 20 mg once daily (but consider reducing to 15 mg once daily if risk of bleeding outweighs risk of recurrent deep-vein thrombosis or pulmonary embolism) if creatinine clearance 15–49 mL/minute. For prophylaxis of stroke and systemic embolism in atrial fibrillation, reduce dose to 15 mg once daily if creatinine clearance 15–49 mL/minute. When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery and prophylaxis of atherothrombotic events in acute coronary syndrome, use with caution if creatinine clearance 15–29 mL/minute.

Use with caution if concomitant use of drugs that increase plasma-rivaroxaban concentration (consult product literature).

Avoid if creatinine clearance less than 15 mL/minute; manufacturer recommends Cockcroft and Gault formula to calculate creatinine clearance.

**MONITORING REQUIREMENTS**
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- No routine anticoagulant monitoring required (INR tests are unreliable).

**DIRECTIONS FOR ADMINISTRATION** Tablets may be crushed and mixed with water or apple puree just before administration.

**PRESCRIBING AND DISPENSING INFORMATION** Low-dose rivaroxaban, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers. Treatment should be started as soon as possible after the patient has been stabilised following the acute coronary event, at the earliest 24 hours after admission to hospital, and at the time when parenteral anticoagulation therapy would normally be discontinued; the usual duration of treatment is 12 months.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (April 2009) NICE TA170
- Rivaroxaban is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery. www.nice.org.uk/TA170
- Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation (May 2012) NICE TA256
- Rivaroxaban is an option for the prevention of stroke and systemic embolism (in accordance with its licensed indication) in patients with non-valvular atrial fibrillation and with at least one of the following risk factors:
  - previous stroke or transient ischaemic attack
  - congestive heart failure
  - age ≥75 years
  - diabetes mellitus
  - hypertension
- The risks and benefits of rivaroxaban compared with warfarin should be discussed with the patient. www.nice.org.uk/TA256
- Rivaroxaban for the treatment of deep-vein thrombosis and prevention of recurrent deep-vein thrombosis and pulmonary embolism (July 2012) NICE TA261
- Rivaroxaban is an option for the treatment of deep-vein thrombosis and prevention of recurrent deep-vein thrombosis and pulmonary embolism in adults after diagnosis of acute deep-vein thrombosis. www.nice.org.uk/TA261
- Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (June 2013) NICE TA287
- Rivaroxaban is an option for treating pulmonary embolism and preventing recurrent deep-vein thrombosis and pulmonary embolism in adults. www.nice.org.uk/TA287
- Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (March 2015) NICE TA335
- Rivaroxaban is an option within its marketing authorisation, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in patients who have had an acute coronary syndrome with elevated cardiac biomarkers. The patient’s risk of bleeding should be carefully assessed before treatment is initiated and the risks and benefits of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone should be discussed with the patient.
- A decision on continuation of treatment should be taken no later than 12 months after starting treatment. www.nice.org.uk/TA335

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (January 2012) that rivaroxaban (Xarelto®) is accepted for restricted use within NHS Scotland for the prevention of stroke and systemic embolism in accordance with the licensed indication; use is restricted to patients with poor INR control despite compliance with coumarin anticoagulant therapy, or to patients who are allergic to, or unable to tolerate, a coumarin anticoagulant.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Xarelto (Bayer Plc) ▼
  - Rivaroxaban 2.5 mg Xarelto 2.5mg tablets ▼ 56 tablet Pot £50.40
  - DT price = £50.40

**Thromboembolism** 121
ANTITHROMBOTIC DRUGS > HEPARINOIDS

Danaparoid sodium

**INDICATIONS AND DOSE**

Prevention of deep-vein thrombosis in general or orthopaedic surgery

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 750 units twice daily for 7–10 days, initiate treatment before operation, with last pre-operative dose 1–4 hours before surgery

**Thromboembolic disease in patients with history of heparin-induced thrombocytopenia**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult (body-weight up to 55 kg): Initially 1250 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days
  - Adult (body-weight 55–89 kg): Initially 2500 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days
  - Adult (body-weight 90 kg and above): Initially 3750 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days

**CONTRA-INDICATIONS**

Active peptic ulcer (unless this is the reason for operation), acute bacterial endocarditis, diabetic retinopathy, epidermal anaesthesia (with treatment doses), haemophilia and other haemorrhagic disorders, recent cerebral haemorrhage, severe hypertension, spinal anaesthesia (with treatment doses), thrombocytopenia (unless patient has heparin-induced thrombocytopenia)

**CAUTIONS**

Antibodies to heparins (risk of antibody-induced thrombocytopenia), body-weight over 90 kg, recent bleeding, risk of bleeding

**INTERACTIONS**

Appendix 1 (danaparoid).

Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

Bleeding, hypersensitivity reactions, rash

**PREGNANCY**

Manufacturer advises avoid—limited information available but not known to be harmful.

**BREAST FEEDING**

Amount probably too small to be harmful but manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Caution in moderate impairment (increased risk of bleeding). Avoid in severe impairment unless patient has heparin-induced thrombocytopenia and no alternative available.

**RENAL IMPAIRMENT**

Use with caution in moderate impairment. Avoid in severe impairment unless patient has heparin-induced thrombocytopenia and no alternative available. Increased risk of bleeding in renal impairment, monitor anti-Factor Xa activity.

**MONITORING REQUIREMENTS**

Monitor anti factor Xa activity in patients with body-weight over 90 kg.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Orgaran®), give continuously in Glucose 5% or Sodium chloride 0.9%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Danaparoid sodium (Non-proprietary)
  - Danaparoid sodium 1250 unit per 1 ml
  - Danaparoid sodium

**ANTITHROMBOTIC DRUGS > HEPARINS**

Heparins

**CONTRA-INDICATIONS**

Acute bacterial endocarditis, after major trauma, epidermal anaesthesia with treatment doses, haemophilia and other haemorrhagic disorders, peptic ulcer, recent cerebral haemorrhage, recent surgery to eye, recent surgery to nervous system, severe hypertension, spinal anaesthesia with treatment doses, thrombocytopenia (including history of heparin-induced thrombocytopenia)

**CAUTIONS**

Elderly

**INTERACTIONS**

Appendix 1 (heparins).

Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

Rare: Alopecia (on prolonged use), anaphylaxis, angioedema, hyperkalaemia, hypersensitivity reactions, injection-site reactions, osteoporosis (risk lower with low molecular weight heparins), priapism, rebound hyperlipidaemia (following unfractionated heparin withdrawal), skin necrosis, urticaria

Frequency not known: Haemorrhage, thrombocytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**

- Haemorrhage. If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate is a specific antitoxin (but only partially reverses the effects of low molecular weight heparins).

- Heparin-induced thrombocytopenia. Clinically important heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis.

- Signs of heparin-induced thrombocytopenia include a 30% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be stopped and an alternative anticoagulant, such as danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin.

- Hyperkalaemia. Inhibition of aldosterone secretion by unfractionated or low molecular weight heparin in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy.

**ALLERGY AND CROSS-SENSITIVITY**

Hypersensitivity to unfractionated or low molecular weight heparin.

**MONITORING REQUIREMENTS**

Heparin-induced thrombocytopenia. Platelet counts should be measured just before treatment with unfractionated or low molecular weight heparin, and regular monitoring of platelet counts may be required if given for longer than 4 days. See the British Society for Haematology’s Guidelines on the diagnosis and management of heparin-induced thrombocytopenia.

- Hyperkalaemia: Plasma-potassium concentration should be measured in patients at risk of hyperkalaemia before starting the heparin and monitored regularly thereafter, particularly if treatment is to be continued for longer than 7 days.

### Dalteparin sodium

#### INDICATIONS AND DOSE

**FRAGMIN**

**Treatment of deep-vein thrombosis, with oral anticoagulant treatment** | **Treatment of pulmonary embolism, with oral anticoagulant treatment**
---|---
- **BY SUBCUTANEOUS INJECTION**
- **Adult:** 200 units/kg daily (max. per dose 18 000 units) until adequate oral anticoagulation established

**Treatment of deep-vein thrombosis, with oral anticoagulant treatment (in patients at increased risk of haemorrhage)** | **Treatment of pulmonary embolism, with oral anticoagulant treatment (in patients at increase risk of haemorrhage)**
---|---
- **BY SUBCUTANEOUS INJECTION**
- **Adult:** 100 units/kg twice daily until adequate oral anticoagulation established

**Unstable coronary artery disease**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** 120 units/kg every 12 hours (max. per dose 10 000 units twice daily) for 5–8 days

**Prevention of clotting in extracorporeal circuits**

- TO THE DEVICE AS A FLUSH
- **Adult:** (consult product literature)

**FRAGMIN GRADUATED SYRINGES**

**Unstable coronary artery disease (including non-ST-segment-elevation myocardial infarction)**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** 120 units/kg every 12 hours (max. per dose 10 000 units twice daily) for up to 8 days

**Patients with unstable coronary artery disease (including non-ST-segment-elevation myocardial infarction)**

- **awaiting angiography or revascularisation and having already had 5 days treatment with dalteparin**
- **BY SUBCUTANEOUS INJECTION**
- **Adult (body-weight up to 70 kg and male):** 5000 units every 12 hours until the day of the procedure (max. 45 days).
- **Adult (body-weight up to 80 kg and female):** 5000 units every 12 hours until the day of the procedure (max. 45 days).
- **Adult (body-weight 70 kg and above and male):** 7500 units every 12 hours until the day of the procedure (max. 45 days).
- **Adult (body-weight 80 kg and above and female):** 7500 units every 12 hours until the day of the procedure (max. 45 days).

**FRAGMIN SINGLE-DOSE SYRINGES**

**Prophylaxis of deep-vein thrombosis in surgical patients—moderate risk**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** Initially 2500 units for 1 dose, dose to be given 1–2 hours before surgery, then 2500 units every 24 hours

**Prophylaxis of deep-vein thrombosis in surgical patients—high risk**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** Initially 2500 units for 1 dose, dose to be administered 1–2 hours before surgery, followed by 2500 units after 8–12 hours, then 5000 units every 24 hours, alternatively initially 5000 units for 1 dose, dose to be given on the evening before surgery, followed by 5000 units after 24 hours, then 5000 units every 24 hours

**Prophylaxis of deep-vein thrombosis in medical patients**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** 5000 units every 24 hours

**Treatment of deep-vein thrombosis, with oral anticoagulant treatment** | **Treatment of pulmonary embolism, with oral anticoagulant treatment**
---|---
- **BY SUBCUTANEOUS INJECTION**
- **Adult (body-weight up to 46 kg):** 7500 units once daily until adequate oral anticoagulation established
- **Adult (body-weight 46–56 kg):** 10 000 units once daily until adequate oral anticoagulation established
- **Adult (body-weight 57–68 kg):** 12 500 units once daily until adequate oral anticoagulation established
- **Adult (body-weight 69–82 kg):** 15 000 units once daily until adequate oral anticoagulation established
- **Adult (body-weight 83 kg and above):** 18 000 units once daily until adequate oral anticoagulation established

**Extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours**

- **BY SUBCUTANEOUS INJECTION**
- **Adult (body-weight 40–45 kg):** 7500 units once daily for 30 days, then 7500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- **Adult (body-weight 46–56 kg):** 10 000 units once daily for 30 days, then 7500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- **Adult (body-weight 57–68 kg):** 12 500 units once daily for 30 days, then 10 000 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- **Adult (body-weight 69–82 kg):** 15 000 units once daily for 30 days, then 12 500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- **Adult (body-weight 83–98 kg):** 18 000 units once daily for 30 days, then 15 000 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- **Adult (body-weight 99 kg and above):** 18 000 units once daily for 30 days, then 18 000 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature

**Treatment of venous thromboembolism in pregnancy**

- **BY SUBCUTANEOUS INJECTION**
- **Adult (body-weight up to 50 kg):** 5000 units twice daily, use body-weight in early pregnancy to calculate the dose
- **Adult (body-weight 50–69 kg):** 6000 units twice daily, use body-weight in early pregnancy to calculate the dose
- **Adult (body-weight 70–89 kg):** 8000 units twice daily, use body-weight in early pregnancy to calculate the dose
- **Adult (body-weight 90 kg and above):** 10 000 units twice daily, use body-weight in early pregnancy to calculate the dose

**UNLICENSED USE** Not licensed for treatment of venous thromboembolism in pregnancy.
Enoxaparin sodium

**INDICATIONS AND DOSE**

**Treatment of venous thromboembolism in pregnancy**

- **By subcutaneous injection**
  - Adult (body-weight up to 50 kg): 40 mg twice daily, dose based on early pregnancy body-weight

**Prophylaxis of deep-vein thrombosis, especially in surgical patients—moderate risk**

- **By subcutaneous injection**
  - Adult: 20 mg for 1 dose, dose to be given approximately 2 hours before surgery, then 20 mg every 24 hours

**Prophylaxis of deep-vein thrombosis, especially surgical patients—high risk (e.g. orthopaedic surgery)**

- **By subcutaneous injection**
  - Adult: 40 mg for 1 dose, dose to be given 12 hours before surgery, then 40 mg every 24 hours

**Prophylaxis of deep-vein thrombosis in medical patients**

- **By subcutaneous injection**
  - Adult: 40 mg every 24 hours

**Treatment of deep-vein thrombosis | Treatment of pulmonary embolism**

- **By subcutaneous injection**
  - Adult: 1.5 mg/kg every 24 hours until adequate oral anticoagulation established

**Treatment of acute ST-segment elevation myocardial infarction (patients not undergoing percutaneous coronary intervention)**

- **Initially by intravenous injection**
  - Adult 18–74 years: Initially 30 mg, followed by (by subcutaneous injection) 1 mg/kg for 1 dose, then (by subcutaneous injection) 1 mg/kg every 12 hours (max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only

- **By subcutaneous injection**
  - Adult 75 years and over: 750 micrograms/kg every 12 hours (max. per dose 75 mg), maximum dose applies for the first two doses only

**Treatment of acute ST-segment elevation myocardial infarction (patients undergoing percutaneous coronary intervention)**

- **Initially by intravenous injection**
  - Adult 18–74 years: Initially 30 mg, followed by (by subcutaneous injection) 1 mg/kg for 1 dose, then (by subcutaneous injection) 1 mg/kg every 12 hours (max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only, then (by intravenous injection) 300 micrograms/kg for 1 dose, dose to be given at the time of procedure if the last subcutaneous dose was given more than 8 hours previously

- **Initially by subcutaneous injection**
  - Adult 75 years and over: 750 micrograms/kg every 12 hours (max. per dose 75 mg), maximum dose applies for the first two doses only, then (by intravenous injection) 300 micrograms/kg for 1 dose, dose to be given at the time of procedure if the last subcutaneous dose was given more than 8 hours previously

**Unstable angina | Non-ST-segment-elevation myocardial infarction**

- **By subcutaneous injection**
  - Adult: 1 mg/kg every 12 hours usually for 2–8 days (minimum 2 days)

**Prevention of clotting in extracorporeal circuits**

- **To the device as a flush**
  - Adult: (consult product literature)

**Dose equivalence and conversion**

- 1 mg equivalent to 100 units.

**Unlicensed use**

- Not licensed for treatment of venous thromboembolism in pregnancy.
Treatment of deep-vein thrombosis

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Loading dose 5000 units, alternatively (by intravenous injection) loading dose 75 units/kg, followed by (by continuous infusion) 18 units/kg/hour, alternatively (by subcutaneous injection) 15 000 units every 12 hours, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly.

Thromboprophylaxis in medical patients

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000 units every 8–12 hours

Thromboprophylaxis in surgical patients

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000 units for 1 dose, to be taken 2 hours before surgery, then 5000 units every 8–12 hours

Thromboprophylaxis during pregnancy

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000–10 000 units every 12 hours, to be administered with monitoring. **Important:** prevention of prosthetic heart-valve thrombosis in pregnancy calls for specialist management.

Haemodialysis

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 1000–5000 units, followed by (by continuous intravenous infusion) 250–1000 units/hour

Prevention of clotting in extracorporeal circuits

- **TO THE DEVICE AS A FLUSH**
  - Adult: (consult product literature)
  - To maintain patency of catheters, cannulas, other indwelling intravenous infusion devices
    - **TO THE DEVICE AS A FLUSH**
    - Adult: 10–200 units, to be flushed through every 4–8 hours, not for therapeutic use

Heparin (unfractionated)

- **INDICATIONS AND DOSE**
  - **Treatment of mild to moderate pulmonary embolism**
  - **Treatment of unstable angina**
  - **Treatment of acute peripheral arterial occlusion**
    - **INITIALLY BY INTRAVENOUS INJECTION**
      - Adult: Loading dose 5000 units, alternatively (by intravenous injection) loading dose 75 units/kg, followed by (by continuous intravenous infusion) 18 units/kg/hour, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly.

- **Treatment of severe pulmonary embolism**
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Loading dose 10 000 units, followed by (by continuous intravenous infusion) 18 units/kg/hour, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly.

Heparin (unfractionated) (Non-proprietary)

<table>
<thead>
<tr>
<th>Heparin sodium 1000 unit per 1 ml</th>
<th>10 ampoule</th>
<th>£14.85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin sodium 5000 units/5ml solution for injection ampoules</td>
<td>10 ampoule</td>
<td>£87.93</td>
</tr>
<tr>
<td>Heparin sodium 10,000 units/10ml solution for injection ampoules</td>
<td>10 ampoule</td>
<td>£64.50–£64.59</td>
</tr>
</tbody>
</table>

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
- **Solution for injection**
  - Clexane (Sanofi)
    - **Exciipients:** May contain Benzyl alcohol
      - Enoxaparin sodium 100 mg per 1 ml: Clexane 60mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £39.26 DT price = £39.26
      - Clexane 300mg/3ml solution for injection multidose vials | 1 vial | £12.32
      - Clexane 80mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £55.13 DT price = £55.13
      - Clexane 40mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £30.27 DT price = £30.27
      - Clexane 100mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £72.30 DT price = £72.30
      - Clexane 20mg/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £20.86 DT price = £20.86
    - **Enoxaparin sodium 150 mg per 1 ml**
      - Clexane Forte 120mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £87.93 DT price = £87.93
      - Clexane Forte 150mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £99.91 DT price = £99.91

**PRECAUTIONS**

- Low body-weight (increased risk of bleeding)
- Not known to be harmful, low molecular weight heparins do not cross the placenta. Multidose vial contains benzyl alcohol—avoid.
- Due to the relatively high molecular weight of enoxaparin and inactivation in the gastro-intestinal tract, passage into breast-milk and absorption by the nursing infant are likely to be negligible; however manufacturers advise avoid.
- Manufacturer advises caution—no information available.
- Risk of bleeding increased; reduce dose if eGFR less than 30 ml/minute/1.73 m²—consult product literature for details. Use of unfractionated heparin may be preferable.
- Routine monitoring of anti-Factor Xa activity is not usually required during treatment with enoxaparin, but may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).
- When administered in conjunction with a thrombolytic, enoxaparin should be given between 15 minutes before and 30 minutes after the start of thrombolytic therapy.

**MEDICATIONS**

- **Hepatic Impairment**
  - Risk of bleeding increased; reduce dose if eGFR less than 30 ml/minute/1.73 m²—consult product literature for details. Use of unfractionated heparin may be preferable.
- **Renal Impairment**
  - Risk of bleeding increased in severe renal impairment (including oesophageal varices).
- **Breast Feeding**
  - Not excreted into milk due to high molecular weight.
- **Hepatic Impairment**
  - Risk of bleeding increased—reduce dose or avoid in severe impairment (including oesophageal varices).
- **Renal Impairment**
  - Risk of bleeding increased in severe impairment—dose may need to be reduced.
- **Directions for Administration**
  - For **intravenous infusion devices**
    - **To the device as a flush**
      - Adult: 10–200 units, to be flushed through every 4–8 hours, not for therapeutic use.

**PRESCRIBING AND DISPENSING INFORMATION**

- Doses listed take into account the guidelines of the British Society for Haematology.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion.
Heparin sodium 5000 unit per 1 ml Heparin sodium 5,000 units/1 ml solution for injection ampoules | 10 ampoule (PoM) £29.04 Heparin sodium 25,000 units/5ml solution for injection vials | 10 vial (PoM) £45.00–£94.60 Heparin sodium 25,000 units/5ml solution for injection ampoules | 10 ampoule (PoM) £75.78 Heparin calcium 25000 unit per 1 ml Heparin calcium 5,000 units/0.2ml solution for injection ampoules | 10 ampoule (PoM) £76.95 Heparin sodium 5000 units/0.2ml solution for injection ampoules | 10 ampoule (PoM) £37.35

Infusion

- Heparin (unfractionated) (Non-proprietary)
  - Heparin sodium 2 unit per 1 ml Heparin sodium 1,000 units/500ml infusion Viaflex bags | 1 bag (PoM) no price available Heparin sodium 2,000 units/1,000ml infusion Viaflex bags | 1 bag (PoM) no price available
  - Heparin sodium 5 unit per 1 ml Heparin sodium 5,000 units/1litre infusion Viaflex bags | 1 bag (PoM) no price available

Intravenous flush

EXCIPIENTS: May contain Benzyl alcohol
- Heparin (unfractionated) (Non-proprietary)
  - Heparin sodium 10 unit per 1 ml Heparin sodium 50 units/5ml patency solution ampoules | 10 ampoule (PoM) £14.96 Heparin sodium 50 units/5ml I.V. flush solution ampoules | 10 ampoule (PoM) £14.96
  - Heparin sodium 100 unit per 1 ml Heparin sodium 200 units/2ml I.V. flush solution ampoules | 10 ampoule (PoM) £15.68 Heparin sodium 200 units/2ml patency solution ampoules | 10 ampoule (PoM) £15.68

Prevention of clotting in extracorporeal circuits

- TO THE DEVICE AS A FLUSH
- Adult: (consult product literature)

INNOHEP® 10,000 UNITS/ML

Prophylaxis of deep-vein thrombosis (general surgery)

- BY SUBCUTANEOUS INJECTION
  - Adult: 3500 units for 1 dose, to be given 2 hours before surgery, then 3500 units every 24 hours

Prophylaxis of deep-vein thrombosis (orthopaedic surgery)

- BY SUBCUTANEOUS INJECTION
  - Adult: Initially 50 units/kg for 1 dose, to be given 2 hours before surgery, then 50 units/kg every 24 hours, alternatively initially 4500 units for 1 dose, dose to be given 12 hours before surgery, then 4500 units every 24 hours

Prevention of clotting in extracorporeal circuits

- TO THE DEVICE AS A FLUSH
- Adult: (consult product literature)

INNOHEP® 20,000 UNITS/ML

Extended treatment of venous thromboembolism in patients with solid tumours | Prophylaxis of venous thromboembolism in patients with solid tumours

- BY SUBCUTANEOUS INJECTION
  - Adult: 175 units/kg once daily for up to 6 months

Treatment of deep-vein thrombosis | Treatment of pulmonary embolism

- BY SUBCUTANEOUS INJECTION
  - Adult: 175 units/kg once daily until adequate oral anticoagulation established, treatment regimens do not require anticoagulation monitoring

Treatment of venous thromboembolism in pregnancy

- BY SUBCUTANEOUS INJECTION
  - Adult: 175 units/kg once daily, dose based on early pregnancy body-weight, treatment regimens do not require anticoagulation monitoring

- UNLICENSED USE Not licensed for the treatment of venous thromboembolism in pregnancy.

- SIDE-EFFECTS
  - Uncommon Headache
  - PREGNANCY Not known to be harmful, low molecular weight heparins do not cross the placenta. Vials contain benzyl alcohol—manufacturer advises avoid.
  - BREAST FEEDING Due to the relatively high molecular weight of tinzaparin and inactivation in the gastrointestinal tract, passage into breast-milk and absorption by the nursing infant are likely to be negligible; however manufacturer advise avoid.
  - RENAL IMPAIRMENT Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m². Risk of bleeding may be increased. Unfractionated heparin may be preferable. In renal impairment monitoring of anti–Factor Xa may be required if eGFR less than 30 mL/minute/1.73 m²
  - MONITORING REQUIREMENTS Routine monitoring of anti–Factor Xa activity is not usually required during treatment with tinzaparin, but may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol, sulfites
- INNOHEP (LEO Pharma)
  - Tinzaparin sodium 10000 unit per 1 ml Innohep 20,000 units/2ml solution for injection vials | 10 vial (PoM) £105.66 DT price = £105.66
  - Tinzaparin sodium 20000 unit per 1 ml Innohep 18,000 units/0.9ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (PoM) £64.25 | 10 pre-filled disposable injection (PoM) £107.08 DT price = £107.08
  - Innohep 8,000 units/0.4ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (PoM) £28.56 | 10 pre-filled disposable injection (PoM) £47.60 DT price = £47.60
  - Innohep 4,000 units/0.2ml solution for injection vials | 1 vial (PoM) £34.20 DT price = £34.20
  - Innohep 16,000 units/0.8ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (PoM) £57.12 | 10 pre-filled disposable injection (PoM) £95.20
  - Innohep 12,000 units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (PoM) £42.84 | 10 pre-filled disposable injection (PoM) £71.40 DT price = £71.40
  - Innohep 14,000 units/0.7ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (PoM) £49.98 | 10 pre-filled disposable injection (PoM) £83.30 DT price = £83.30
  - Innohep 10,000 units/0.5ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (PoM) £35.70 | 10 pre-filled disposable injection (PoM) £59.50

ANTITHROMBOTIC DRUGS > THROMBIN INHIBITORS, DIRECT

Argatroban monohydrate

- INDICATIONS AND DOSE
  - Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment
    - INITIALLY BY CONTINUOUS INTRAVENOUS INFUSION
    - Adult: Initially 2 micrograms/kg/minute, dose to be adjusted according to activated partial thromboplastin time, (by intravenous infusion) increased to up to 10 micrograms/kg/minute maximum duration of treatment 14 days
  - Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment (for dose in cardiac surgery, percutaneous coronary intervention, or critically ill patients)
    - BY CONTINUOUS INTRAVENOUS INFUSION
      - Adult: (consult product literature)
Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment (when initiating concomitant warfarin treatment)

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Reduced to 2 micrograms/kg/minute, dose should be temporarily reduced and INR measured after 4–6 hours; warfarin should be initiated at intended maintenance dose (do not give loading dose of warfarin); consult product literature for further details

- **CAUTIONS** Bleeding disorders, diabetics, retinopathy, gastrointestinal ulceration, immediately after lumbar puncture, major surgery, severe hypertension, renal impairment

- **INTERACTIONS** → Appendix 1 (argatroban)
  - Caution with concomitant use of drugs that increase risk of bleeding.

- **SIDE-EFFECTS**
  - Common or very common: Haemorrhage, nausea, purpura
  - Uncommon: Alopecia, constipation, deafness, diarrhoea, dizziness, fever, gastritis, headache, hepatic failure, hepatomegaly, hiccups, hyperbilirubinaemia, hypertension, hypoglycaemia, hypotension, malaise, muscle weakness, myalgia, rash, renal impairment, sweating, syncope, tachycardia, visual disturbance, vomiting

- **PREGNANCY** Manufacturer advises avoid unless essential—limited information available.

- **BREAST FEEDING** Avoid—no information available.

- **HEPATIC IMPAIRMENT** Reduce initial dose to 500 nanograms/kg/minute in moderate impairment. Avoid in severe impairment or in patients with hepatic impairment undergoing percutaneous coronary intervention.

- **MONITORING REQUIREMENTS** Determine activated partial thromboplastin time 2 hours after start of treatment, then 2 or 4 hours after infusion rate altered (consult product literature), and at least once daily thereafter.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Exembol®) give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute each 2.5–mL vial with 250 mL infusion fluid.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for infusion**
    - **EXCIPIENTS**: May contain Ethanol
    - **Exembol** (Mitsubishi Tanabe Pharma Europe Ltd)
      - Argatroban monohydrate 100 mg per 1 mL
      - Exembol 250mg/2.5mL concentrate for solution for infusion vials | 1 vial [POM] no price available

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**Bivalirudin**

- **DRUG ACTION** Bivalirudin, a hirudin analogue, is a thrombin inhibitor.

- **INDICATIONS AND DOSE**
  - **Unstable angina or non-ST-segment elevation myocardial infarction in patients planned for urgent or early intervention (in addition to aspirin and clopidogrel)**
    - **INITIALLY BY INTRAVENOUS INJECTION**
    - Adult: Initially 100 micrograms/kg, then (by intravenous infusion) 250 micrograms/kg/hour (for up to 72 hours in medically managed patients)

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**Unstable angina or non-ST-segment elevation myocardial infarction (in addition to aspirin and clopidogrel) in patients proceeding to percutaneous coronary intervention or coronary artery bypass surgery without cardiopulmonary bypass**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 100 micrograms/kg for 1 dose, then (by intravenous injection) 500 micrograms/kg for 1 dose, then (by intravenous infusion) 1.75 mg/kg/hour for duration of procedure; (by intravenous infusion) reduced to 250 micrograms/kg/hour for 4–12 hours as necessary following percutaneous coronary intervention, for patients proceeding to coronary artery bypass surgery with cardiopulmonary bypass, discontinue intravenous infusion 1 hour before procedure and treat with unfractionated heparin

Anticoagulation in patients undergoing percutaneous coronary intervention including patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (in addition to aspirin and clopidogrel)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 750 micrograms/kg, followed immediately by (by intravenous infusion) 1.75 mg/kg/hour during procedure and for up to 4 hours after procedure, then (by intravenous infusion) reduced to 250 micrograms/kg/hour for a further 4–12 hours if necessary

- **CONTRA-INDICATIONS** Active bleeding, bleeding disorders, severe hypertension, subacute bacterial endocarditis

- **CAUTIONS** Brachytherapy procedures, previous exposure to lepirudin (theoretical risk from lepirudin antibodies)

- **INTERACTIONS** → Appendix 1 (bivalirudin).
  - Caution with concomitant use of drugs that increase risk of bleeding.

- **SIDE-EFFECTS**
  - Common or very common: Bleeding (discontinue), ecchymosis
  - Uncommon: Allergic reactions, anaemia, headache, hypotension, isolated reports of anaphylaxis, nausea, thrombocytopenia
  - Rare: Back pain, bradycardia, dyspnoea, tachycardia, thrombosis, vomiting

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

- **BREAST FEEDING** Manufacturer advises caution—no information available.

- **RENAI IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².
  - When used for percutaneous coronary intervention: Reduce rate of infusion to 1.4 mg/kg/hour if eGFR 30–60 mL/minute/1.73 m² and monitor blood clotting parameters.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Angiox®), give continuously in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 250-mg vial with 5 mL water for injections then withdraw 5 mL and dilute to 50 mL with infusion fluid.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (Tas)**
    - Bivalirudin for the treatment of ST-segment elevation myocardial infarction (July 2011) NICE TA230
    - Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.
    - www.nice.org.uk/TA230
**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (November 2008) that bivalirudin (Angiox®) is accepted for restricted use within NHS Scotland for patients with acute coronary syndromes planned for urgent or early intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

The Scottish Medicines Consortium has advised (August 2010) that bivalirudin (Angiox®) is accepted for restricted use within NHS Scotland as an anticoagulant in patients undergoing percutaneous coronary intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Angiox** (The Medicines Company UK Ltd)
  - Bivalirudin 250 mg Angiox 250mg powder for solution for injection vials | 10 vial pack no price available

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**Dabigatran etexilate**

**INDICATIONS ACTION** Dabigatran etexilate is a direct thrombin inhibitor with a rapid onset of action.

**INDICATIONS AND DOSE**

**Prophylaxis of venous thromboembolism following total knee replacement surgery**
- **BY MOUTH**
  - Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 220 mg once daily for 9 days, to be taken 12–24 hours after initial dose
  - Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 9 days, to be taken 12–24 hours after initial dose

**Prophylaxis of venous thromboembolism following total knee replacement surgery in patients receiving concomitant treatment with amiodarone or verapamil**
- **BY MOUTH**
  - Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 9 days, to be taken 12–24 hours after initial dose
  - Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 9 days, to be taken 12–24 hours after initial dose

**Prophylaxis of venous thromboembolism following total hip replacement surgery**
- **BY MOUTH**
  - Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 220 mg once daily for 27–34 days, to be taken 12–24 hours after initial dose
  - Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 27–34 days, to be taken 12–24 hours after initial dose

**Prophylaxis of venous thromboembolism following total hip replacement surgery in patients receiving concomitant treatment with amiodarone or verapamil**
- **BY MOUTH**
  - Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 150 mg daily for 27–34 days, to be taken 12–24 hours after initial dose
  - Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 27–34 days, to be taken 12–24 hours after initial dose

**DOSE EQUIVALENCE AND CONVERSION**

For information on changing from, or to, other anticoagulants, consult product literature.

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**Treatment of deep-vein thrombosis | Treatment of pulmonary embolism | Prophylaxis of recurrent deep-vein thrombosis | Prophylaxis of recurrent pulmonary embolism**
- **BY MOUTH**
  - Adult 18–74 years: 150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant
  - Adult 75–79 years: 110–150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant
  - Adult 80 years and over: 110 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant

**Treatment of deep-vein thrombosis in patients with moderate renal impairment | Treatment of deep-vein thrombosis in patients at increased risk of bleeding | Treatment of pulmonary embolism in patients with moderate renal impairment | Treatment of pulmonary embolism in patients at increased risk of bleeding**
- **BY MOUTH**
  - Adult: 110–150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant

**Treatment of deep-vein thrombosis in patients receiving concomitant treatment with verapamil | Treatment of pulmonary embolism in patients receiving concomitant treatment with verapamil | Prophylaxis of recurrent deep-vein thrombosis in patients receiving concomitant treatment with verapamil | Prophylaxis of recurrent pulmonary embolism in patients receiving concomitant treatment with verapamil**
- **BY MOUTH**
  - Adult: 110 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant

**Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and with one or more risk factors such as previous stroke or transient ischaemic attack, symptomatic heart failure, age ≥75 years, diabetes mellitus, or hypertension**
- **BY MOUTH**
  - Adult 18–74 years: 150 mg twice daily
  - Adult 75–79 years: 110–150 mg twice daily
  - Adult 80 years and over: 110 mg twice daily

**Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and with one or more risk factors such as previous stroke or transient ischaemic attack, symptomatic heart failure, age ≥75 years, diabetes mellitus, or hypertension in patients receiving concomitant treatment with verapamil**
- **BY MOUTH**
  - Adult: 110 mg twice daily

**Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and with one or more risk factors such as previous stroke or transient ischaemic attack, symptomatic heart failure, age ≥75 years, diabetes mellitus, or hypertension, in patients at increased risk of bleeding | Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and with one or more risk factors such as previous stroke or transient ischaemic attack, symptomatic heart failure, age ≥75 years, diabetes mellitus, or hypertension, in patients with moderate renal impairment**
- **BY MOUTH**
  - Adult: 110–150 mg twice daily
**CONTRA-INDICATIONS** Active bleeding - do not use as anticoagulant for prosthetic heart valve, malignant neoplasms, oesophageal varices, recent brain surgery, recent gastro-intestinal ulcer, recent intracranial haemorrhage, recent ophthalmic surgery, recent spine surgery, significant risk of major bleeding - vascular aneurysm

**CAUTIONS** Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis - give initial dose at least 2 hours after catheter removal and monitor neurological signs) - bacterial endocarditis - bleeding disorders - body-weight less than 50 kg - elderly - gastritis - gastro-oesophageal reflux - oesophagitis - recent biopsy - recent major trauma - thrombocytopenia

**INTERACTIONS** → Appendix 1 (dabigatran). Caution in concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - anaemia - diarrhoea - dyspepsia - haemorrhage - nausea
- **Uncommon** Dysphagia - gastro-intestinal ulcer - gastro-oesophageal reflux - hepatobiliary disorders - oesophagitis - thrombocytopenia - vomiting

**PREGNANCY** Manufacturer advises avoid unless essential — toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid — no information available.

**HEPATIC IMPAIRMENT** Avoid in severe liver disease, especially if prothrombin time already prolonged.

**RENAL IMPAIRMENT** When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery, reduce initial dose to 75 mg and subsequent doses to 150 mg once daily if creatinine clearance 30–50 mL/minute; reduce dose to 75 mg once daily if creatinine clearance 30–50 mL/minute and patient receiving concomitant treatment with verapamil. When used for treatment of deep-vein thrombosis and pulmonary embolism, prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism, prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation, consider reduced dose of 110 mg twice daily if creatinine clearance 30–50 mL/minute, based on individual assessment of thromboembolic risk and risk of bleeding. Avoid if creatinine clearance less than 30 mL/minute. In renal impairment monitor renal function at least annually (manufacturer recommends Cockcroft and Gault formula to calculate creatinine clearance).

**MONITORING REQUIREMENTS**
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- No routine anticoagulant monitoring required (INR tests are unreliable).
- Assess renal function (manufacturer recommends Cockcroft and Gault formula to calculate creatinine clearance) before treatment in all patients and at least annually in elderly.

**DIRECTIONS FOR ADMINISTRATION** When given concomitantly with amiodarone or verapamil, doses should be taken at the same time.

**PRESCRIBING AND DISPENSING INFORMATION** Dabigatran etexilate is given orally for prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery; it is also licensed for the treatment of deep-vein thrombosis and pulmonary embolism, and prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism in adults. Duration of treatment should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e. recent surgery, trauma, immobilisation, and longer duration of treatment should be based on permanent risk factors, or idiopathic deep-vein thrombosis or pulmonary embolism.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (September 2008) NICE TA157
  Dabigatran etexilate is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery.
  www.nice.org.uk/TA157
- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (March 2012) NICE TA249
  Dabigatran etexilate is an option for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with one or more of the following risk factors:
  - previous stroke, transient ischaemic attack, or systemic embolism
  - left ventricular ejection fraction <40% or symptomatic heart failure
  - age ≥75 years
  - age ≥65 years in patients with diabetes mellitus, coronary artery disease, or hypertension
  The risks and benefits of dabigatran compared to warfarin should be discussed with the patient.
  www.nice.org.uk/TA249
- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (December 2014) NICE TA327
  Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.
  www.nice.org.uk/TA327

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**

- **Dabigatran etexilate (as Dabigatran etexilate mesilate)**
  - 75 mg Pradaxa 75 mg capsules |
  - 10 capsule DT price £8.50 |
  - 60 capsule DT price £51.00
- **Dabigatran etexilate (as Dabigatran etexilate mesilate)**
  - 110 mg Pradaxa 110 mg capsules |
  - 10 capsule DT price £8.50 |
  - 60 capsule DT price £51.00
- **Dabigatran etexilate (as Dabigatran etexilate mesilate)**
  - 150 mg Pradaxa 150 mg capsules |
  - 60 capsule DT price £51.00

**ANTITHROMBOTIC DRUGS**

**Tissue plasminogen activators**

**Urokinase**

**INDICATIONS AND DOSE**

**Deep-vein thrombosis (thromboembolic occlusive vascular disease)**
- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 4400 units/kg, to be given over 10–20 minutes, followed by 100 000 units/hour for 2–3 days

**Pulmonary embolism (thromboembolic occlusive vascular disease)**
- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 4400 units/kg, to be given over 10–20 minutes, followed by 4400 units/hour for 12 hours continued →
Occlusive peripheral arterial disease (thromboembolic occlusive vascular disease)
- **BY INTRA-ARTERIAL INFUSION**
- Adult: (consult product literature)

Occluded central venous catheters (blocked by fibrin clots)
- **BY INTRA-ARTERIAL INFUSION**
- Adult: Inject directly into occluded catheter, to be dissolved in sodium chloride 0.9% to a concentration of 5000 units/mL; use a volume sufficient to fill the catheter lumen; leave for 20–60 minutes then aspirate the lysate; repeat if necessary

Occluded arteriovenous haemodialysis shunts (blocked by fibrin clots)
- **BY INTRA-ARTERIAL INFUSION, OR BY INTRA-ARTERIAL INFUSION**
- Adult: (consult product literature)

**SYNER-KINASE®**

Deep-vein thrombosis (thromboembolic occlusive vascular disease)
- **BY INTRAVENOUS INFUSION**
- Adult: Initially 4400 units/kg, to be given over 10 minutes, dose to be made up in 15 mL sodium chloride 0.9%, followed by 4400 units/kg/hour for 12–24 hours

Pulmonary embolism (thromboembolic occlusive vascular disease)
- **INITIALLY BY INTRAVENOUS INFUSION**
- Adult: Initially 4400 units/kg, to be given over 10 minutes, dose to be made up in 15 mL sodium chloride 0.9%, followed by (by intravenous infusion) 4400 micrograms/kg/hour for 12 hours, alternatively (by intra-arterial injection) initially 15 000 units/kg, to be injected into pulmonary artery, subsequent doses adjusted according to response; maximum 3 doses per day

Occlusive peripheral arterial disease
- **BY INTRA-ARTERIAL INFUSION**
- Adult: (consult product literature)

Occluded intravenous catheters and cannulas (blocked by fibrin clots)
- **BY INTRA-ARTERIAL INFUSION, OR BY INTRA-ARTERIAL INFUSION**
- Adult: 5000–25 000 units, to be injected directly into catheter or cannula, dose dissolved in suitable volume of sodium chloride 0.9% to fill the catheter or cannula lumen; leave for 20–60 minutes then aspirate the lysate; repeat if necessary

- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Dose reduction may be required.
- **RENAL IMPAIRMENT** Dose reduction may be required.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Syner-KINASE®), give continuously or intermittently in Sodium chloride 0.9%.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Urokinase (Non-proprietary)**
  - Urokinase 10000 unit
  - Urokinase 10,000 unit powder for solution for injection vials | 1 vial (POM) £33.79
  - Urokinase 50000 unit
  - Urokinase 50,000 unit powder for solution for injection vials | 1 vial (POM) £69.70
  - Urokinase 100000 unit
  - Urokinase 100,000 unit powder for solution for injection vials | 1 vial (POM) £106.17
  - Urokinase 250000 unit
  - Urokinase 250,000 unit powder for solution for injection vials | 1 vial (POM) £185.65
  - Urokinase 500000 unit
  - Urokinase 500,000 unit powder for solution for injection vials | 1 vial (POM) £365.00

- **Syner-KINASE** Syner-KINASE 10,000 unit powder for solution for injection vials | 1 vial (POM) £35.95 (Hospital only)
  - Syner-KINASE 25,000 unit powder for solution for injection vials | 1 vial (POM) £45.95 (Hospital only)
  - Syner-KINASE 100,000 unit powder for solution for injection vials | 1 vial (POM) £112.95 (Hospital only)
  - Syner-KINASE 250,000 unit powder for solution for injection vials | 1 vial (POM) no price available (Hospital only)
  - Syner-KINASE 500,000 unit Syner-KINASE 500,000 unit powder for solution for injection vials | 1 vial (POM) no price available (Hospital only)

**Vitamin K antagonists**
- **CONTRA-INDICATIONS** Avoid use within 48 hours postpartum - haemorrhagic stroke - significant bleeding
- **CAUTIONS** Bacterial endocarditis (use only if warfarin otherwise indicated) - conditions in which risk of bleeding is increased - history of gastrointestinal bleeding - peptic ulcer - postpartum (delay warfarin until risk of haemorrhage is low—usually 5–7 days after delivery) - recent ischaemic stroke - recent surgery - uncontrolled hypertension
- **INTERACTIONS** Appendix 1 (coumarins, phenindione).
  - Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may affect warfarin control.
  - Caution if concomitant use of drugs that increase risk of bleeding. Avoid cranberry juice.
- **SIDE-EFFECTS** Alopecea - diarrhoea - haemorrhage - hepatic dysfunction - jaundice - nausea - pancreatitis - purpurea - pyrexia - rash - skin necrosis (increased risk in patients with protein C or protein S deficiency) - vomiting - ‘purple toes’
- **CONCEPTION AND CONTRACEPTION** Women of child-bearing age should be warned of the danger of teratogenicity.
- **PREGNANCY** Should not be given in the first trimester of pregnancy. Warfarin, acenocoumarol, and phenindione cross the placenta with risk of congenital malformations, and placental, fetal, or neonatal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, they should be avoided in pregnancy, especially in the first and third trimesters (difficult decisions may have to be made, particularly in women with prosthetic heart valves, atrial fibrillation, or with a history of recurrent venous thrombosis or pulmonary embolism). Stopping these drugs before the sixth week of gestation may largely avoid the risk of fetal abnormality.
- **MONITORING REQUIREMENTS**
  - The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.
  - It is essential that the INR be determined daily or on alternate days in early days of treatment, then at longer intervals (depending on response), then up to every 12 weeks.
  - Change in patient’s clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing.
- **PATIENT AND CARER ADVICE** Anticoagulant treatment booklets should be issued to all patients or their carers; these booklets include advice for patients on anticoagulant treatment, an alert card to be carried by the patient at all times, and a section for recording of INR results and dosage information. In England, Wales, and Northern Ireland, they are available for purchase from:
Acenocoumarol (Nicoumalone)

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism | Transient ischaemic attacks

- **BY MOUTH**
  - Adult: Initially 2–4 mg once daily for 2 days, alternatively initially 6 mg on day 1, then 4 mg on day 2; maintenance 1–8 mg daily, adjusted according to response, dose to be taken at the same time each day, lower doses may be required in patients over 65 years, liver disease, severe heart failure with hepatic congestion, and malnutrition.

**CAUTIONS**
- Patients over 65 years

**SIDE-EFFECTS**
- Rare Anorexia
- Very rare Vasculitis

**BREAST FEEDING** Risk of haemorrhage; increased by vitamin K deficiency—manufacturer recommends prophylactic vitamin K for the infant (consult product literature).

**HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment, especially if prothrombin time is already prolonged.

**RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.

**PATIENT AND CARER ADVICE** Anticoagulant card to be provided. Patient counselling is advised for phenindione tablets (may turn urine pink or orange).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 10, 14</th>
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<tbody>
<tr>
<td>Phenindione (non-proprietary)</td>
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<tr>
<td>Phenindione 10 mg Phenindione 10 mg tablets</td>
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<tr>
<td>Phenindione 25 mg Phenindione 25 mg tablets</td>
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<td>Phenindione 50 mg Phenindione 50 mg tablets</td>
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**Phenindione**

**INDICATIONS AND DOSE**

- Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism

- **BY MOUTH**
  - Adult: Initially 200 mg on day 1, then 100 mg on day 2, then, adjusted according to response; maintenance 50–150 mg daily

**SIDE-EFFECTS**
- Agranulocytosis - eosinophilia - exanthema - exfoliative dermatitis - fever - hypersensitivity reactions - leucopenia - micro-adenopathy - renal damage - urine coloured pink or orange

**BREAST FEEDING** Avoid. Risk of haemorrhage; increased by vitamin K deficiency.

**HEPATIC IMPAIRMENT** Avoid in severe impairment, especially if prothrombin time is already prolonged.

**RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.

**PATIENT AND CARER ADVICE** Anticoagulant card to be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 10</th>
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<tr>
<td>Acenocoumarol (non-proprietary)</td>
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<tr>
<td>Acenocoumarol 1 mg Acenocoumarol 1 mg tablets</td>
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<tr>
<td>Sintrome (Merus Labs Luxco S.a R.L.)</td>
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<tr>
<td>Acenocoumarol 1 mg Sintrome 1 mg tablets</td>
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**Warfarin sodium**

- **INDICATIONS AND DOSE**
  - Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism | Transient ischaemic attacks

- **BY MOUTH**
  - Adult: Initially 5–10 mg, to be taken on day 1; subsequent doses dependent on the prothrombin time, reported as INR (international normalised ratio), a lower induction dose can be given over 3–4 weeks in patients who do not require rapid anticoagulation, elderly patients to be given a lower induction dose; maintenance 3–9 mg daily, to be taken at the same time each day

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: WARFARIN: REPORTS OF CALCIPHYLAXIS (JULY 2016)

An EU-wide review has concluded that on rare occasions, warfarin use may lead to calciphylaxis—patients should be advised to consult their doctor if they develop a painful skin rash; if calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin. The MHRA has advised that calciphylaxis is most commonly observed in patients with known risk factors such as end-stage renal disease, however cases have also been reported in patients with normal renal function.
4 Blood pressure conditions

4.1 Hypertension

Hypertension

Overview

Lowering raised blood pressure decreases the risk of stroke, coronary events, heart failure, and renal impairment. Advice on antihypertensive therapy in this section takes into account the recommendations of NICE clinical guidance 127 (August 2011), Hypertension—Clinical management of primary hypertension in adults.

Possible causes of hypertension (e.g. renal disease, endocrine causes), contributory factors, risk factors, and the presence of any complications of hypertension, such as left ventricular hypertrophy, should be established. Patients should be given advice on lifestyle changes to reduce blood pressure or cardiovascular risk; these include smoking cessation, weight reduction, reduction of excessive intake of alcohol and caffeine, reduction of dietary salt, reduction of total and saturated fat, increasing exercise, and increasing fruit and vegetable intake.

Thresholds and targets for treatment

Patients presenting with a blood pressure of 140/90 mmHg or higher when measured in a clinic setting, should be offered ambulatory blood pressure monitoring (or home blood pressure monitoring if ambulatory blood pressure monitoring is unsuitable) to confirm the diagnosis and stage of hypertension.

Stage 1 hypertension:

- Clinic blood pressure 140/90 mmHg or higher, and ambulatory daytime average or home blood pressure average 135/85 mmHg or higher
- Treat patients under 80 years who have stage 1 hypertension and target-organ damage (e.g. left ventricular hypertrophy, chronic kidney disease, hypertensive retinopathy), cardiovascular disease, renal disease, diabetes, or a 10 year cardiovascular risk ≥ 20%; in the absence of these conditions, advise lifestyle changes and review annually. For patients under 40 years with stage 1 hypertension but no overt target-organ damage, cardiovascular disease, renal disease, or diabetes, consider seeking specialist advice for evaluation of secondary causes of hypertension

Stage 2 hypertension:

- Clinic blood pressure 160/100 mmHg or higher, and ambulatory daytime average or home blood pressure average 150/95 mmHg or higher
- Treat all patients who have stage 2 hypertension, regardless of age

Severe hypertension:

- Clinic systolic blood pressure ≥ 180 mmHg or clinic diastolic blood pressure ≥ 110 mmHg; treat promptly—see Hypertensive Crises, below.

A target clinic blood pressure below 140/90 mmHg is suggested for patients under 80 years; a target ambulatory or home blood pressure average (during the patient’s waking hours) of below 135/85 mmHg is suggested for patients under 80 years; see also Hypertension in the Elderly, below. A target clinic blood pressure below 130/80 mmHg should be considered for those with established atherosclerotic cardiovascular disease, or diabetes in the presence of kidney, eye, or cerebrovascular disease. In some individuals it may not be possible to reduce blood pressure below the suggested targets despite the use of appropriate therapy.

Drug treatment of hypertension

A single antihypertensive drug is often inadequate in the management of hypertension, and additional antihypertensive drugs are usually added in a step-wise manner until control is achieved. Unless it is necessary to lower the blood pressure urgently (see Hypertensive Crises), an interval of at least 4 weeks should be allowed to determine response; clinicians should ensure antihypertensive drugs are titrated to the optimum or maximum tolerated dose at each step of treatment. Response to drug treatment may be affected by age and ethnicity.

Patients under 55 years:

Step 1

- ACE inhibitor; if not tolerated, offer an angiotensin-II receptor antagonist. If both ACE inhibitors and angiotensin-II receptor antagonists are contra-indicated or not tolerated, consider a beta-blocker; beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or at high risk of developing diabetes

Step 2

- ACE inhibitor or angiotensin-II receptor antagonist in combination with a calcium-channel blocker. If a calcium-channel blocker is not tolerated or if there is
evidence of, or a high risk of, heart failure, give a thiazide-related diuretic (e.g. chlortalidone or indapamide). If a beta-blocker was given at Step 1, add a calcium channel blocker in preference to a thiazide-related diuretic (see Step 1).

Step 3

- ACE inhibitor or angiotensin-II receptor antagonist in combination with a calcium-channel blocker and a thiazide-related diuretic

Step 4 (resistant hypertension)

- Consider seeking specialist advice

- Add low-dose spironolactone [unlicensed indication], or use high-dose thiazide-related diuretic if plasma-potassium concentration above 4.5 mmol/litre

- Monitor renal function and electrolytes

- If additional diuretic therapy is contra-indicated, ineffective, or not tolerated, consider an alpha-blocker or a beta-blocker

Patients over 55 years, and patients of any age who are of African or Caribbean family origin:

Step 1

- Calcium-channel blocker; if not tolerated or if there is evidence of, or a high risk of, heart failure, give a thiazide-related diuretic (e.g. chlortalidone or indapamide)

Step 2

- Calcium-channel blocker or thiazide-related diuretic in combination with an ACE inhibitor or angiotensin-II receptor antagonist (an angiotensin-II receptor antagonist in combination with a calcium-channel blocker is preferred in patients of African or Caribbean family origin)

Steps 3 and 4

- Treat as for patients under 55 years

Other measures to reduce cardiovascular risk

Aspirin p. 114 reduces the risk of cardiovascular events and myocardial infarction. Unduly high blood pressure must be controlled before aspirin is given. Unless contra-indicated, aspirin is recommended for all patients with established cardiovascular disease. Use of aspirin in primary prevention, in those with or without diabetes, is of unproven benefit. For the role of aspirin in the prevention of stroke in patients with atrial fibrillation, see Arrhythmias p. 93.

Statins are also of benefit in cardiovascular disease or in those who are at high risk of developing cardiovascular disease.

Hypertension in the elderly

Benefit from antihypertensive therapy is evident up to at least 80 years of age, but it is probably inappropriate to apply a strict age limit when deciding on drug therapy. Patients who reach 80 years of age while taking antihypertensive drugs should continue treatment, provided that it continues to be of benefit and does not cause significant side-effects. If patients are aged over 80 years when diagnosed with stage 1 hypertension, the decision to treat should be based on the presence of other comorbidities; patients with stage 2 hypertension should be treated as for patients over 55 years. A target clinic blood pressure below 150/90 mmHg is suggested for patients over 80 years; the suggested target ambulatory or home blood pressure average (during the patient’s waking hours) is below 145/85 mmHg.

Isolated systolic hypertension

Isolated systolic hypertension (systolic pressure ≥ 160 mmHg, diastolic pressure < 90 mmHg) is common in patients over 60 years, and is associated with an increased cardiovascular disease risk; it should be treated as for patients with both a raised systolic and diastolic blood pressure. Patients with severe postural hypotension should be referred to a specialist.

Hypertension in diabetes

For patients with diabetes, a target clinic blood pressure below 140/80 mmHg is suggested (below 130/80 mmHg is advised if kidney, eye, or cerebrovascular disease are also present). However, in some individuals, it may not be possible to achieve this level of control despite appropriate therapy. Most patients require a combination of antihypertensive drugs.

Hypertension is common in type 2 diabetes, and antihypertensive treatment prevents macrovascular and microvascular complications. In type 1 diabetes, hypertension usually indicates the presence of diabetic nephropathy. An ACE inhibitor (or an angiotensin-II receptor antagonist) may have a specific role in the management of diabetic nephropathy; in patients with type 2 diabetes, an ACE inhibitor (or an angiotensin-II receptor antagonist) can delay progression of microalbuminuria to nephropathy.

Hypertension in renal disease

A target clinic blood pressure below 140/90 mmHg is suggested (below 130/80 mmHg is advised in patients with chronic kidney disease and diabetes, or if proteinuria exceeds 1 g in 24 hours). An ACE inhibitor (or an angiotensin-II receptor antagonist) should be considered for patients with proteinuria; however, ACE inhibitors should be used with caution in renal impairment. Thiazide diuretics may be ineffective and high doses of loop diuretics may be required.

Hypertension in pregnancy

Hypertensive complications in pregnancy can be hazardous for both the mother and the fetus, and are associated with a significant risk of morbidity and mortality; complications can occur in pregnant women with pre-existing chronic hypertension, or in those who develop hypertension in the latter half of pregnancy.

Labetalol hydrochloride p. 140 is widely used for treating hypertension in pregnancy. Methyldopa p. 136 is considered safe for use in pregnancy. Modified-release preparations of nifedipine p. 153 [unlicensed] are also used. The following advice takes into account the recommendations of NICE Clinical Guideline 107 (August 2010), Hypertension in Pregnancy.

Pregnant women with chronic hypertension who are already receiving antihypertensive treatment should have their drug therapy reviewed. In uncomplicated chronic hypertension, a target blood pressure of < 150/100 mmHg is recommended; women with target-organ damage as a result of chronic hypertension, and in women with chronic hypertension who have given birth, a target blood pressure of < 140/90 mmHg is advised. Long-term antihypertensive treatment should be reviewed 2 weeks following the birth. Women managed with methyldopa during pregnancy should discontinue treatment and restart their original antihypertensive medication within 2 days of the birth.

Pregnant women are at high risk of developing pre-eclampsia and if they have chronic kidney disease, diabetes mellitus, autoimmune disease, chronic hypertension, or if they have had hypertension during a previous pregnancy; these women are advised to take aspirin p. 114 once daily [unlicensed indication] from week 12 of pregnancy until the baby is born. Women with more than one moderate risk factor (first pregnancy, aged ≥ 40 years, pregnancy interval > 10 years, BMI ≥ 35 kg/m² at first visit, multiple pregnancy, or family history of pre-eclampsia) for developing pre-eclampsia are also advised to take aspirin once daily [unlicensed indication] from week 12 of pregnancy until the baby is born.

Women with pre-eclampsia or gestational hypertension who present with a blood pressure over 150/100 mmHg, should receive initial treatment with
oral labetalol hydrochloride to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg. If labetalol hydrochloride is unsuitable, methyldopa or modified-release nifedipine may be considered. Women with gestational hypertension or pre-eclampsia who have been managed with methyldopa during pregnancy should discontinue treatment within 2 days of the birth. Women with a blood pressure of ≥160/110 mmHg who require critical care during pregnancy or after birth should receive immediate treatment with either oral or intravenous labetalol hydrochloride, intravenous hydralazine hydrochloride p. 171, or oral modified-release nifedipine to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg.

Also see use of magnesium sulfate p. 924 in pre-eclampsia and eclampsia.

**Hypertensive crises**

If blood pressure is reduced too quickly in the management of hypertensive crises, there is a risk of reduced organ perfusion leading to cerebral infarction, blindness, deterioration in renal function, and myocardial ischaemia.

A hypertensive emergency is defined as severe hypertension with acute damage to the target organs (e.g. signs of papilloedema or retinal haemorrhage, or the presence of clinical conditions such as acute coronary syndromes, acute aortic dissection, acute pulmonary oedema, hypertensive encephalopathy, acute cerebral infarction, intracerebral or subarachnoid haemorrhage, eclampsia, or rapidly progressing renal failure); prompt treatment with intravenous antihypertensive therapy is generally required. Over the first few minutes or within 2 hours, blood pressure should be reduced by 20–25%. When intravenous therapy is indicated, treatment options include sodium nitroprusside p. 173 [unlicensed], nicardipine hydrochloride p. 152, labetalol hydrochloride, glyceryl trinitrate p. 207, phentolamine mesilate p. 173, hydralazine hydrochloride, or esmolol hydrochloride p. 145; choice of drug is dependent on concomitant conditions and clinical status of the patient.

Severe hypertension (blood pressure ≥180/110 mmHg) without acute target-organ damage is defined as a hypertensive urgency; blood pressure should be reduced gradually over 24–48 hours with oral antihypertensive therapy, such as labetalol hydrochloride, or the calcium-channel blockers amiodipine p. 147 or felodipine p. 150. Use of sublingual nifedipine is not recommended.

Also see advice on short-term management of hypertensive episodes in phaeochromocytoma.

**Phaeochromocytoma**

Long-term management of phaeochromocytoma involves surgery. However, surgery should not take place until there is adequate blockade of both alpha- and beta-adrenoceptors; the optimal choice of drug therapy remains unclear. Alpha-blockers are used in the short-term management of hypertensive episodes in phaeochromocytoma. Once alpha blockade is established, tachycardia can be controlled by the cautious addition of a beta-blocker; a cardioselective beta-blocker is preferred.

Phenoxybenzamine hydrochloride p. 172, a powerful alpha-blocker, is effective in the management of phaeochromocytoma but it has many side-effects. Phentolamine mesilate is a short-acting alpha-blocker used mainly during surgery of phaeochromocytoma; its use for the diagnosis of phaeochromocytoma has been superseded by measurement of catecholamines in blood and urine.

Metirosine (available from ‘special-order’ manufacturers or specialist importing companies) inhibits the enzyme tyrosine hydroxylase, and hence the synthesis of catecholamines. It is rarely used in the pre-operative management of phaeochromocytoma, and long term in patients unsuitable for surgery; an alpha-adrenoceptor blocking drug may also be required. Metirosine should not be used to treat essential hypertension.

**Antihypertensive drugs**

**Vasodilator antihypertensive drugs**

Vasodilators have a potent hypotensive effect, especially when used in combination with a beta-blocker and a thiazide. **Important:** see Hypertension (hypertensive crises) for a warning on the hazards of a very rapid fall in blood pressure.

Hydralazine hydrochloride p. 171 is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used; when used alone it causes tachycardia and fluid retention.

Sodium nitroprusside p. 173 [unlicensed] is given by intravenous infusion to control severe hypertensive emergencies when parenteral treatment is necessary. Minoxidil p. 172 should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilatation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide p. 216, in high dosage) are mandatory. Hypertrichosis is troublesome and renders this drug unsuitable for females.

Prazosin p. 717, doxazosin p. 716, and terazosin p. 719 have alpha-blocking and vasodilator properties.

Ambrisentan p. 174, bosentan p. 175, iloprost p. 174, macitentan p. 175, sildenafil p. 744, and tadalafil p. 746 are licensed for the treatment of pulmonary arterial hypertension and should be used under specialist supervision. Epoprostenol p. 109 can be used in patients with primary pulmonary hypertension resistant to other treatments. Bosentan is also licensed to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. Riociguat p. 176 is licensed for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension; it should be used under specialist supervision.

Sitaxentan has been withdrawn from the market because the benefit of treatment does not outweigh the risk of severe hepatotoxicity.

**Centrally acting antihypertensive drugs**

Methyldopa p. 136 is a centrally acting antihypertensive; it may be used for the management of hypertension in pregnancy.

Clonidine hydrochloride p. 136 has the disadvantage that sudden withdrawal of treatment may cause severe rebound hypertension.

Moxonidine p. 137, a centrally acting drug, is licensed for mild to moderate essential hypertension. It may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

**Adrenergic neurone blocking drugs**

Adrenergic neurone blocking drugs prevent the release of noradrenaline from postganglionic adrenergic neurones. These drugs do not control supine blood pressure and may cause postural hypotension. For this reason they have largely fallen from use, but may be necessary with other therapy in resistant hypertension.

Guanethidine monosulfate p. 173, which also depletes the nerve endings of noradrenaline, is licensed for rapid control of blood pressure, however alternative treatments are preferred.

**Alpha-adrenoceptor blocking drugs**

Prazosin has post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia. It may, however,
reduce blood pressure rapidly after the first dose and should be introduced with caution. Doxazosin, indoramin p. 717, and terazosin have properties similar to those of prazosin. Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension.

**Prostatic hyperplasia**
Alfuzosin hydrochloride p. 715, doxazosin, indoramin, prazosin, tamsulosin hydrochloride p. 718, and terazosin are indicated for benign prostatic hyperplasia.

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**Drugs affecting the renin-angiotensin system**

**Angiotensin-converting enzyme inhibitors**
Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. They have many uses and are generally well tolerated. The main indications of ACE inhibitors are shown below.

**Heart failure**
ACE inhibitors are used in all grades of heart failure, usually combined with a beta-blocker. Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. However, a low dose of spironolactone p. 180 may be beneficial in severe heart failure and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Profound first-dose hypotension may occur when ACE inhibitors are introduced to patients with heart failure who are already taking a high dose of a loop diuretic (e.g. furosemide 80 mg daily or more). Temporary withdrawal of the loop diuretic reduces the risk, but may cause severe rebound pulmonary oedema. Therefore, for patients on high doses of loop diuretics, the ACE inhibitor may need to be initiated under specialist supervision. An ACE inhibitor can be initiated in the community in patients who are receiving a low dose of a diuretic or who are not otherwise at risk of serious hypotension; nevertheless, care is required and a very low dose of the ACE inhibitor is given initially.

**Hypertension**
An ACE inhibitor may be the most appropriate initial drug for hypertension in younger Caucasian patients; Afro-Caribbean patients, those aged over 55 years, and those with primary aldosteronism respond less well. ACE inhibitors are particularly indicated for hypertension in patients with type 1 diabetes with nephropathy. They may reduce blood pressure very rapidly in some patients particularly in those receiving diuretic therapy.

**Diabetic nephropathy**
ACE inhibitors have a role in the management of diabetic nephropathy.

**Prophylaxis of cardiovascular events**
ACE inhibitors are used in the early and long-term management of patients who have had a myocardial infarction. ACE inhibitors may also have a role in preventing cardiovascular events.

**Initiation under specialist supervision**
ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in those with severe heart failure or in those:

- receiving multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent);
- receiving concomitant angiotensin-II receptor antagonist or aliskiren;
- with hypovolaemia;
- with hyponatraemia (plasma-sodium concentration below 130 mmol/litre);
- with hypotension (systolic blood pressure below 90 mmHg);
- with unstable heart failure;
- receiving high-dose vasodilator therapy;
- known renovascular disease.

**Renal effects**
Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below present); hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced. Although ACE inhibitors now have a specialised role in some forms of renal disease, including chronic kidney disease, they also occasionally cause impairment of renal function which may progress and become severe in other circumstances (at particular risk are the elderly). A specialist should be involved if renal function is significantly reduced as a result of treatment with an ACE inhibitor.

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

In patients with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore not recommended in patients known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly.

ACE inhibitors should also be used with particular caution in patients who may have undiagnosed and clinically silent renovascular disease. This includes patients with peripheral vascular disease or those with severe generalised atherosclerosis.

**ACE inhibitors in combination with other drugs**
See also, *Concomitant use of drugs affecting the renin-angiotensin system*, below.

**Concomitant diuretics**
ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.

**Combination products**
Products incorporating an ACE inhibitor with a thiazide diuretic or a calcium-channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug and who have been stabilised on the individual components of the combination in the same proportions.
**Angiotensin-II receptor antagonists**

Azilsartan medoxomil p. 166, candesartan cilexetil p. 166, eprosartan p. 166, irbesartan p. 167, losartan potassium p. 167, olmesartan medoxomil p. 168, telmisartan p. 169, and valsartan p. 170 are angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are less likely to cause the persistent dry cough which can complicate ACE inhibitor therapy. They are therefore a useful alternative for patients who have to discontinue an ACE inhibitor because of persistent cough.

An angiotensin-II receptor antagonist may be used as an alternative to an ACE inhibitor in the management of heart failure or diabetic nephropathy. Candesartan cilexetil and valsartan are also licensed as adjuncts to ACE inhibitors under specialist supervision, in the management of heart failure when other treatments are unsuitable.

**Renal effects**

Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis (see also Renal effects under Angiotensin-converting enzyme inhibitors, above).

**Renin inhibitor**

Aliskiren is a renin inhibitor that is licensed for the treatment of hypertension.

**Concomitant use of drugs affecting the renin-angiotensin system**

Combination therapy with two drugs affecting the renin-angiotensin system (ACE inhibitors, angiotensin-II receptor antagonists, and aliskiren p. 171 is not recommended due to an increased risk of hyperkalaemia, hypotension, and renal impairment, compared to use of a single drug. Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor with an angiotensin-II receptor antagonist. There is some evidence that the benefits of combination use of an ACE inhibitor with candesartan or valsartan may outweigh the risks in selected patients with heart failure for whom other treatments are unsuitable, however, the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparing diuretic is not recommended.

For patients currently taking combination therapy, the need for continued combined therapy should be reviewed. If combination therapy is considered essential, it should be carried out under specialist supervision, with close monitoring of blood pressure, renal function, and electrolytes (particularly potassium); monitoring should be considered at the start of treatment, then monthly, and also after any change in dose or during intercurrent illness.

**Prevention of recurrent migraine** Prevention of vascular headache

- **BY MOUTH**
  - Adult: Initially 50 micrograms daily up to 100 micrograms daily as necessary
  - Adult: Initially 50 micrograms days 1 and 2, then increased if necessary to 100 micrograms daily

**SIDE-EFFECTS**

- **Common or very common** Constipation, dizziness, dry mouth, headache, malaise, nausea, postural hypotension, salivary gland pain, sexual dysfunction, sleep disturbances, vomiting
- **Uncommon** Bradycardia, delusion, hallucination, paraesthesia, pruritus, rash, Raynaud’s syndrome, urticaria
- **Rare** Alopecia, AV block, colonic pseudo-obstruction, decreased lacrimation, gynaecomastia, nasal dryness
- **Frequency not known** Bradyarrhythmia, confusion, fluid retention, hepatitis, impaired visual accommodation

**PREGNANCY**

May lower fetal heart rate. Avoid oral use unless potential benefit outweighs risk. Avoid using injection.

**BREAST FEEDING**

Avoid—present in milk.

**RENAL IMPAIRMENT**

Use with caution in severe impairment—reduce initial dose and increase gradually.

**TREATMENT CESSATION**

In hypertension, must be withdrawn gradually to avoid severe rebound hypertension.

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks: Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.
- **LESS SUITABLE FOR PRESCRIBING** Clonidine is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, injection.

**Tablet**

Cautionary and Advisory Labels 3, 8

- **Clonidine hydrochloride (Non-proprietary)**
  - Clonidine hydrochloride 25 microgram tablets | 112 tablets (PFl) £9.15 OT price = £5.30
  - Catapres (Boehringer Ingelheim Ltd) Clonidine hydrochloride 100 microgram tablets | 100 tablet (PFl) £8.04 OT price = £8.04
  - Dixarit (Boehringer Ingelheim Ltd) Clonidine hydrochloride 25 microgram tablets | 112 tablet (PFl) £6.99 OT price = £5.30
- **Clonidine hydrochloride 25 microgram tablets | 112 tablet (PFl) £9.15 OT price = £5.30
  - Catapres (Boehringer Ingelheim Ltd) Clonidine hydrochloride 100 microgram tablets | 100 tablet (PFl) £8.04 OT price = £8.04
  - Dixarit (Boehringer Ingelheim Ltd) Clonidine hydrochloride 25 microgram tablets | 112 tablet (PFl) £6.99 OT price = £5.30

**Clonidine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: Initially 50–100 micrograms 3 times a day, increase dose every second or third day, usual maximum dose 1.2 mg daily

**Methyldopa**

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: Initially 250 mg 2–3 times a day, dose should be increased gradually at intervals of at least 2 days; maximum 3 g per day
EFFECT ON LABORATORY TESTS

RENAL IMPAIRMENT

HEPATIC IMPAIRMENT

BREAST FEEDING

INTERACTIONS

CAUTIONS

CONTRA-INDICATIONS

SIDE-EFFECTS

CONTRA-INDICATIONS

Acute porphyria p. 930 • depression • phaeochromocytoma

CAUTIONS

History of depression

INTERACTIONS • Appendix 1 (methyldopa).

SIDE-EFFECTS • Atenorhoea • arthralgia • asthenia • Bell’s palsy • bone-marrow depression • bradycardia • decreased libido • depression • dizziness • drug fever • dry mouth • eosinophilia • exacerbatio of angina • failure of ejaculation • gastro-intestinal disturbances • gynaecomastia • haemolytic anaemia • headache • hepatitis • hyperprolactinaemia • hypersensitivity reactions • impaired mental acuity • impotence • jaundice • leucopenia • lupus erythematosus-like syndrome • mild psychosis • myalgia • myocardiitis • nasal congestion • nightmares • oedema • pancreatitis • paraesthesia • parkinsonism • pericarditis • postural hypotension • rashes • sedation • sialadenitis • stomatitis • thrombocytopenia • toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

Side-effects are minimised if the daily dose is kept below 1 g.

PREGNANCY

Not known to be harmful.

BREAST FEEDING

Amount too small to be harmful.

HEPATIC IMPAIRMENT

Manufacturer advises caution in history of liver disease. Avoid in active liver disease.

RENAL IMPAIRMENT

Start with small dose. Increased sensitivity to hypotensive and sedative effect.

MONITORING REQUIREMENTS

Monitor blood counts and liver-function before treatment and at intervals during first 6–12 weeks or if unexplained fever occurs.

EFFECT ON LABORATORY TESTS

Interference with laboratory tests. Positive direct Coombs test in up to 20% of patients (may affect blood cross-matching).

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 8

Methyldopa (Non-proprietary)

Methyldopa anhydroys 125 mg • Methyldopa 125mg tablets • Methyldopa 125mg tablets 56 tablet (Dom) £121.70 DT price = £112.95

Methyldopa anhydroys 250 mg • Methyldopa 250mg tablets • Methyldopa 250mg tablets 56 tablet (Dom) £16.26 DT price = £5.37

Methyldopa anhydroys 500 mg • Methyldopa 500mg tablets • Methyldopa 500mg tablets 56 tablet (Dom) £25.18 DT price = £9.57

Aldomet (Aspen Pharma Trading Ltd)

Methyldopa anhydroys 250 mg • Aldomet 250mg tablets • Aldomet 250mg tablets 60 tablet (Dom) £6.15

Methyldopa anhydroys 500 mg • Aldomet 500mg tablets • Aldomet 500mg tablets 30 tablet (Dom) £4.55

Moxonidine

INDICATIONS AND DOSE

Mild to moderate essential hypertension

BY MOUTH

Adult: 200 micrograms once daily for 3 weeks, dose to be taken in the morning, then increased if necessary to 400 micrograms daily in 1–2 divided doses (max. per dose 400 micrograms), maximum daily dose to be given in 2 divided doses; maximum 600 micrograms per day

CONTRA-INDICATIONS

Bradycardia • conduction disorders • second- or third-degree AV block • severe heart failure • sick sinus syndrome • sino-atrial block

CAUTIONS

First-degree AV block • moderate heart failure • severe coronary artery disease • unstable angina

INTERACTIONS • Appendix 1 (moxonidine).

SIDE-EFFECTS

Common or very common • Back pain • diarrhoea • dizziness • dry mouth • dyspepsia • insomnia • nausea • pruritus • rash • somnolence • vomiting

Uncommon • Angioedema • bradycardia • neck pain • nervousness • oedema • tinnitus

PREGNANCY

Manufacturer advises avoid—no information available.

BREAST FEEDING

Present in milk—manufacturer advises avoid.

RENAL IMPAIRMENT

Max. single dose 200 micrograms and max. daily dose 400 micrograms if eGFR 30–60 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

TREATMENT CESSION

Avoid abrupt withdrawal (if concomitant treatment with beta-blocker has to be stopped, discontinue beta-blocker first, then moxonidine after a few days).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3

Moxonidine (Non-proprietary)

Moxonidine 200 microgram • Moxonidine 200 microgram tablets 28 tablet (Dom) £10.40 DT price = £1.54

Moxonidine 300 microgram • Moxonidine 300 microgram tablets 28 tablet (Dom) £12.30 DT price = £1.53

Moxonidine 400 microgram • Moxonidine 400 microgram tablets 28 tablet (Dom) £14.24 DT price = £1.70

Physiotens (BGP Products Ltd)

Moxonidine 200 microgram • Physiotens 200 microgram tablets 28 tablet (Dom) £9.72 DT price = £1.54

Moxonidine 300 microgram • Physiotens 300 microgram tablets 28 tablet (Dom) £11.49 DT price = £1.53

Moxonidine 400 microgram • Physiotens 400 microgram tablets 28 tablet (Dom) £13.26 DT price = £1.70

BETA-ADRENOCEPTOR BLOCKERS

Beta-adrenerceptor blocking drugs

Overview

Beta-adrenerceptor blocking drugs (beta-blockers) block the beta-adrenerceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.

Many beta-blockers are now available and in general they are all equally effective. There are, however, differences between them, which may affect choice in treating particular diseases or individual patients.

Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors.

Oxprenolol hydrochloride p. 141, pindolol p. 141, acebutolol p. 143, and celiprolol hydrochloride p. 145 have intrinsic sympathomimetic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less coldness of the extremities.

Some beta-blockers are lipid soluble and some are water soluble. Atenolol p. 143, celiprolol hydrochloride, nadolol p. 141, and sotalol hydrochloride p. 102 are the most water-soluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares.

Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.
 Beta-blockers with a relatively short duration of action have to be given two or three times daily. Many of these are, however, available in modified-release formulations so that administration once daily is adequate for hypertension. For angina twice-daily treatment may sometimes be needed even with a modified-release formulation. Some beta-blockers, such as atenolol, bisoprolol fumarate p. 144, celiprolol hydrochloride, and nadolol, have an intrinsically longer duration of action and need to be given only once daily.

 Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in patients with second- or third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care is required when initiating a beta-blocker in those with stable heart failure.

 Labetalol hydrochloride p. 140, celiprolol hydrochloride, carvedilol p. 139, and nebivolol p. 146 are beta-blockers that have, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance. There is no evidence that these drugs have important advantages over other beta-blockers in the treatment of hypertension.

 Beta-blockers can precipitate bronchospasm and should therefore usually be avoided in patients with a history of asthma. When there is no suitable alternative, it may be necessary for a patient with well-controlled asthma, or chronic obstructive pulmonary disease (without significant reversible airways obstruction), to receive treatment with a beta-blocker for a co-existing condition (e.g. heart failure or following myocardial infarction). In this situation, a cardioselective beta-blocker should be selected and initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects. Atenolol, bisoprolol fumarate, metoprolol tartrate p. 145, nebivolol, and (to a lesser extent) acebutolol, have less effect on the beta (bronchial) receptors and are, therefore, relatively cardioselective, but they are not cardiospecific. They have a lesser effect on airways resistance but are not free of this side-effect.

 Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA), and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers).

 Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia, thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

 Hypertension

 The mode of action of beta-blockers in hypertension is not understood, but they reduce cardiac output, alter baroreceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma renin secretion. It is possible that a central effect may also partly explain their mode of action.

 Beta-blockers are effective for reducing blood pressure but other antihypertensives are usually more effective for reducing the incidence of stroke, myocardial infarction, and cardiovascular mortality, especially in the elderly. Other antihypertensives are therefore preferred for routine initial treatment of uncomplicated hypertension.

 In general, the dose of a beta-blocker does not have to be high.

 Beta-blockers can be used to control the pulse rate in patients with phaeochromocytoma. However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis. For this reason phenoxybenzamine hydrochloride p. 172 should always be used together with the beta-blocker.

 Angina

 By reducing cardiac work beta-blockers improve exercise tolerance and relieve symptoms in patients with angina (see management of stable angina and acute coronary syndromes for further details). As with hypertension there is no good evidence of the superiority of any one drug, although occasionally a patient will respond better to one beta-blocker than to another. There is some evidence that sudden withdrawal may cause an exacerbation of angina and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease.

 Myocardial infarction

 For specific comments see management of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction.

 Several studies have shown that some beta-blockers can reduce the recurrence rate of myocardial infarction. However, uncontrolled heart failure, hypotension, bradycardias, and obstructive airways disease render beta-blockers unsuitable in some patients following a myocardial infarction. Atenolol and metoprolol tartrate may reduce early mortality after intravenous and subsequent oral administration in the acute phase, while acebutolol, metoprolol tartrate, propranolol hydrochloride p. 142, and timolol maleate p. 142 have protective value when started in the early convalescent phase. The evidence relating to other beta-blockers is less convincing; some have not been tested in trials of secondary prevention.

 Arrhythmias

 Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation, especially in patients with thyrotoxicosis. Beta-blockers are also useful in the management of supraventricular tachycardias, and are used to control those following myocardial infarction.

 Esmolol hydrochloride p. 145 is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias, sinus tachycardia, or hypertension, particularly in the peri-operative period. It may also be used in other situations, such as acute myocardial infarction, when sustained beta-blockade might be hazardous.

 Sotalol hydrochloride p. 102, a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity, is used for prophylaxis in paroxysmal supraventricular arrhythmias. It also suppresses ventricular ectopic beats and non-sustained ventricular tachycardia. It has been shown to be more effective than lidocaine in the termination of spontaneous sustained ventricular tachycardia due to coronary disease or cardiomyopathy. However, it may induce torsade de points in susceptible patients.

 Heart failure

 Beta-blockers may produce benefit in heart failure by blocking sympathetic activity. Bisoprolol fumarate p. 144 and carvedilol p. 139 reduce mortality in any grade of stable heart failure; nebivolol p. 146 is licensed for stable mild to moderate heart failure in patients over 70 years. Treatment should be initiated by those experienced in the management of heart failure.
Thyrotoxicosis
Beta-blockers are used in pre-operative preparation for thyroidectomy. Administration of propranolol hydrochloride p. 142 can reverse clinical symptoms of thyrotoxicosis within 4 days. Routine tests of increased thyroid function remain unaltered. The thyroid gland is rendered less vascular thus making surgery easier.

Other uses
Beta-blockers have been used to alleviate some symptoms of anxiety; probably patients with palpitation, tremor, and tachycardia respond best. Beta-blockers are also used in the prophylaxis of migraine. Betaxolol p. 1037, carteolol hydrochloride p. 1036, levoxbunolol hydrochloride p. 1036, and timolol maleate p. 142 are used topically in glaucoma.

Beta-adrenoceptor blockers (systemic)

CONTRA-INDICATIONS
Asthma - cardiogenic shock - hypotension - marked bradycardia - metabolic acidosis - phaeochromocytoma (apart from specific use with alpha-blockers) - Prinzmetal's angina - second-degree AV block - severe peripheral arterial disease - sick sinus syndrome - third-degree AV block - uncontrolled heart failure

INTERACTIONS
Bronchospasm
Beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma, bronchospasm or a history of obstructive airways disease. However, when there is no alternative, a cardioselective beta-blocker can be given to these patients with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

CAUTIONS
Diabetes - first-degree AV block - history of obstructive airways disease (introduce cautiously) - myasthenia gravis - portal hypertension (risk of deterioration in liver function) - psoriasis - symptoms of hypoglycaemia may be masked - symptoms of thyrotoxicosis may be masked

INDICATIONS AND DOSE

Carvedilol

INDICATIONS AND DOSE

Hypertension
BY MOUTH
Adult: Initially 12.5 mg once daily for 2 days, then increased to 25 mg once daily; increased if necessary up to 50 mg daily, dose to be increased at intervals of at least 2 weeks and can be given as a single dose or in divided doses

Angina
BY MOUTH
Adult: Initially 12.5 mg twice daily for 2 days, then increased to 25 mg twice daily

Adjunct to diuretics, digoxin, or ACE inhibitors in symptomatic chronic heart failure
BY MOUTH
Adult: Initially 3.125 mg twice daily, dose to be taken with food, then increased to 6.25 mg twice daily, then increased to 12.5 mg twice daily, then increased to 25 mg twice daily, dose should be increased at intervals of at least 2 weeks up to the highest tolerated dose, max. 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg; max. 50 mg twice daily in patients over 85 kg

CONTRA-INDICATIONS
Acute or decompensated heart failure requiring intravenous inotropes

SIDE-EFFECTS
Allergic skin reactions - angina - AV block - changes in liver enzymes - depressed mood - disturbances of micturition - influenza-like symptoms - leucopenia - nasal stuffiness - postural hypotension - thrombocytopenia - wheezing

SIDE-EFFECTS, FURTHER INFORMATION
Bradycardia With administration by intravenous injection, excessive bradycardia can occur and may be countered with intravenous injection of atropine sulfate.

Overdose
Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. For details on the management of poisoning, see Beta-blockers, under Emergency treatment of poisoning p. 1204.

ALLERGY AND CROSS-SENSITIVITY
Caution is advised in patients with a history of hypersensitivity—may increase sensitivity to allergens and result in more serious hypersensitivity response. Furthermore beta-adrenoceptor blockers may reduce response to adrenaline (epinephrine).

PREGNANCY
Beta-blockers may cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; the risk is greater in severe hypertension.

BREAST FEEDING
With systemic use in the mother, infants should be monitored as there is a risk of possible toxicity due to beta-blockade. However, the amount of most beta-blockers present in milk is too small to affect infants.

MONITORING REQUIREMENTS
Monitor lung function (in patients with a history of obstructive airway disease).

TREATMENT CESSATION
Avoid abrupt withdrawal especially in obstructive airways disease. Sudden cessation of a beta-blocker can cause a rebound worsening of myocardial ischaemia and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped.

BETA-ADRENOCEPTOR BLOCKERS

ALPHA- AND BETA-ADRENOCEPTOR BLOCKERS

above
Labetalol hydrochloride

**INDICATIONS AND DOSE**

**Controlled hypotension in anaesthesia**
- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: (consult product literature or local protocols)

**Hypertension of pregnancy**
- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 20 mg/hour, then increased if necessary to 40 mg/hour after 30 minutes, then increased if necessary to 80 mg/hour after 30 minutes, then increased if necessary to 160 mg/hour after 30 minutes, adjusted according to response; Usual maximum 160 mg/hour
  - **BY MOUTH**
  - Adult: Use dose for hypertension

**Hypertension following myocardial infarction**
- **BY INTRAVENOUS INFUSION**
  - Adult: 15 mg/hour, then increased to up to 120 mg/hour, dose to be increased gradually

**Hypertensive emergencies**
- **BY INTRAVENOUS INJECTION**
  - Adult: 50 mg, to be given over at least 1 minute, then 50 mg every 5 minutes if required until a satisfactory response occurs; maximum 200 mg per course
  - **BY INTRAVENOUS INFUSION**
  - Adult: Initially 2 mg/minute until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 100 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day
  - Elderly: Initially 50 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day

**BY INTRAVENOUS INJECTION**
- Adult: 50 mg, dose to be given over at least 1 minute, then 50 mg after 5 minutes if required; maximum 200 mg per course

**BY INTRAVENOUS INFUSION**
- Adult: Initially 2 mg/minute until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg

**CAUTIONS**
- Liver damage

**SIDE-EFFECTS**
- Rare: Lichenoid rash
- **Frequency not known**
  - Difficulty in micturition, epigastric pain, liver damage, nausea, postural hypotension, vomiting

**PREGNANCY**
- The use of labetalol in maternal hypertension is not known to be harmful, except possibly in the first trimester. If labetalol is used close to delivery, infants should be monitored for signs of alpha-blockade (as well as beta-blockade).

**BREAST FEEDING**
- Infants should be monitored as there is a risk of possible toxicity due to alpha-blockade (in addition to beta-blockade).

**HEPATIC IMPAIRMENT**
- Avoid—severe hepatocellular injury reported.

**RENO/L IMPAIRMENT**
- Dose reduction may be required.

**MONITORING REQUIREMENTS**
- Liver damage
  - Severe hepatocellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or jaundice) labetalol should be stopped and not restarted.

**EFFECT ON LABORATORY TESTS**
- Interferes with laboratory tests for catecholamines.

**DIRECTIONS FOR ADMINISTRATION**
- For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride and glucose. Dilute to a concentration of 1 mg/mL; suggested volume 200 mL; adjust rate with in-line burette. Avoid upright position during and for 3 hours after intravenous administration.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 8**

- **Carvedilol (Non-proprietary)**
  - Carvedilol 6.25 mg
  - Carvedilol 12.5 mg
  - Carvedilol 25 mg
  - Carvedilol 3.125 mg

**Solution for injection**

- **Labetalol hydrochloride 5 mg per 1 ml**
  - Labetalol 100 mg/20 ml solution for injection ampoules | 5 ampoule (PO) £44.44–£53.33
**BETA-ADRENOCEPTOR BLOCKERS**  
**NON-SELECTIVE**

### Nadolol

#### INDICATIONS AND DOSE

**Hypertension**  
- **BY MOUTH**  
  - **Adult:** Initially 80 mg once daily, then increased in steps of up to 80 mg every week if required, doses higher than the maximum are rarely necessary; maximum 240 mg per day

**Angina**  
- **BY MOUTH**  
  - **Adult:** Initially 40 mg once daily, then increased if necessary up to 160 mg daily, doses should be increased at weekly intervals, maximum dose rarely is used; maximum 240 mg per day

**Arrhythmias**  
- **BY MOUTH**  
  - **Adult:** Initially 40 mg once daily, then increased in steps of 40 mg every week, adjusted according to response; maintenance 80–160 mg once daily

**Thyrotoxicosis (adjunct)**  
- **BY MOUTH**  
  - **Adult:** 80–160 mg once daily

**BREAST FEEDING** Water soluble beta-blockers such as nadolol are present in breast milk in greater amounts than other beta blockers.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAL IMPAIRMENT** Increase dosage interval if eGFR less than 50 mL/minute/1.73 m².

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**  
- **CAUTIONARY AND ADVISORY LABELS 8**
  - Nadolol hydrochloride (Non-proprietary) Nadolol hydrochloride 20 mg Nadolol 20 mg tablets | 56 tablet £5.37
  - Nadolol hydrochloride 40 mg Nadolol 40 mg tablets | 56 tablet £7.22

**Modified-release tablet**  
- **CAUTIONARY AND ADVISORY LABELS 8, 25**
  - Nadolol hydrochloride (Non-proprietary) Nadolol hydrochloride 160 mg Nadolol 160 mg modified-release tablets | 28 tablet £7.96

### Pindolol

#### INDICATIONS AND DOSE

**Hypertension**  
- **BY MOUTH**  
  - **Adult:** Initially 5 mg 2–3 times a day, alternatively 15 mg once daily, doses to be increased as required at weekly intervals; maintenance 15–30 mg daily; maximum 45 mg per day

**Angina**  
- **BY MOUTH**  
  - **Adult:** 2.5–5 mg up to 3 times a day

**RENAL IMPAIRMENT** May adversely affect renal function in severe impairment—manufacturer advises avoid.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**  
- **CAUTIONARY AND ADVISORY LABELS 8**
  - Pindolol (Non-proprietary) Pindolol 5 mg | 100 tablet £0.00
  - Pindolol 10 mg | 100 tablet £0.00

**Modified-release tablet**

- **Visken (AMCo)**
  - Pindolol 5 mg Visken 5 mg tablets | 100 tablet £0.00
  - Pindolol 15 mg Visken 15 mg tablets | 28 tablet £0.00

### Pindolol with clopamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, pindolol above.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**  
- **CAUTIONARY AND ADVISORY LABELS 8**
  - Viskaldix (AMCo) Clopamide 5 mg, Pindolol 10 mg | 28 tablet £0.00

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**Oxrenolol hydrochloride**

#### INDICATIONS AND DOSE

**Hypertension | Angina**  
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult:** 80–160 mg daily in 2–3 divided doses, then increased if necessary up to 320 mg daily
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - **Adult:** Initially 160 mg once daily, then increased if necessary up to 320 mg daily

**Arrhythmias**  
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult:** 40–240 mg daily in 2–3 divided doses; maximum 240 mg per day

**Anxiety symptoms (short-term use)**  
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult:** 40–80 mg daily in 1–2 divided doses

**HEPATIC IMPAIRMENT** Reduce dose.

- **RENAL IMPAIRMENT** May adversely affect renal function in severe impairment—manufacturer advises avoid.
Propranolol hydrochloride

**INDICATIONS AND DOSE**

**Thyrotoxicosis (adjunct)**
- **Adult:** 10–40 mg 3–4 times a day

**Thyrotoxic crisis**
- **By Intravenous injection**: Adult: 1 mg, to be given over 1 minute, dose may be repeated if necessary at intervals of 2 minutes, maximum total dose is 5 mg in anaesthesia; maximum 10 mg per course

**Hypertension**
- **By mouth**
  - **Adult:** Initially 80 mg twice daily, dose should be increased at weekly intervals as required; maintenance 160–320 mg daily

**Prophylaxis of variceal bleeding in portal hypertension**
- **By mouth**
  - **Adult:** Initially 40 mg twice daily, then increased to 80 mg twice daily (max. per dose 160 mg twice daily), dose to be adjusted according to heart rate

**Phaeochromocytoma (only with an alpha-blocker) in preparation for surgery**
- **By mouth**
  - **Adult:** 60 mg daily for 3 days before surgery

**Phaeochromocytoma (only with an alpha-blocker) in patients unsuitable for surgery**
- **By mouth**
  - **Adult:** 30 mg daily

**Angina**
- **By mouth**
  - **Adult:** Initially 40 mg 2–3 times a day; maintenance 120–240 mg daily

**Hypertrophic cardiomyopathy / Anxiety tachycardia**
- **By mouth**
  - **Adult:** 10–40 mg 3–4 times a day

**Anxiety with symptoms such as palpitation, sweating and tremor**
- **By mouth**
  - **Adult:** 40 mg once daily, then increased if necessary to 40 mg 3 times a day

**Prophylaxis after myocardial infarction**
- **By mouth**
  - **Adult:** Initially 40 mg 4 times a day for 2–3 days, then 80 mg twice daily, start treatment 5 to 21 days after infarction

**Essential tremor**
- **By mouth**
  - **Adult:** Initially 40 mg 2–3 times a day; maintenance 80–160 mg daily

**Migraine prophylaxis**
- **By mouth**
  - **Adult:** 80–240 mg daily in divided doses

**Arrhythmias**
- **By mouth**
  - **Adult:** 10–40 mg 3–4 times a day
- **By intravenous injection**
  - **Adult:** 1 mg, to be given over 1 minute, dose may be repeated if necessary at intervals of 2 minutes, maximum 10 mg per course (5 mg in anaesthesia)

**SIDE-EFFECTS**
- **Rare** Dry eyes (reversible on withdrawal)
- **Hepatic impairment** Reduce oral dose.
- **Renal impairment** Manufacturer advises caution; dose reduction may be required.

**Prescribing and dispensing information** Modified-release preparations can be used for once daily administration.

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **Propranolol hydrochloride (Non-proprietary)**
  - **Propranolol hydrochloride 10 mg** Propranolol 10 mg tablets | 28 tablet | £1.47 DT price = £0.89
  - **Propranolol hydrochloride 40 mg** Propranolol 40 mg tablets | 28 tablet | £1.85 DT price = £0.89
  - **Propranolol hydrochloride 80 mg** Propranolol 80 mg tablets | 28 tablet | £0.89 DT price = £0.89
  - **Propranolol hydrochloride 160 mg** Propranolol 160 mg tablets | 56 tablet | £5.89 DT price = £5.87

**Modified-release capsule**

- **CAUTIONARY AND ADVISORY LABELS**
  - **Propranolol hydrochloride (Non-proprietary)**
    - **Propranolol hydrochloride 80 mg** Propranolol 80 mg modified-release capsules | 28 capsule | £4.95 DT price = £4.95
    - **Propranolol hydrochloride 160 mg** Propranolol 160 mg modified-release capsules | 28 capsule | £4.88 DT price = £4.88
  - **Bedranol SR** (Sandoz Ltd, Almus Pharmaceuticals Ltd)
    - **Propranolol hydrochloride 80 mg** Bedranol SR 80 mg capsules | 28 capsule | £4.16 DT price = £4.16
    - **Propranolol hydrochloride 160 mg** Bedranol SR 160 mg capsules | 28 capsule | £4.59–5.09 DT price = £4.88
  - **Beta-Prograne** (Tillomed Laboratories Ltd, Actavis UK Ltd, Teva UK Ltd)
    - **Propranolol hydrochloride 160 mg** Beta-Prograne 160 mg modified-release capsules | 28 capsule | £4.11 DT price = £4.11
  - **Half Beta-Prograne** (Teva UK Ltd, Tillomed Laboratories Ltd, Actavis UK Ltd)
    - **Propranolol hydrochloride 80 mg** Half Beta-Prograne 80 mg modified-release capsules | 28 capsule | £4.95 DT price = £4.95

**Oral solution**

- **CAUTIONARY AND ADVISORY LABELS**
  - **Propranolol hydrochloride (Non-proprietary)**
    - **Propranolol hydrochloride 1 mg per 1 ml** Propranolol 5 mg/5 ml oral solution sugar-free free sugar-free | 150 ml | £15.50 DT price = £15.50
    - **Propranolol hydrochloride 2 mg per 1 ml** Propranolol 10 mg/5 ml oral solution sugar-free free sugar-free | 150 ml | £20.45 DT price = £20.45
    - **Propranolol hydrochloride 8 mg per 1 ml** Propranolol 40 mg/5 ml oral solution sugar-free free sugar-free | 150 ml | £31.50 DT price = £31.50
    - **Propranolol hydrochloride 10 mg per 1 ml** Propranolol 50 mg/5 ml oral solution sugar-free free sugar-free | 150 ml | £24.98 DT price = £24.98

Timolol maleate

**INDICATIONS AND DOSE**

**Hypertension**
- **By mouth**
  - **Adult:** Initially 10 mg daily in 1–2 divided doses, then increased if necessary up to 60 mg daily, doses to be increased gradually. Doses above 30 mg daily given in divided doses, usual maintenance 10–30 mg daily; maximum 60 mg per day

**Angina**
- **By mouth**
  - **Adult:** Initially 5 mg twice daily, then increased in steps of 10 mg daily (max. per dose 30 mg twice daily), to be increased every 3–4 days

**Prophylaxis after myocardial infarction**
- **By mouth**
  - **Adult:** Initially 5 mg twice daily for 2 days, then increased if tolerated to 10 mg twice daily
Migraine prophylaxis
▶ BY MOUTH
▶ Adult: 10–20 mg daily in 1–2 divided doses

- **BREAST FEEDING** Manufacturer advises avoidance.
- **HEPATIC IMPAIRMENT** Dose reduction may be necessary.
- **RENAL IMPAIRMENT** Manufacturer advises caution—dose reduction may be required.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 8
  ▶ Timolol maleate (Non-proprietary)
    Timolol maleate 10 mg Timolol 10mg tablets | 30 tablet [P] £19.47–£21.69 DT price = £20.58

### Timolol with amiloride and hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, timolol maleate p. 142, amiloride hydrochloride p. 218, hydrochlorothiazide p. 158.

- **INDICATIONS AND DOSE**
  **Hypertension**
  ▶ BY MOUTH
  ▶ Adult: 1–2 tablets daily

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 8
  ▶ Timolol with amiloride and hydrochlorothiazide (Non-proprietary)
    Amiloride hydrochloride 2.5 mg, Timolol maleate 10 mg,
    Hydrochlorothiazide 25 mg Timolol 10mg / Amiloride Hydrochlorothiazide 25mg tablets | 28 tablet [P] £29.87

### Timolol with bendroflumethiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, timolol maleate p. 142, bendroflumethiazide p. 157.

- **INDICATIONS AND DOSE**
  **Hypertension**
  ▶ BY MOUTH
  ▶ Adult: 1–2 tablets daily; maximum 4 tablets per day

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 8
  ▶ Timolol with bendroflumethiazide (Non-proprietary)
    Bendroflumethiazide 2.5 mg, Timolol maleate 10 mg Timolol 10mg / Bendroflumethiazide 2.5mg tablets | 30 tablet [P] £23.75–£28.49 DT price = £27.42

### BETA-ADRENOCEPTOR BLOCKERS

- **SELECTIVE**

#### Acebutolol

- **INDICATIONS AND DOSE**
  **Hypertension**
  ▶ BY MOUTH
  ▶ Adult: Initially 400 mg daily for 2 weeks, alternatively initially 200 mg twice daily for 2 weeks, then increased if necessary to 400 mg twice daily; maximum 1.2 g per day
  **Angina**
  ▶ BY MOUTH
  ▶ Adult: Initially 400 mg daily, alternatively initially 200 mg twice daily; maximum 1.2 g per day
  **Arrhythmias**
  ▶ BY MOUTH
  ▶ Adult: 0.4–1.2 g daily in 2–3 divided doses
  **Severe angina**
  ▶ BY MOUTH
  ▶ Adult: Initially 300 mg 3 times a day; maximum 1.2 g per day

- **BREAST FEEDING** Acebutolol and water soluble beta-blockers are present in breast milk in greater amounts than other beta-blockers.
- **RENAL IMPAIRMENT** Halve dose if eGFR 25–50 mL/minute/1.73 m²; use quarter dose if eGFR less than 25 mL/minute/1.73 m²; do not administer more than once daily.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 8
  ▶ Acebutolol (as Acebutolol hydrochloride) 400 mg Acebutolol 400mg tablets | 28 tablet [P] £18.62 DT price = £18.62
  ▶ Sectral (Sanofi)
    Acebutolol (as Acebutolol hydrochloride) 400 mg Sectral 400mg tablets | 28 tablet [P] £18.62 DT price = £18.62
  **Capsule**
  CAUTIONARY AND ADVISORY LABELS 8
  ▶ Acebutolol (as Acebutolol hydrochloride) 100 mg Acebutolol 100mg capsules | 84 capsule [P] £15.30 DT price = £14.97
  ▶ Sectral (Sanofi)
    Acebutolol (as Acebutolol hydrochloride) 200 mg Sectral 200mg capsules | 56 capsule [P] £19.20 DT price = £19.18

#### Atenolol

- **INDICATIONS AND DOSE**
  **Hypertension**
  ▶ BY MOUTH
  ▶ Adult: 25–50 mg daily, higher doses are rarely necessary
  **Angina**
  ▶ BY MOUTH
  ▶ Adult: 100 mg daily in 1–2 divided doses
**Arrhythmias**
- **BY MOUTH**
  - Adult: 50–100 mg daily
- **BY INTRAVENOUS INJECTION**
  - Adult: 2.5 mg every 5 minutes (max. per dose 10 mg), repeated if necessary, given at a rate of 1 mg/minute
- **BY INTRAVENOUS INFUSION**
  - Adult: 150 micrograms/kg every 12 hours if required, to be given over 20 minutes

**Migraine prophylaxis**
- **BY MOUTH**
  - Adult: 50–200 mg daily in divided doses

**Easy intervention within 12 hours of myocardial infarction**
- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 5 mg, to be given over 5 minutes, followed by (by mouth) 50 mg after 15 minutes, then (by mouth) 50 mg after 12 hours, then (by mouth) 100 mg daily

- **UNLICENSED USE** Use of atenolol for migraine prophylaxis is an unlicensed indication.
- **BREAST FEEDING** Water soluble beta-blockers such as atenolol are present in breast milk in greater amounts than other beta blockers.
- **RENAL IMPAIRMENT**
  - With oral use: Max. 50 mg daily if eGFR 15–35 mL/minute/1.73 m²; max. 25 mg daily or 50 mg on alternate days if eGFR less than 15 mL/minute/1.73 m².
  - With intravenous use: Max. 10 mg on alternate days if eGFR 15–35 mL/minute/1.73 m²; max. 10 mg every 4 days if eGFR less than 15 mL/minute/1.73 m².
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Tenormin®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Suggested infusion time 20 minutes.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 8
  - **Atenolol (Non-proprietary)**
    - Atenolol 25 mg Atenolol 25mg tablets | 28 tablet POSS £1.39 DT price = £0.76
    - Atenolol 50 mg Atenolol 50mg tablets | 28 tablet POSS £1.44 DT price = £0.83
    - Atenolol 100 mg Atenolol 100mg tablets | 28 tablet POSS £1.74 DT price = £0.97
  - **Tenormin (AstraZeneca UK Ltd)**
    - Atenolol 50 mg Tenormin LS 50mg tablets | 28 tablet POSS £5.11 DT price = £0.83
    - Atenolol 100 mg Tenormin 100mg tablets | 28 tablet POSS £6.49 DT price = £0.79

**Oral solution**
- **Atenolol (Non-proprietary)**
  - Atenolol 5 mg per 1 ml Atenolol 25mg/5ml oral solution sugar free sugar-free | 300 ml POSS £6.72 DT price = £5.59

**Solution for injection**
- **Tenormin (AstraZeneca UK Ltd)**
  - Atenolol 500 microgram per 1 ml Tenormin 5mg/10ml solution for injection ampoules | 10 ampoule POSS £34.45 (Hospital only)

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**Atenolol with nifedipine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, atenolol p. 143, nifedipine p. 153.

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: 1 capsule daily, increased if necessary to 1 capsule twice daily
      - Elderly: 1 capsule daily
  - **Angina**
    - **BY MOUTH**
      - Adult: 1 capsule twice daily

- **PRESCRIBING AND DISPENSING INFORMATION** Only indicated when calcium-channel blocker or beta-blocker alone proves inadequate.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Modified-release capsule**
- **CAUTIONARY AND ADVISORY LABELS** 8, 25
  - **Tenif (AstraZeneca UK Ltd)**
  - **Nifedipine 20 mg, Atenolol 50 mg** Tenif 50mg/20mg modified-release capsules | 28 capsule POSS £12.76 DT price = £12.76

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**Bisoprolol fumarate**

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: 5–10 mg once daily; maximum 20 mg per day
  - **Adjunct in heart failure**
    - **BY MOUTH**
      - Adult: Initially 1.25 mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5 mg once daily for 4 weeks, then increased if tolerated to 3.75 mg once daily for 1 week, then increased if tolerated to 5 mg once daily for 4 weeks, then increased if tolerated to 7.5 mg once daily for 4 weeks, then increased if tolerated to 10 mg once daily; maximum 10 mg per day

- **CONTRA-INDICATIONS** Acute or decompensated heart failure requiring intravenous inotropes · sino-atrial block
- **CAUTIONS** Ensure heart failure not worsening before increasing dose
- **SIDE-EFFECTS**
  - Uncommon: Cramp · depression · muscle weakness
  - Rare: Hearing impairment · hypertriglyceridaemia · syncope
  - Very rare: Conjunctivitis
- **HEPATIC IMPAIRMENT** Max. 10 mg daily in severe impairment.
- **RENAL IMPAIRMENT** Reduce dose if eGFR less than 20 mL/minute/1.73 m² (max. 10 mg daily).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 8
  - **Bisoprolol fumarate (Non-proprietary)**
    - Bisoprolol fumarate 1.25 mg Bisoprolol 1.25mg tablets | 28 tablet POSS £7.43 DT price = £0.86
    - Bisoprolol fumarate 2.5 mg Bisoprolol 2.5mg tablets | 28 tablet POSS £4.39 DT price = £0.84
    - Bisoprolol fumarate 3.75 mg Bisoprolol 3.75mg tablets | 28 tablet POSS £6.50 DT price = £1.12
**Celiprolol hydrochloride**

**INDICATIONS AND DOSE**
- Mild to moderate hypertension
  - **BY MOUTH**
  - Adult: 200 mg once daily, dose to be taken in the morning, then increased if necessary to 400 mg once daily

**SIDE-EFFECTS**
- Rare: Depression, pneumonia
- Frequency not known: Hot flushes

**BREAST FEEDING**
Manufacturers advise avoidance.

**HEPATIC IMPAIRMENT**
Consider dose reduction.

**RENAL IMPAIRMENT**
Reduce dose by half if eGFR 15–40 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m².

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

| Co-tendine (Non-proprietary) | Chlortalidone 12.5 mg, Atenolol 50 mg | Co-tendine 50mg/12.5mg tablets | 28 tablet | £4.85 DT price | £2.08
| Chlortalidone 25 mg, Atenolol 100 mg | Co-tendine 100mg/25mg tablets | 28 tablet | £4.85 DT price | £1.99
| Tenoret (AstraZeneca UK Ltd) | Chlortalidone 12.5 mg, Atenolol 50 mg | Tenoret 50mg/12.5mg tablets | 28 tablet | £5.18 DT price | £2.08
| Tenoretic (AstraZeneca UK Ltd) | Chlortalidone 25 mg, Atenolol 100 mg | Tenoretic 100mg/25mg tablets | 28 tablet | £5.18 DT price | £1.99

**Metoprolol tartrate**

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: Initially 100 mg daily, increased if necessary to 200 mg daily in 2–3 divided doses, high doses are rarely required; maximum 400 mg per day
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: 200 mg once daily

**Angina**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: 50–100 mg 2–3 times a day
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: 200–400 mg daily

**Pharmaceutical pricing**

| Chlortalidone 12.5 mg, Atenolol 50 mg | Co-tendine 50mg/12.5mg tablets | £4.85 DT price | £2.08
| Chlortalidone 25 mg, Atenolol 100 mg | Co-tendine 100mg/25mg tablets | £4.85 DT price | £1.99
| Tenoret (AstraZeneca UK Ltd) | Chlortalidone 12.5 mg, Atenolol 50 mg | Tenoret 50mg/12.5mg tablets | £5.18 DT price | £2.08
| Tenoretic (AstraZeneca UK Ltd) | Chlortalidone 25 mg, Atenolol 100 mg | Tenoretic 100mg/25mg tablets | £5.18 DT price | £1.99

**PREGNANCY**
Avoid. Diuretics not used to treat hypertension in pregnancy.

**BREAST FEEDING**
Atenolol present in milk in greater amounts than some other beta-blockers. Possible toxicity due to beta-blockade—monitor infant. Large doses of chlortalidone may suppress lactation.

**RENAI IMPAIRMENT**
Avoid if eGFR less than 30 mL/minute/1.73 m²—consider alternative treatment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

| Co-tendine (Non-proprietary) | Chlortalidone 12.5 mg, Atenolol 50 mg | Co-tendine 50mg/12.5mg tablets | 28 tablet | £4.85 DT price | £2.08
| Chlortalidone 25 mg, Atenolol 100 mg | Co-tendine 100mg/25mg tablets | 28 tablet | £4.85 DT price | £1.99
| Tenoret (AstraZeneca UK Ltd) | Chlortalidone 12.5 mg, Atenolol 50 mg | Tenoret 50mg/12.5mg tablets | 28 tablet | £5.18 DT price | £2.08
| Tenoretic (AstraZeneca UK Ltd) | Chlortalidone 25 mg, Atenolol 100 mg | Tenoretic 100mg/25mg tablets | 28 tablet | £5.18 DT price | £1.99

**SIDE-EFFECTS**
Allergic interstitial nephritis, jaundice
Arrhythmias
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Usual dose 50 mg 2–3 times a day, then increased if necessary up to 300 mg daily in divided doses
- **BY INTRAVENOUS INJECTION**
  - Adult: Up to 5 mg, dose to be given at a rate of 1–2 mg/minute, then up to 5 mg after 5 minutes if required, total dose of 10–15 mg

Migraine prophylaxis
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 100–200 mg daily in divided doses
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 200 mg daily

Hyperthyroidism (adjunct)
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 50 mg 4 times a day

In surgery
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: Initially 2–4 mg, given at induction or to control arrhythmias developing during anaesthesia, then 2 mg, repeated if necessary; maximum 10 mg per course

**Early intervention within 12 hours of infarction**
- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 5 mg every 2 minutes, to a max. of 15 mg, followed by (by mouth) 50 mg every 6 hours for 48 hours, to be taken 15 minutes after intravenous injection; (by mouth) maintenance 200 mg daily in divided doses

- **HEPATIC IMPAIRMENT** Reduce dose in severe impairment.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS 8**
  - Nebivolol (as Nebivolol hydrochloride) 2.5 mg
  - Nebivolol 2.5mg tablets | 28 tablet (Pom) £69.94 DT price = £32.18
  - Nebivolol (as Nebivolol hydrochloride) 5 mg
  - Nebivolol 5mg tablets | 28 tablet (Pom) £63.93 DT price = £31.90
  - Nebivolol (as Nebivolol hydrochloride) 10 mg
  - Nebivolol 10mg tablets | 28 tablet (Pom) £3.96 DT price = £3.96
  - Nebilet (A. Menarini Farmaceutica Internazionale SRL)
  - Nebivolol (as Nebivolol hydrochloride) 5 mg
  - Nebilet 5mg tablets | 28 tablet (Pom) £9.23 DT price = £4.40

**CALCIFIC CHANNEL BLOCKERS**

Calcium-channel blockers

**Overview**
Calcium-channel blockers differ in their predilection for the various possible sites of action and, therefore, their therapeutic effects are disparate, with much greater variation than those of beta-blockers. There are important differences between verapamil hydrochloride p. 155, diltiazem hydrochloride p. 148, and the dihydropyridine calcium-channel blockers (amlodipine p. 147, felodipine p. 150, lacidipine p. 151, lercanidipine hydrochloride p. 152, nicardipine hydrochloride p. 152, nifedipine p. 153, and nimodipine p. 108). Verapamil hydrochloride and diltiazem hydrochloride should usually be avoided in heart failure because they may further depress cardiac function and cause clinically significant deterioration.

Verapamil hydrochloride is used for the treatment of angina, hypertension, and arrhythmias. It is a highly negatively inotropic calcium-channel blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with beta-blockers. Constipation is the most common side-effect.

Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than does verapamil hydrochloride, and unlike verapamil hydrochloride it has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work.

Nicardipine hydrochloride has similar effects to those of nifedipine and may produce less reduction of myocardial contractility. Amlodipine and felodipine also resemble nifedipine and nicardipine hydrochloride in their effects and do not reduce myocardial contractility and they do not produce clinical deterioration in heart failure. They have a

- **CONTRA-INDICATIONS** Acute or decompensated heart failure requiring intravenous inotropes
- **SIDE-EFFECTS** Depression - oedema
- **BREAST FEEDING** Manufacturers advise avoidance.
- **HEPATIC IMPAIRMENT** No information available—manufacturer advises avoid.
- **RENAL IMPAIRMENT** Manufacturer advises avoid in heart failure if serum creatinine greater than 250 micromol/litre.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS 8**
  - Nebivolol (Non-proprietary)
  - Nebivolol (as Nebivolol hydrochloride) 2.5 mg
  - Nebivolol 2.5mg tablets | 28 tablet (Pom) £69.94 DT price = £32.18
  - Nebivolol (as Nebivolol hydrochloride) 5 mg
  - Nebivolol 5mg tablets | 28 tablet (Pom) £63.93 DT price = £31.90
  - Nebivolol (as Nebivolol hydrochloride) 10 mg
  - Nebivolol 10mg tablets | 28 tablet (Pom) £3.96 DT price = £3.96
  - Nebilet (A. Menarini Farmaceutica Internazionale SRL)
  - Nebivolol (as Nebivolol hydrochloride) 5 mg
  - Nebilet 5mg tablets | 28 tablet (Pom) £9.23 DT price = £4.40

- **INDICATIONS AND DOSE**
  - Essential hypertension
    - **BY MOUTH**
      - Adult: 5 mg daily
      - Elderly: Initially 2.5 mg daily, then increased if necessary to 5 mg daily
  - Hypertension in patient with renal impairment
    - **BY MOUTH**
      - Adult: Initially 2.5 mg once daily, then increased if necessary to 5 mg once daily

Nebivolol

**Solution for injection**
- **Betacaloc (AstraZeneca UK Ltd)**
  - Nebivolol tartrate 1 mg per 1 ml
  - Betacaloc I.V. 5mg/5ml solution for injection ampoules | 5 ampoule (Pom) £5.02 (Hospital only)
Calcium-channel blockers

**DRUG ACTION** Calcium-channel blockers (less correctly called ‘calcium-antagonists’) interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

**SIDE-EFFECTS**

**Overdose** Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur.

For details on the management of poisoning, see Calcium-channel blockers, under Emergency treatment of poisoning p. 1204.

**TREATMENT CESSION** There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of myocardial ischaemia.

Amlodipine

**DRUG ACTION** Amlodipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Prophylaxis of angina**

- **BY MOUTH**
  - Adult: Initially 5 mg once daily; maximum 10 mg per day

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 5 mg once daily; maximum 10 mg per day

**DOSE EQUIVALENCE AND CONVERSION**

- Tablets from various suppliers may contain different salts (e.g. amlodipine besilate, amlodipine maleate, and amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable.

**CONTRA-INDICATIONS** Cardiogenic shock • Significant aortic stenosis • Unstable angina

**INTERACTIONS** Appendix 1 (calcium-channel blockers).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain • Dizziness • Fatigue • Flushing • Headache • Nausea • Oedema • Palpitation • Sleep disturbances

- **Uncommon** Alopecia • Arthralgia • Asthenia • Back pain • Chest pain • Dry mouth • Dyspnoea • Gastro-intestinal disturbances • Gynaecomastia • Hypotension • Impotence • Mood changes • Muscle cramps • Myalgia • Parasthesia • Pruritus • Purpura • Rash • Rhinitis • Skin discoloration • Sweating • Syncope • Taste disturbances • Tinnitus • Tremor • Urinary disturbances • Visual disturbances • Weight changes

- **Very rare** Angioedema • Arrhythmias • Cholestasis • Coughing • Gastritis • Gingival hyperplasia • Hepatitis • Hyperglycaemia • Jaundice • Myocardial infarction • Pancreatitis • Peripheral neuropathy • Tachycardia • Thrombocytopenia • Urticaria • Vasculitis

- **Frequency not known** Erythema multiforme

**Overdose** In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**PREGNANCY** No information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** May need dose reduction—half-life prolonged.

**DIRECTIONS FOR ADMINISTRATION** Tablets may be dispersed in water.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Amlodipine (Non-proprietary)**
  - Amlodipine 5 mg Amlodipine 5mg tablets | 28 tablet [POM] £9.42 DT price = £0.73
  - Amlodipine 10 mg Amlodipine 10mg tablets | 28 tablet [POM] £14.07 DT price = £0.78
  - Istin (Pfizer Ltd)
    - Amlodipine 5 mg Istin 5mg tablets | 28 tablet [POM] £11.08 DT price = £0.73
    - Amlodipine 10 mg Istin 10mg tablets | 28 tablet [POM] £16.55 DT price = £0.78
Amiodipine with valsartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, amiodipine p. 147, valsartan p. 170.

**INDICATIONS AND DOSE**

Hypertension in patients stabilised on the individual components in the same proportions

- **BY MOUTH**
  - Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Exforge** (Novartis Pharmaceuticals UK Ltd)
  - Amlodipine (as Amlodipine besilate) 5 mg, Valsartan 80 mg
    - 10 tablet pack [Pf] £20.11 DT price = £20.11
  - Amlodipine (as Amlodipine besilate) 10 mg, Valsartan
    - 10 tablet pack [Pf] £26.51 DT price = £26.51
  - Amlodipine (as Amlodipine besilate) 5 mg, Valsartan
    - 16 tablet pack [Pf] £26.51 DT price = £26.51

Diltiazem hydrochloride

**INDICATIONS AND DOSE**

Prophylaxis and treatment of angina

- **BY MOUTH**
  - Adult: Initially 60 mg 3 times a day, adjusted according to response; maximum 360 mg per day
  - Elderly: Initially 60 mg twice daily, adjusted according to response; maximum 360 mg per day

**ADIZEM-SR® CAPSULES**

Mild to moderate hypertension

- **BY MOUTH**
  - Adult: 120 mg twice daily, dose form not appropriate for initial dose titration
  - Angina
    - **BY MOUTH**
      - Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily, dose form not appropriate for initial dose titration in the elderly

**ADIZEM-XL®**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 240 mg once daily, increased if necessary to 300 mg once daily
  - Elderly: Initially 120 mg once daily, increased if necessary up to 300 mg once daily

**ANGITIL® SR**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 90 mg twice daily; increased if necessary to 120–180 mg twice daily

**ANGITIL® XL**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 240 mg once daily; increased if necessary to 300 mg once daily, dose form not appropriate for initial dose titration in the elderly

**DILCARDIA® SR**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily
  - Elderly: Initially 60 mg twice daily; increased if necessary to 90 mg twice daily

**DILZEM® SR**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 180 mg once daily; increased if necessary to 360 mg once daily
  - Elderly: Initially 120 mg once daily; increased if necessary to 360 mg once daily

**DILZEM® XL**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 240 mg once daily; increased if necessary to 300 mg once daily
  - Elderly: Initially 120 mg once daily; increased if necessary up to 180 mg twice daily

**SLOZEM®**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 240 mg once daily; increased if necessary to 360 mg once daily
  - Elderly: Initially 120 mg once daily; increased if necessary to 360 mg once daily

**TILDIE RETARD®**

Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 90–120 mg twice daily; increased if necessary to 360 mg daily in divided doses
  - Elderly: Initially 120 mg once daily; increased if necessary to 120 mg twice daily

**TILDIE LA**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 200 mg once daily, to be taken with or before food, increased if necessary to 300–400 mg once daily; maximum 500 mg per day
  - Elderly: Initially 200 mg once daily, increased if necessary to 300 mg once daily

**VIAZEM® XL**

Angina | Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 180 mg once daily, adjusted according to response to 240 mg once daily; maximum 360 mg per day
  - Elderly: Initially 120 mg once daily, adjusted according to response
Tildiem Retard®

Angina

- **BY MOUTH**
- **Adult:** 180–300 mg once daily, increased if necessary to 480 mg once daily
- **Elderly:** Initially 120 mg once daily, increased if necessary to 480 mg once daily

Mild to moderate hypertension

- **BY MOUTH**
- **Adult:** 180–300 mg once daily, increased if necessary to 360 mg once daily
- **Elderly:** Initially 120 mg once daily, increased if necessary to 360 mg once daily

For treatment of angina, dose form not appropriate for initial titration; up to 120 mg twice a day may be required.

Slozem® Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

Dilzem® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

Angitil® XL Dose form not appropriate for initial dose titration.

Dilocardia® SR Dose for angina and mild to moderate hypertension—initially 60 mg twice a day; maximum 90 mg twice a day.

Tildiem® LA Dose for angina and mild to moderate hypertension—initially 200 mg daily; increased if necessary to 300 mg daily.

Viazem® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily, adjusted according to response.

Adizem-XL® Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

Zemtard® Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 · left ventricular failure with pulmonary congestion · second- or third-degree AV block (unless pacemaker fitted) · severe bradycardia · sick sinus syndrome

- **CAUTIONS** Bradycardia (avoid if severe) · first degree AV block · heart failure · prolonged PR interval · significantly impaired left ventricular function

- **INTERACTIONS** → Appendix 1 (calcium-channel blockers).

- **SIDE-EFFECTS**
- **Common or very common** Asthenia · AV block · bradycardia · dizziness · gastro-intestinal disturbances · headache · hot flushes · hypotension · malaise · oedema (notably of ankles) · palpitation · sino-atrial block
- **Rare** Erythema multiforme · exfoliative dermatitis · photosensitivity · rashes
- **Frequency not known** Depression · extrapyramidal symptoms · gum hyperplasia · gynaecomastia · hepatitis

Overdose

In overdose, diltiazem has a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole.

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Significant amount present in milk—no evidence of harm but avoid unless no safer alternative.

- **HEPATIC IMPAIRMENT** Reduce dose.

Tildiem Retard® Dose for mild to moderate hypertension—initially 120 mg once a day; increased if necessary to 120 mg twice a day.

For treatment of angina, dose form not appropriate for initial titration; up to 120 mg twice a day may be required.

Slozem® Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

Dilzem® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

Angitil® XL Dose form not appropriate for initial dose titration.

Dilocardia® SR Dose for angina and mild to moderate hypertension—initially 60 mg twice a day; maximum 90 mg twice a day.

Tildiem® LA Dose for angina and mild to moderate hypertension—initially 200 mg daily; increased if necessary to 300 mg daily.

Viazem® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily, adjusted according to response.

Adizem-XL® Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

Zemtard® Dose for angina and mild to moderate hypertension—initially 120 mg once daily.

- **PRESCRIBING AND DISPENSING INFORMATION** The standard formulations containing 60 mg diltiazem hydrochloride are licensed as generics and there is no requirement for brand name dispensing. Although their means of formulation has called for the strict designation ‘modified-release’, their duration of action corresponds to that of tablets requiring administration more frequently. Different versions of modified-release preparations containing more than 60 mg diltiazem hydrochloride may not have the same clinical effect. To avoid confusion between these different formulations of diltiazem, prescribers should specify the brand to be dispensed.

- **PATIENT AND CARER ADVICE**

Tildiem Retard® Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

- **Diltiazem hydrochloride (Non-proprietary)**

  | Diltiazem hydrochloride 60 mg | Diltiazem 60mg modified-release tablets | 84 tablet | £41.59 DT price = £41.59 | 100 tablet | £49.51 |

  | Diltiazem hydrochloride 90 mg | Diltiazem 90mg modified-release tablets | 56 tablet | no price available DT price = £7.27 |

  | Diltiazem hydrochloride 120 mg | Diltiazem 120mg modified-release tablets | 56 tablet | no price available DT price = £7.15 |

- **Retalzem** (Kent Pharmaceuticals Ltd)

  | Diltiazem hydrochloride 60 mg | Retalzem 60 modified-release tablets | 100 tablet | £41.50 |

  | Tildiem (Sanofi)

  | Diltiazem hydrochloride 60 mg | Tildiem 60mg modified-release tablets | 90 tablet | £7.96 |

  | Tildiem Retard (Sanofi)

  | Diltiazem hydrochloride 90 mg | Tildiem Retard 90mg tablets | 56 tablet | £7.27 DT price = £7.27 |

  | Diltiazem hydrochloride 120 mg | Tildiem Retard 120mg tablets | 56 tablet | £7.15 DT price = £7.15 |

**Modified-release capsule**

**CAUTIONARY AND ADVISORY LABELS** 25

- **Diltiazem hydrochloride (Non-proprietary)**

  | Diltiazem hydrochloride 60 mg | Diltiazem 60mg modified-release capsules | 56 capsule | £6.04 DT price = £6.04 |

  | Diltiazem hydrochloride 90 mg | Diltiazem 90mg modified-release capsules | 56 capsule | £8.50 DT price = £8.50 |

  | Diltiazem hydrochloride 120 mg | Diltiazem 120mg modified-release capsules | 28 capsule | £8.40 |

  | 56 capsule | £8.40 |
**Diltiazem hydrochloride 180 mg**  Diltiazem 180mg modified-release capsules  |  28 capsule (Posm) £54.20  |  56 capsule (Posm) no price available
**Diltiazem hydrochloride 240 mg**  Diltiazem 240mg modified-release capsules  |  28 capsule (Posm) £10.50 DT price = £11.52
**Diltiazem hydrochloride 300 mg**  Diltiazem 300mg modified-release capsules  |  28 capsule (Posm) £8.31 DT price = £9.01
**Diltiazem hydrochloride 360 mg**  Diltiazem 360mg modified-release capsules  |  28 capsule (Posm) no price available DT price = £13.85
  **Adizem-SR (Napp Pharmaceuticals Ltd)**
**Diltiazem hydrochloride 90 mg**  Adizem-SR 90mg capsules  |  56 capsule (Posm) £8.50 DT price = £8.50
**Diltiazem hydrochloride 120 mg**  Adizem-SR 120mg capsules  |  56 capsule (Posm) £9.45
**Diltiazem hydrochloride 180 mg**  Adizem-SR 180mg capsules  |  56 capsule (Posm) £11.15
  **Adizem-XL (Napp Pharmaceuticals Ltd)**
**Diltiazem hydrochloride 120 mg**  Adizem-XL 120mg capsules  |  28 capsule (Posm) £9.14
**Diltiazem hydrochloride 180 mg**  Adizem-XL 180mg capsules  |  28 capsule (Posm) £10.37
**Diltiazem hydrochloride 200 mg**  Adizem-XL 200mg capsules  |  28 capsule (Posm) £6.30 DT price = £6.29
**Diltiazem hydrochloride 240 mg**  Adizem-XL 240mg capsules  |  28 capsule (Posm) £11.52 DT price = £11.52
**Diltiazem hydrochloride 300 mg**  Adizem-XL 300mg capsules  |  28 capsule (Posm) £9.14 DT price = £9.01
  **Angitil SR (Chiesi Ltd)**
**Diltiazem hydrochloride 90 mg**  Angitil SR 90mg capsules  |  56 capsule (Posm) £7.03 DT price = £8.50
**Diltiazem hydrochloride 120 mg**  Angitil SR 120mg capsules  |  56 capsule (Posm) £6.91
**Diltiazem hydrochloride 180 mg**  Angitil SR 180mg capsules  |  56 capsule (Posm) £11.27
  **Angitil XL (Chiesi Ltd)**
**Diltiazem hydrochloride 240 mg**  Angitil XL 240 capsules  |  28 capsule (Posm) £7.94 DT price = £11.52
**Diltiazem hydrochloride 300 mg**  Angitil XL 300 capsules  |  28 capsule (Posm) £6.98 DT price = £9.01
  **Dilcardia SR (Mylan Ltd)**
**Diltiazem hydrochloride 60 mg**  Dilcardia SR 60mg capsules  |  56 capsule (Posm) £6.03 DT price = £6.04
**Diltiazem hydrochloride 90 mg**  Dilcardia SR 90mg capsules  |  56 capsule (Posm) £6.61 DT price = £8.50
**Diltiazem hydrochloride 120 mg**  Dilcardia SR 120mg capsules  |  56 capsule (Posm) £10.69
  **Dilizem SR (Teva UK Ltd)**
**Diltiazem hydrochloride 60 mg**  Dilizem SR 60 capsules  |  56 capsule (Posm) £6.04 DT price = £6.04
**Diltiazem hydrochloride 90 mg**  Dilizem SR 90 capsules  |  56 capsule (Posm) £6.29 DT price = £8.50
**Diltiazem hydrochloride 120 mg**  Dilizem SR 120 capsules  |  56 capsule (Posm) £12.89
**Dilizem XL (Teva UK Ltd)**
**Diltiazem hydrochloride 120 mg**  Dilizem XL 120 capsules  |  28 capsule (Posm) £7.78
**Diltiazem hydrochloride 180 mg**  Dilizem XL 180 capsules  |  28 capsule (Posm) £11.55
**Diltiazem hydrochloride 240 mg**  Dilizem XL 240 capsules  |  28 capsule (Posm) £11.52 DT price = £11.52
  **Slozem (Merck Serono Ltd)**
**Diltiazem hydrochloride 120 mg**  Slozem 120mg capsules  |  28 capsule (Posm) £7.00
**Diltiazem hydrochloride 180 mg**  Slozem 180mg capsules  |  28 capsule (Posm) £7.80
**Diltiazem hydrochloride 240 mg**  Slozem 240mg capsules  |  28 capsule (Posm) £8.03 DT price = £8.03
**Diltiazem hydrochloride 300 mg**  Slozem 300mg capsules  |  28 capsule (Posm) £8.50 DT price = £9.01
  **Tildiem LA (Sanofi)**
**Diltiazem hydrochloride 200 mg**  Tildiem LA 200 capsules  |  28 capsule (Posm) £6.29 DT price = £6.29
**Diltiazem hydrochloride 300 mg**  Tildiem LA 300 capsules  |  28 capsule (Posm) £9.01 DT price = £9.01
  **Viazem XL (Thornton & Ross Ltd)**
**Diltiazem hydrochloride 120 mg**  Viazem XL 120mg capsules  |  28 capsule (Posm) £6.60
**Diltiazem hydrochloride 180 mg**  Viazem XL 180mg capsules  |  28 capsule (Posm) £7.36
**Diltiazem hydrochloride 240 mg**  Viazem XL 240mg capsules  |  28 capsule (Posm) £7.74 DT price = £11.52

**Felodipine**

- **DRUG ACTION** Felodipine is a dihydropyridine calcium-channel blocker.

- **INDICATIONS AND DOSE**

  - **Prophylaxis of angina**

    - **BY MOUTH**

      - Adult: Initially 5 mg once daily; increased if necessary to 10 mg once daily, to be taken in the morning

      - Elderly: Initially 2.5 mg once daily; increased if necessary to 10 mg once daily, to be taken in the morning

  - **Hypertension**

    - **BY MOUTH**

      - Adult: Initially 5 mg once daily; usual maintenance 5–10 mg once daily, to be taken in the morning, doses above 20 mg daily rarely needed

      - Elderly: Initially 2.5 mg daily; usual maintenance 5–10 mg once daily, to be taken in the morning, doses above 20 mg daily rarely needed

- **CONTRA-INDICATIONS** Cardiac outflow obstruction - significant cardiac valvular obstruction (e.g. aortic stenosis) - uncontrolled heart failure - unstable angina - within 1 month of myocardial infarction

- **CAUTIONS**

  - Predisposition to tachycardia - severe left ventricular dysfunction - withdraw if cardiogenic shock develops - withdraw if existing pain worsens shortly after initiating treatment - withdraw if ischaemic pain occurs shortly after initiating treatment

- **INTERACTIONS** → Appendix 1 (calcium-channel blockers).

- **SIDE-EFFECTS**

  - Common or very common Flushing - headache - peripheral oedema

  - Uncommon Abdominal pain - dizziness - malaise - nausea - palpitation - paraesthesia - pruritus - rash - tachycardia

  - Rare Arthralgia - impotence - myalgia - syncope - vomiting

  - Very rare Gum hyperplasia - leucocytoclastic vasculitis - photosensitivity - urinary frequency

- **PREGNANCY** Avoid; toxicity in animal studies; may inhibit labour.

- **BREAST FEEDING** Present in milk but amount probably too small to be harmful.

- **HEPATIC IMPAIRMENT** Dose reduction may be required.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Modified-release tablet**

  CAUTIONARY AND ADVISORY LABELS 25

  - **Felodipine (Non-proprietary)**

    - Felodipine 2.5 mg Felodipine 2.5mg modified-release tablets  |  28 tablet (Posm) no price available DT price = £6.31

    - Felodipine 5 mg Felodipine 5mg modified-release tablets  |  28 tablet (Posm) £4.21 DT price = £4.21
Felodipine 10 mg | Felodipine 10 mg modified-release tablets | 28 tablet (Pod) £5.66 DT price = £5.66
▶ Cardioplex XL (Thea Ltd) | Cardioplex XL 2.5 mg tablets | 28 tablet (Pod) £5.68 DT price = £5.68
▶ Felodipine 2.5 mg | Felodipine XL 2.5 mg tablets | 28 tablet (Pod) £4.21 DT price = £4.21
▶ Felodipine 5 mg | Felodipine XL 5 mg tablets | 28 tablet (Pod) £3.87 DT price = £3.87
▶ Felodipine 10 mg | Cardioplex XL 10 mg tablets | 28 tablet (Pod) £5.68 DT price = £5.68
▶ Folicol (Teva UK Ltd) | Folicol XL 2.5 mg tablets | 28 tablet (Pod) £6.31 DT price = £6.31
▶ Folicol 5 mg | Folicol XL 5 mg tablets | 28 tablet (Pod) £4.21 DT price = £4.21
▶ Folicol 10 mg | Folicol XL 10 mg tablets | 28 tablet (Pod) £7.21 DT price = £7.21
▶ Neofel XL (Genus Pharmaceuticals Ltd) | Neofel XL 2.5 mg tablets | 28 tablet (Pod) £5.68 DT price = £5.68
▶ Neofel 5 mg | Neofel XL 5 mg tablets | 28 tablet (Pod) £3.79 DT price = £3.79
▶ Neofel 10 mg | Neofel XL 10 mg tablets | 28 tablet (Pod) £5.66 DT price = £5.66
▶ Neofel XL (Kent Pharmaceuticals Ltd, Almus Pharmaceuticals Ltd, Actavis UK Ltd) | Neofel XL 2.5 mg tablets | 28 tablet (Pod) £6.31 DT price = £6.31
▶ Neofel 5 mg | Neofel XL 5 mg tablets | 28 tablet (Pod) £4.21 DT price = £4.21
▶ Neofel 10 mg | Neofel XL 10 mg tablets | 28 tablet (Pod) £5.66 DT price = £5.66
▶ Parmid XL (Sandoz Ltd) | Parmid XL 2.5 mg tablets | 28 tablet (Pod) £5.36 DT price = £5.36
▶ Pinefeld XL (Tilomed Laboratories Ltd) | Pinefeld XL 10 mg tablets | 28 tablet (Pod) £11.98 DT price = £11.98
▶ Plendid (AstraZeneca UK Ltd) | Plendid 2.5 mg modified-release tablets | 28 tablet (Pod) £6.31 DT price = £6.31
▶ Plendid 5 mg | Plendid 5 mg modified-release tablets | 28 tablet (Pod) £4.21 DT price = £4.21
▶ Plendid 10 mg | Plendid 10 mg modified-release tablets | 28 tablet (Pod) £5.66 DT price = £5.66
▶ Vascalpha (Actavis UK Ltd, Almus Pharmaceuticals Ltd) | Vascalpha 2.5 mg modified-release tablets | 28 tablet (Pod) £7.16–7.29 DT price = £7.16–7.29
▶ Vascalpha 5 mg | Vascalpha 5 mg modified-release tablets | 28 tablet (Pod) £9.63–9.81 DT price = £9.63–9.81

Combinations available: Ramipril with felodipine, p. 165

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**Lacidipine**

**Drug action** | Lacidipine is a dihydropyridine calcium-channel blocker.

**Indications and dose**

**Hypertension**

▶ By mouth

▶ Adult: 2.5 mg twice daily for 3–4 weeks, then increased if necessary to 5 mg twice daily, dose increased exceptionally up to 10 mg twice daily.

▶ Elderly: 1.25 mg twice daily, increased if necessary after 3–4 weeks according to response; maintenance 2.5–5 mg once daily may be sufficient

**Contra-indications** | Acute porphyrias p. 930; cardiogenic shock; diet or within 1 month of myocardial infarction; unstable angina

**Caution** | Chronic heart failure; poor cardic reserve; severe aortic stenosis; sick sinus syndrome (if pacemaker not fitted)

**Interactions** | → Appendix 1 (calcium-channel blockers).

**Side-effects**

▶ Common or very common | Abdominal discomfort; dizziness; dyspnoea; fatigue; flushing; headache; palpitation; peripheral oedema; polyuria; rash; tachycardia

▶ Uncommon | Hypotension; weight gain

**Frequency not known** | Gynaecomastia; hepatitis

**Overdose** | In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**Pregnancy** | May inhibit labour. Risk to fetus should be balanced against risk of uncontrolled maternal hypertension.

**Breastfeeding** | Manufacturer advises avoid—present in milk in animal studies.

**Hepatic impairment** | 1.25 mg twice daily, increased if necessary after 3–4 weeks according to response; maintenance dose of 2.5 mg or 5 mg once daily may be sufficient.

**Renal impairment** | Use with caution.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

▶ Isradipine (Non-proprietary) | Isradipine 2.5 mg | 56 tablet (Pod) £184.56 DT price = £184.56

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**Isradipine**

**Indications and dose**

**Hypertension**

▶ By mouth

▶ Adult: 6–12 mg once daily for 14–21 days, then increased if necessary to 14–21 mg once daily.

▶ Elderly: 6 mg once daily, increased if necessary after 14–21 days according to response; maintenance 14–21 mg once daily may be sufficient.

**Contra-indications** | Acute porphyrias p. 930; aortic stenosis; avoid within 1 month of myocardial infarction; cardiogenic shock; unstable angina

**Caution** | Cardiac conduction abnormalities; poor cardiac reserve

**Interactions** | → Appendix 1 (calcium-channel blockers).

**Side-effects**

▶ Common or very common | Dizziness; flushing; headache; oedema; palpitation

▶ Rare | Aggravation of angina; asthenia; erythema; gastrointestinal disturbances; gum hyperplasia; mood disturbances; muscle cramps; polyuria; pruritus; skin rash

**Overdose** | In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**Pregnancy** | Manufacturer advises avoid; may inhibit labour.

**Breastfeeding** | Manufacturer advises avoid—no information available.

**Hepatic impairment** | Antihypertensive effect possibly increased.
• **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Tablet**
  - **Lacidipine (Non-proprietary)**
    - Lacidipine 2 mg Lacidipine 2mg tablets | 28 tablet (PO) £6.85 DT price = £2.40
    - Lacidipine 4 mg Lacidipine 4mg tablets | 28 tablet (PO) £6.85 DT price = £2.53
  - **Molap (Rivopharm (UK) Ltd)**
    - Lacidipine 4 mg Molap 4mg tablets | 28 tablet (PO) £3.66 DT price = £2.53
  - **Motens (GliaxSmithKline UK Ltd)**
    - Lacidipine 2 mg Motens 2mg tablets | 28 tablet (PO) £2.95 DT price = £2.40
    - Lacidipine 4 mg Motens 4mg tablets | 28 tablet (PO) £3.10 DT price = £2.53

## Lercanidipine hydrochloride

**DRUG ACTION** Lercanidipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Mild to moderate hypertension**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 10 mg once daily; increased if necessary to 20 mg daily, dose can be adjusted after 2 weeks

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 930 • aortic stenosis • uncontrolled heart failure • unstable angina • within 1 month of myocardial infarction

- **CAUTIONS**
  - Left ventricular dysfunction • sick sinus syndrome (if pacemaker not fitted)

- **INTERACTIONS** → Appendix 1 (calcium-channel blockers).

**SIDE-EFFECTS**

- **Uncommon** Dizziness • flushing • headache • palpitation • peripheral oedema • tachycardia

- **Rare** Angina • asthenia • drowsiness • gastro-intestinal disturbances • myalgia • polyuria • rash

- **Very rare** Gingival hyperplasia • hypotension • myocardial infarction

**Overdose**

In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**PREGNANCY**

Manufacturer advises avoid—no information available.

**BREAST FEEDING**

Manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Avoid in severe disease.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Lercanidipine hydrochloride (Non-proprietary)**
  - Lercanidipine hydrochloride 10 mg Lercanidipine 10mg tablets | 28 tablet (PO) £12.57 DT price = £4.68
  - Lercanidipine hydrochloride 20 mg Lercanidipine 20mg tablets | 28 tablet (PO) £15.99 DT price = £5.67
  - Zanidip (Recordati Pharmaceuticals Ltd)
    - Lercanidipine hydrochloride 10 mg Zanidip 10mg tablets | 28 tablet (PO) £5.70 DT price = £4.68
    - Lercanidipine hydrochloride 20 mg Zanidip 20mg tablets | 28 tablet (PO) £10.82 DT price = £5.67

## Nicardipine hydrochloride

**DRUG ACTION** Nicardipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Prophylaxis of angina**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 20 mg 3 times a day, then increased to 30 mg 3 times a day, dose increased after at least 3 days; usual dose 60–120 mg daily

**Mild to moderate hypertension**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 20 mg 3 times a day, then increased to 30 mg 3 times a day, dose increased after at least 3 days; usual dose 60–120 mg daily

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 30 mg twice daily; increased if necessary up to 45 mg twice daily. usual dose 30–60 mg twice daily

**Life-threatening hypertension (specialist use only)**

- **Postoperative hypertension (specialist use only)**

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Initially 1–5 mg/hour, then adjusted in steps of 500 micrograms/hour after 30 minutes, adjusted according to response, maximum rate 15 mg/hour

**Life-threatening hypertension in patients with hepatic or renal impairment (specialist use only)**

- **Postoperative hypertension in patients with hepatic or renal impairment (specialist use only)**

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Initially 1–5 mg/hour, then adjusted in steps of 500 micrograms/hour after 30 minutes, adjusted according to response, maximum rate 15 mg/hour

**Acute life-threatening hypertension in pregnancy (specialist use only)**

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Initially 1–5 mg/hour, then adjusted in steps of 500 micrograms/hour after 30 minutes, adjusted according to response, usual maximum rate 4 mg/hour in treatment of pre-eclampsia (maximum rate 15 mg/hour)

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**

Acute porphyrias p. 930 • cardiogenic shock • significant or advanced aortic stenosis • unstable or acute attacks of angina

**SPECIFIC CONTRA-INDICATIONS**

- With intravenous use avoid within 8 days of myocardial infarction • compensatory hypertension

- With oral use avoid within 1 month of myocardial infarction

**CAUTIONS**

**GENERAL CAUTIONS**

Congestive heart failure • elderly • pulmonary oedema • significantly impaired left ventricular function • stroke • withdraw if ischaemic pain occurs or existing pain worsens within 30 minutes of initiating treatment or increasing dose

**SPECIFIC CAUTIONS**

- With intravenous use Elevated intracranial pressure • portal hypertension

**INTERACTIONS** → Appendix 1 (calcium-channel blockers).
Nifedipine

**INDICATIONS AND DOSE**

**Raynaud’s syndrome**
- **By mouth using immediate-release medicines**
  - Adult: Initially 5 mg 3 times a day, then adjusted according to response to 20 mg 3 times a day

**Angina prophylaxis (not recommended)**
- **By mouth using immediate-release medicines**
  - Adult: Initially 5 mg 3 times a day, then adjusted according to response to 20 mg 3 times a day

**Postponement of premature labour**
- **By mouth using immediate-release medicines**
  - Adult: Initially 20 mg, followed by 10–20 mg 3–4 times a day, adjusted according to uterine activity

**Hiccups in palliative care**
- **By mouth using immediate-release medicines**
  - Adult: 10 mg 3 times a day

**ADALAT RETARD®**

**Hypertension | Angina prophylaxis**
- **By mouth**
  - Adult: 10 mg twice daily, adjusted according to response to 40 mg twice daily

**ADALAT®**

**Angina prophylaxis (not recommended) | Raynaud’s phenomenon**
- **By mouth using immediate-release medicines**
  - Adult: Initially 5 mg 3 times a day, then adjusted according to response to 20 mg 3 times a day

**DOSE EQUIVALENT AND CONVERSION**
- For Adalat®: Adalat liquid gel capsules contain 5 mg nifedipine in 0.17 mL and 10 mg nifedipine in 0.34 mL.

**ADALAT® LA**

**Hypertension**
- **By mouth**
  - Adult: 20–30 mg once daily, increased if necessary up to 90 mg once daily

**Angina prophylaxis**
- **By mouth**
  - Adult: 30 mg once daily, increased if necessary up to 90 mg once daily

**ADIPINE® MR**

**Hypertension | Angina prophylaxis**
- **By mouth**
  - Adult: 10 mg twice daily, adjusted according to response to 40 mg twice daily

**ADIPINE® XL**

**Hypertension | Angina prophylaxis**
- **By mouth**
  - Adult: 30 mg daily, increased if necessary up to 90 mg daily

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**SIDE-EFFECTS**

- Atioventricular block
- Depression
- Dizziness
- Drowsiness
- Dyspnoea
- Flushing
- Frequency of micturition
- Gastro-intestinal disturbances
- Gingival hyperplasia
- Headache
- Hypotension
- Impotence
- Insomnia
- Nausea
- Palpitations
- Paraesthesia
- Paralytic ileus
- Peripheral oedema
- Pruritus
- Pulmonary oedema
- Rash
- Tachycardia
- Thrombocytopenia
- Tinnitus
- Vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Hypotension and reflex tachycardia Systemic hypotension and reflex tachycardia with rapid reduction of blood pressure may occur—during intravenous use consider stopping infusion or decreasing dose by half.

**Overdose**

In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**PREGNANCY**

May inhibit labour. Not to be used in multiple pregnancy (twins or more) unless there is no other acceptable alternative. Toxicity in animal studies. Risk of severe maternal hypotension and fatal foetal hypoxia—avoid excessive decrease in blood pressure. For treatment of acute life-threatening hypertension only.

**BREAST FEEDING**

Manufacturer advises avoid—present in breast milk.

**HEPATIC IMPAIRMENT**

- With oral use
  - Use with caution—consider using lowest initial dose and extending dosing interval according to individual response.
- With intravenous use
  - Use with caution—use lower initial dose.

**RENAI IMPAIRMENT**

- With oral use
  - Consider using lowest initial dose and extending dosing interval according to individual response.
- With intravenous use
  - Use with caution—use lower initial dose.

**MONITORING REQUIREMENTS**

Monitor blood pressure and heart rate at least every 5 minutes during intravenous infusion, and then until stable, and continue monitoring for at least 12 hours after end of infusion.

**DIRECTIONS FOR ADMINISTRATION**

Intravenous nifedipine should only be administered under the supervision of a specialist and in a hospital or intensive care setting in which patients can be closely monitored.

For **intravenous infusion** give continuously in **Glucose 5%**; dilute dose in infusion fluid to a final concentration of 100–200 micrograms/mL (undiluted solution via central venous line only) and give via volumetric infusion pump or syringe driver; protect from light; to minimise peripheral venous irritation, change site of infusion every 12 hours; risk of adsorption on to plastic of infusion set in the presence of saline solutions— incompatible with bicarbonate or alkaline solutions—consult product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**
- **Nicardipine hydrochloride (Non-proprietary)**
  - Nicardipine hydrochloride 20 mg: Nicardipine 20 mg capsules | 56 capsule [POM] £8.38 DT price = £6.00
  - Nicardipine hydrochloride 30 mg: Nicardipine 30 mg capsules | 56 capsule [POM] £9.73 DT price = £6.37
- **Cardene (Astellas Pharma Ltd)**
  - Nicardipine hydrochloride 20 mg: Cardene 20 mg capsules | 56 capsule [POM] £5.00 DT price = £6.00
  - Nicardipine hydrochloride 30 mg: Cardene 30 mg capsules | 56 capsule [POM] £6.96 DT price = £6.37

**Modified-release capsule**

*CAUTIONARY AND ADVISORY LABELS* 25
- **Cardene SR (Astellas Pharma Ltd)**
  - Nicardipine hydrochloride 30 mg: Cardene SR 30 mg capsules | 56 capsule [POM] £7.15 DT price = £7.15
  - Nicardipine hydrochloride 45 mg: Cardene SR 45 mg capsules | 56 capsule [POM] £10.40 DT price = £10.40

**Solution for infusion**

- **Nicardipine hydrochloride (Non-proprietary)**
  - Nicardipine hydrochloride 1 mg per 1 ml: Nicardipine 1 mg/10 ml solution for injection ampoules | 5 ampoule [POM] £50.00
  - Nicardipine hydrochloride 2.5 mg per 1 ml: Cardene LV, 25 mg/10 ml solution for infusion ampoules | 10 ampoule [POM] no price available

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**BNF 73**

**Hypertension 153**

**Cardiovascular system**

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**21-Nov-2016**
Coracten® SR
Hypertension | Angina prophylaxis
▶ BY MOUTH
▶ Adult: Initially 10 mg twice daily, increased if necessary up to 40 mg twice daily

Coracten® XL
Hypertension | Angina prophylaxis
▶ BY MOUTH
▶ Adult: Initially 30 mg daily, increased if necessary up to 90 mg daily

Fortipine® LA 40
Hypertension | Angina prophylaxis
▶ BY MOUTH
▶ Adult: Initially 40 mg once daily, increased if necessary up to 80 mg daily in 1–2 divided doses

Nifedipress® MR
Hypertension | Angina prophylaxis
▶ BY MOUTH
▶ Adult: 10 mg twice daily, adjusted according to response to 40 mg twice daily

Tensipine® MR
Hypertension | Angina prophylaxis
▶ BY MOUTH
▶ Adult: Initially 10 mg twice daily, adjusted according to response to 40 mg twice daily

Valni® XL
Severe hypertension | Prophylaxis of angina
▶ BY MOUTH
▶ Adult: 30 mg once daily, increased if necessary up to 90 mg once daily

Unlicensed Use
Not licensed for use in postponing premature labour.

Contra-Indications
Acute attacks of angina - cardiogenic shock - significant aortic stenosis - unstable angina - within 1 month of myocardial infarction

Caution
Diabetes mellitus - elderly - heart failure - poor cardiac reserve - severe hypotension - short-acting formulations are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia - significantly impaired left ventricular function (heart failure deterioration observed) - withdraw if ischaemic pain occurs or existing pain worsens shortly after initiating treatment

Adalat® LA
Crohn’s disease - decreased lumen diameter of the gastro-intestinal tract - history of gastro-intestinal obstruction - history of oesophageal obstruction - inflammatory bowel disease

Caution
Dose form not appropriate for use where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease (including Crohn’s disease).

Valni® XL
Decreased lumen diameter of gastro-intestinal tract - history of gastro-intestinal obstruction - history of oesophageal obstruction - inflammatory bowel disease

Caution
Dose form not appropriate for use where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease, or ileostomy after proctocolectomy.

Interactions
Appendix 1 (calcium-channel blockers).

Side-effects
Common or very common
- Asthenia - dizziness - gastrointestinal disturbance - headache - hypotension - lethargy - oedema - palpitation - vasodilatation

Uncommon

Rare
- Anorexia - gyn hyperplasia - hyperglycaemia - male infertility - mood disturbances - photosensitivity reactions - purpura

Frequency not known
- Agranulocytosis - anaphylaxis - bezoar formation (with some modified-release preparations) - dysphagia - gynaecomastia - intestinal obstruction - intestinal ulcer

Overdose
In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

Pregnancy
May inhibit labour; manufacturer advises avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension. Use only if other treatment options are not indicated or have failed.

Breast Feeding
Amount too small to be harmful but manufacturers advise avoid.

Hepatic Impairment
Dose reduction may be required in severe liver disease.

Some modified-release formulations may not be suitable for dose titration in hepatic disease—consult product literature.

Adalat® LA
Dose form not appropriate.

Valni® XL
Dose form not appropriate.

Directions for Administration
Fortipine® LA 40
Take with or just after food, or a meal.

Prescribing and Dispensing Information
Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed.

Palliative Care
For further information on the use of nifedipine in palliative care, see www.palliativedrugs.com/formulary/en/nifedipine.html.

Patient and Carer Advice
Adalat® LA
Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy.

Medicinal Forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral drops

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Adalat LA (Bayer Plc)
Nifedipine 20 mg Adalat LA 20 tablets | 28 tablet POM £5.27
Nifedipine 30 mg Adalat LA 30 tablets | 28 tablet POM £6.65 DT price = £6.85
Nifedipine 60 mg Adalat LA 60 tablets | 28 tablet POM £9.03 DT price = £9.03
▶ Adalat retard (Bayer Plc)
Nifedipine 10 mg Adalat retard tablets | 56 tablet POM £7.34 DT price = £7.34
Nifedipine 20 mg Adalat retard tablets | 56 tablet POM £8.81
▶ Adipine MR (Chiesi Ltd)
Nifedipine 10 mg Adipine MR 10 tablets | 56 tablet POM £3.73 DT price = £3.73
Nifedipine 20 mg Adipine MR 20 tablets | 56 tablet POM £5.21
> **Adipine XL** (Chiesi Ltd)
> Nifedipine 30 mg Adipine XL 30mg tablets | 28 tablet PPM £4.70
> DT price = £6.85
> Nifedipine 60 mg Adipine XL 60mg tablets | 28 tablet PPM £7.10
> DT price = £9.03
> **Fortiplus LA** (AMCo)
> Nifedipine 40 mg Fortiplus LA 40 tablets | 30 tablet PPM £14.40
> DT price = £14.40
> Nifedipress MR (Dexcel-Pharma Ltd)
> Nifedipine 10 mg Nifedipress MR 10 tablets | 56 tablet PPM £9.32
> DT price = £7.34
> Nifedipine 20 mg Nifedipress MR 20 tablets | 56 tablet PPM £10.06
> **Tensipine MR** (Genus Pharmaceuticals Ltd)
> Nifedipine 10 mg Tensipine MR 10 tablets | 56 tablet PPM £3.65
> DT price = £7.34
> Nifedipine 20 mg Tensipine MR 20 tablets | 56 tablet PPM £4.67
> **Valni XL** (Zentiva)
> Nifedipine 30 mg Valni XL 30mg tablets | 28 tablet PPM £9.14 DT price = £6.85
> Nifedipine 60 mg Valni XL 60mg tablets | 28 tablet PPM £21.85
> DT price = £19.03

**Capsule**

- **Nifedipine (Non-proprietary)**
  - Nifedipine 5 mg Nifedipine 5mg capsules | 84 capsule PPM £19.99
    DT price = £19.14
  - Nifedipine 10 mg Nifedipine 10mg capsules | 84 capsule PPM £21.00 DT price = £11.46

- **Adalat** (Bayer Plc)
  - Nifedipine 5 mg Adalat 5mg capsules | 90 capsule PPM £5.73
  - Nifedipine 10 mg Adalat 10mg capsules | 90 capsule PPM £7.30

**Modified-release capsule**

- **CAUTIONARY AND ADVISORY LABELS** 25

> **Coracten SR** (UCB Pharma Ltd)
> Nifedipine 10 mg Coracten SR 10mg capsules | 60 capsule PPM £3.90 DT price = £3.90
> Nifedipine 20 mg Coracten SR 20mg capsules | 60 capsule PPM £5.41 DT price = £5.41

> **Coracten XL** (UCB Pharma Ltd)
> Nifedipine 30 mg Coracten XL 30mg capsules | 28 capsule PPM £4.89 DT price = £4.89
> Nifedipine 60 mg Coracten XL 60mg capsules | 28 capsule PPM £7.34 DT price = £7.34

**Oral drops**

- **Nifedipine (Non-proprietary)**
  - Nifedipine 20 mg per 1 ml Nifedipin-ratiopharm 20mg/ml oral drops | 30 ml PPM no price available | 100 ml PPM no price available

**Combinations available:** Atenolol with nifedipine, p. 144

### Verapamil hydrochloride

**INDICATIONS AND DOSE**

**Treatment of supraventricular arrhythmias**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 40–120 mg 3 times a day
  - **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, to be given over 2 minutes, preferably with ECG monitoring
  - Elderly: 5–10 mg, to be given over 3 minutes, preferably with ECG monitoring

**Paroxysmal tachyarrhythmias**

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: Initially 5–10 mg, followed by 5 mg after 5–10 minutes if required, to be given over 2 minutes, preferably with ECG monitoring
  - Elderly: Initially 5–10 mg, followed by 5 mg after 5–10 minutes if required, to be given over 3 minutes, preferably with ECG monitoring

**Angina**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 80–120 mg 3 times a day

**Hypertension**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 240–480 mg daily in 2–3 divided doses

**Prophylaxis of cluster headache (initiated under specialist supervision)**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 240–960 mg daily in 3–4 divided doses

**HALF SECURON® SR**

**Hypertension (in patients new to verapamil)**

- **BY MOUTH**
  - Adult: Initially 120 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

**Hypertension**

- **BY MOUTH**
  - Adult: 240 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

**Angina**

- **BY MOUTH**
  - Adult: 240 mg twice daily, may sometimes be reduced to once daily

**Prophylaxis after myocardial infarction where beta-blockers not appropriate**

- **BY MOUTH**
  - Adult: 360 mg daily in divided doses, started at least 1 week after infarction, given as either 240 mg in the morning and 120 mg in the evening or 120 mg 3 times daily

**SECURON® SR**

**Hypertension (in patients new to verapamil)**

- **BY MOUTH**
  - Adult: Initially 120 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

**Hypertension**

- **BY MOUTH**
  - Adult: 240 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

**Angina**

- **BY MOUTH**
  - Adult: 240 mg twice daily, may sometimes be reduced to once daily

**Prophylaxis after myocardial infarction where beta-blockers not appropriate**

- **BY MOUTH**
  - Adult: 360 mg daily in divided doses, started at least 1 week after infarction, given as either 240 mg in the morning and 120 mg in the evening or 120 mg 3 times daily

**UNIVER®**

**Hypertension (in patients new to verapamil)**

- **BY MOUTH**
  - Adult: 120 mg daily; maximum 480 mg per day

**Hypertension**

- **BY MOUTH**
  - Adult: 240 mg daily; maximum 480 mg per day

**Angina**

- **BY MOUTH**
  - Adult: 360 mg daily; maximum 480 mg per day

**VERAPRESS® MR**

**Hypertension**

- **BY MOUTH**
  - Adult: 240 mg daily, increased if necessary to 240 mg twice daily
Angina
- BY MOUTH
- Adult: 240 mg twice daily, may sometimes be reduced to once daily

**VERTAB® SR 240**

Mild to moderate hypertension
- BY MOUTH
- Adult: 240 mg daily, increased if necessary to 240 mg twice daily

**INDICATIONS AND DOSE**

**Hypertension**
- BY MOUTH
- Adult: 1–2 tablets daily, dose to be taken in the morning

**SIDE-EFFEC TS**
- **Common or very common** Constipation
- **Uncommon** Ankle oedema · dizziness · fatigue · flushing · headache · nausea · vomiting
- **Rare** Allergic reactions · angioedema · arthralgia · asystole · bradycardia · erythema · erythromelalgia · gingival hyperplasia after long-term treatment · gynaecomastia after long-term treatment · heart block · heart failure · hypotension · increased prolactin concentration · myalgia · paraesthesia · pruritus · Stevens-Johnson syndrome · urticaria

**SIDE-EFFECTS, FURTHER INFORMATION**
- Intravenous administration or high doses: Hypotension, heart failure, bradycardia, heart block, and asystole are side-effects associated with intravenous administration or high doses.
- **Overdose** In overdose, verapamil has a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole.
- **PREGNANCY** May reduce uterine blood flow with fetal hypoxia. Manufacturer advises avoid in first trimester unless absolutely necessary. May inhibit labour.
- **BREAST FEEDING** Amount too small to be harmful.
- **HEPATIC IMPAIRMENT** Oral dose may need to be reduced.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Tablet**
- **Verapamil hydrochloride (Non-proprietary)**
  - Verapamil hydrochloride 40 mg
    - Verapamil 40mg tablets | 84 tablet (PST) £0.27 DT price = £1.76
  - Verapamil hydrochloride 80 mg
    - Verapamil 80mg tablets | 84 tablet (PST) £0.33 DT price = £2.01
  - Verapamil hydrochloride 120 mg
    - Verapamil 120mg tablets | 28 tablet (PST) £2.01 DT price = £1.60
  - Verapamil hydrochloride 160 mg
    - Verapamil 160mg tablets | 56 tablet (PST) £3.84 DT price = £28.20

**Modified-release tablet**
- **CAUTIONARY AND ADVISORY LABELS**
  - **25**

**Modified-release capsule**
- **CAUTIONARY AND ADVISORY LABELS**
  - **25**

**EXCIPIENTS:** May contain Gluten

**DIURETICS**

**Potassium-Sparing Diuretics**

**Amiloride with cyclopenthiazide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, amiloride hydrochloride p. 218, cyclopenthiazide p. 220.

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
- Adult: 1–2 tablets daily, dose to be taken in the morning

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **EXCIPIENTS:** May contain Gluten
  - **Navispare (AMCO)**
    - Amiloride hydrochloride 2.5 mg, Cyclopenthiazide
      - Navispare 2.5mg/250microgram tablets | 28 tablet (PST) £3.24 DT price = £3.24
Diuretics \(\rightarrow\) Thiazides and Related Diuretics

**Thiazides and related diuretics**

- **Contra-indications**
  - Addison’s disease
  - Hypercalcaemia
  - Hyponatraemia
  - Refractory hypokalaemia
  - Symptomatic hyperuricaemia

- **Cautions**
  - Diabetes
  - Gout
  - Hyperaldosteronism
  - Malnourishment
  - Nephrotic syndrome
  - Systemic lupus erythematosus

**Caution, Further Information**

- **Potassium loss**
  - Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency of the loop diuretic.
  - Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics avoids the need to take potassium supplements.

- **Potassium supplements** or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension.

- **In hepatic failure**, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis.

- **Elderly**
  - Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

- **Existing conditions**
  - Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus.

- **Interactions**
  - [Appendix 1 (diuretics)].

- **Side-effects**
  - **Common or very common**
    - Altered plasma-lipid concentrations
    - Gout
    - Hypercalcaemia
    - Hyperglycaemia
    - Hyperuricaemia
    - Hypochloracemic alkalosis
    - Hypokalaemia
    - Hypomagnesaemia
    - Hypoponatraemia
    - Metabolic and electrolyte disturbances
    - Mild gastrointestinal disturbances
    - Postural hypotension

  - **Uncommon**
    - Agranulocytosis
    - Blood disorders
    - Impotence
    - Leucopenia
    - Thrombocytopenia

- **Frequency not known**
  - Cardiac arrhythmias
  - Dizziness
  - Headache
  - Hypersensitivity reactions
  - Intrahepatic cholestasis
  - Pancreatitis
  - Paraoesophageal
  - Photosensitivity
  - Pneumonitis
  - Pulmonary oedema
  - Severe skin reactions
  - Visual disturbances

- **Pregnancy**
  - Thiazides and related diuretics should not be used to treat gestational hypertension. They may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported.

- **Hepatic impairment**
  - Caution in mild to moderate impairment. Avoid in severe liver disease. Hypokalaemia may precipitate coma in hepatic impairment, although hypokalaemia can be prevented by using a potassium-sparing diuretic. There is an increased risk of hypomagnesaemia in alcoholic cirrhosis.

- **Renal impairment**
  - Thiazides and related diuretics are ineffective if eGFR is less than 30 mL/minute/1.73 m² and should be avoided. Metolazone remains effective if eGFR is less than 30 mL/minute/1.73 m² but is associated with a risk of excessive diuresis. Electrolytes should be monitored in renal impairment.

**Monitoring requirements**

Electrolytes should be monitored, particularly with high doses and long-term use.

**Bendroflumethiazide**

**(Bendrofluzide)**

- **Indications and dose**
  - **Oedema**
    - **By mouth**
    - Adult: Initially 5–10 mg once daily or on alternate days, dose to be taken in the morning, then maintenance 5–10 mg 1–3 times a week

- **Hypertension**
  - **By mouth**
  - Adult: 2.5 mg daily, dose to be taken in the morning, higher doses are rarely necessary

- **Breast feeding**
  - The amount present in milk is too small to be harmful. Large doses may suppress lactation.

- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- Bendroflumethiazide (Non-proprietary)
  - Bendroflumethiazide 2.5 mg
  - Bendroflumethiazide 2.5 mg tablets | 28 tablet [Pos] £3.68 DT price = £0.67 | 500 tablet [Pos] no price available
  - Bendroflumethiazide 5 mg
  - Bendroflumethiazide 5 mg tablets | 28 tablet [Pos] £9.80 DT price = £0.87 | 500 tablet [Pos] no price available
  - Aprinox (AMCo)
  - Bendroflumethiazide 2.5 mg
  - Aprinox 2.5 mg tablets | 500 tablet [Pos] £27.31
  - Neo-Naclex (AMCo)
  - Bendroflumethiazide 2.5 mg
  - Neo-Naclex 2.5 mg tablets | 28 tablet [Pos] £0.33 DT price = £0.67

- Combinations available: Timolol with bendroflumethiazide, p. 143

**Co-amiloizde**

- **Indications and dose**
  - **Hypertension**
    - **By mouth**
    - Adult: Initially 2.5/25 mg daily, increased if necessary up to 5/50 mg daily
  - **Congestive heart failure**
    - **By mouth**
    - Adult: Initially 2.5/25 mg daily; increased if necessary up to 10/100 mg daily, reduce dose for maintenance if possible
  - **Oedema and ascites in cirrhosis of the liver**
    - **By mouth**
    - Adult: Initially 5/50 mg daily; increased if necessary up to 10/100 mg daily, reduce dose for maintenance if possible

- **Dose equivalence and conversion**
  - A mixture of amiloride hydrochloride and hydrochlorothiazide in the mass proportions of 1 part amiloride hydrochloride to 10 parts hydrochlorothiazide.

- **Contra-indications**
  - Anuria
  - Hyperkalaemia

- **Cautions**
  - Diabetes mellitus
  - Elderly

- **Side-effects**
  - Abdominal pain
  - Agitation
  - Alopecia
  - Angina
  - Anorexia
  - Arrhythmias
  - Arthralgia
  - Confusion
  - Constipation
  - Cough
  - Diarrhoea
  - Dizziness
  - Dry mouth
  - Eiiii
  - Feiiii
  - F
  - F
  - G
  - H
  - H
  - Hyponatraemia
  - Impotence
  - Photosensitivity
  - Pneumonitis
2 Cardiovascular system

dyspepsia · dyspnoea · encephalopathy · fever · flatulence · flushing · gastro-intestinal bleeding · headache · hyperkalaemia · insomnia · jaundice · malaise · muscle cramp · nasal congestion · nausea · palpitation · paraesthesia · postural hypotension · pruritus · raised intra-ocular pressure · rash · respiratory distress · restlessness · sexual dysfunction · sweating · thirst · tinnitus · tremor · urinary disturbances · visual disturbance · vomiting · weakness

- **BREAST FEEDING** Avoid—no information regarding amiloride component available. Amount of hydrochlorothiazide in milk probably too small to be harmful. Large doses of hydrochlorothiazide may suppress lactation.

- **RENAL IMPAIRMENT** Manufacturers advise avoid in severe impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

- **MONITORING REQUIREMENTS** Monitor electrolytes.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

  | Tablet | |
  | Co-amlozide (Non-proprietary) | Amiloride hydrochloride 2.5 mg, Hydrochlorothiazide 25 mg | Co-amlozide 2.5mg/25mg tablets | 28 tablet | £6.05 DT price = £6.05
  | Amiloride hydrochloride 5 mg, Hydrochlorothiazide 50 mg | Co-amlozide 5mg/50mg tablets | 28 tablet | £1.29 DT price = £1.05
  | Moduret (Merck Sharp & Dohme Ltd) | Amiloride hydrochloride 2.5 mg, Hydrochlorothiazide 25 mg | Moduret 25 tablets | 28 tablet | £0.86 DT price = £6.05
  | Moduretic (Merck Sharp & Dohme Ltd) | Amiloride hydrochloride 5 mg, Hydrochlorothiazide 50 mg | Moduretic 5mg/50mg tablets | 28 tablet | £1.29 DT price = £1.05

- **BREAST FEEDING** Present in milk—manufacturer advises avoid.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  | Tablet | |
  | Indapamide (Non-proprietary) | Indapamide 1.5 mg | 1 tablet | £3.40 DT price = £3.40
  | Indapamide 1.5 mg modified-release tablets | 30 tablet | £3.40 DT price = £3.40
  | Cardide SR (Teva UK Ltd) | Cardide SR 1.5mg tablets | 30 tablet | £4.32 DT price = £3.40
  | Indipam XL (Actavis UK Ltd) | Indipam XL 1.5mg tablets | 30 tablet | £4.32 DT price = £3.40
  | Natriflex (Servier Laboratories Ltd) | Natriflex 1.5mg tablets | 30 tablet | £1.30 DT price = £1.30

- **CAUTIONS** Acute porphyrias p. 930

- **SIDE-EFFECTS** Diuresis (with doses above 2.5 mg daily) · palpitation

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of hypersensitivity to sulfonamides.

- **MONITORING REQUIREMENTS**

- **INDICATIONS AND DOSE**
  Essential hypertension
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 2.5 mg daily, dose to be taken in the morning

  - **BY MOUTH USING MODIFIED-RELEASE MEDICATIONS**
  - Adult: 1.5 mg daily, dose to be taken preferably in the morning

- **DRUG ACTION** Indapamide is a thiazide-like diuretic with antihypertensive effects. At lower doses, vasodilatation is more prominent than diuresis; the diuretic effect becomes more apparent with higher doses.

- **CONTRA-INDICATIONS** The combination of an ACE inhibitor with aliskiren is contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m² · the combination of an ACE inhibitor with aliskiren is contra-indicated in patients with diabetes mellitus

- **CAUTIONS** Afro-Caribbean patients (may respond less well to ACE inhibitors) · concomitant diuretics · first dose hypotension (especially in patients taking high doses of
diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure) • peripheral vascular disease or generalised atherosclerosis (risk of clinically silent renovascular disease) • primary aldosteronism (patients may respond less well to ACE inhibitors) • the risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended) • use with care (or avoid) in those with a history of idiopathic or hereditary angioedema • use with care in patients with hypertrophic cardiomyopathy • use with care in patients with severe or symptomatic aortic stenosis (risk of hypotension)

CAUTIONS, FURTHER INFORMATION

• Anaphylactoid reactions To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; they should also be withheld before desensitisation with wasp or bee venom.

INTERACTIONS ➔ Appendix 1 (ACE inhibitors).

SIDE-EFFECTS

• Pruritus • abdominal pain • altered liver function tests • angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients) • arthralgia • blood disorders • bronchospasm • cholestatic jaundice • constipation • diarrhoea • dizziness • dyspepsia • eosinophilia • fatigue • fever • fulminant hepatic necrosis • haemolytic anaemia • headache • hepatic failure • hepatitis • hyperkalaemia • hypoglycaemia • leucocytosis • leucopenia • malaise • myalgia • nausea • neutropenia • pancreatitis • paraesthesia • persistent dry cough • photosensitivity • positive antinuclear antibody • profound hypotension • raised erythrocyte sedimentation rate • rash • renal impairment • rhinitis • serositis • sinusitis • sore throat • taste disturbance • thrombocytopenia • urticaria • vasculitis • vomiting

SIDE-EFFECTS, FURTHER INFORMATION

• Hepatic effects In light of reports of cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure, ACE inhibitors should be discontinued if marked elevation of hepatic enzymes or jaundice occur.

• ALLERGY AND CROSS-SENSITIVITY ACE inhibitors are contra-indicated in patients with hypersensitivity to ACE inhibitors (including angioedema).

• PREGNANCY ACE inhibitors should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; skull defects and oligohydramnios have also been reported.

• BREAST FEEDING Information on the use of ACE inhibitors in breast-feeding is limited.

• RENAL IMPAIRMENT Use with caution, starting with low dose, and adjust according to response. Hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced.

• MONITORING REQUIREMENTS Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if side effects mentioned are present).

• DIRECTIONS FOR ADMINISTRATION For hypertension the first dose should preferably be given at bedtime.

doses to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

Elderly: Initially 6.25 mg twice daily, then increased if necessary up to 150 mg daily in 2 divided doses, doses to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

Essential hypertension if used in volume depletion, cardiac decompensation, or renovascular hypertension

BY MOUTH

Adult: Initially 6.25–12.5 mg for 1 dose (under close medical supervision), then 6.25–12.5 mg twice daily; increased if necessary up to 100 mg daily in 1–2 divided doses, doses to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

Heart failure

BY MOUTH

Adult (under close medical supervision): Initially 6.25–12.5 mg 2–3 times a day, then increased if tolerated to up to 150 mg daily in divided doses, dose to be increased gradually at intervals of at least 2 weeks

Short-term treatment within 24 hours of onset of myocardial infarction in clinically stable patients

BY MOUTH

Adult: Initially 6.25 mg, then increased to 12.5 mg after 2 hours, followed by 25 mg after 12 hours; increased if tolerated to 50 mg twice daily for 4 weeks

Prophylaxis of symptomatic heart failure after myocardial infarction in clinically stable patients with asymptomatic left ventricular dysfunction (starting 3–16 days after infarction) (under close medical supervision)

BY MOUTH

Adult: Initially 6.25 mg daily, then increased to 12.5 mg 3 times a day for 2 days, then increased if tolerated to 25 mg 3 times a day, then increased if tolerated to 75–150 mg daily in 2–3 divided doses, doses exceeding 75 mg per day to be increased gradually

Diabetic nephropathy in type 1 diabetes mellitus

BY MOUTH

Adult: 75–100 mg daily in divided doses

SIDE-EFFECTS

Common or very common

• Alopecia • dry mouth • dyspnkea • sleep disorder

Uncommon

• Angina • arhythmia • flushing • pallor • palpitation • Raynaud’s syndrome • tachycardia

Rare

• Anorexia • stomatitis

Very rare

• Allergic alveolitis • blurred vision • cardiac arrest • cardiogenic shock • cerebrovascular events • confusion • depression • eosinophilic pneumonia • glossitis • gynaecomastia • hypotension • impotence • peptic ulcer • photosensitivity • Stevens-Johnson syndrome • syncope

BREAST FEEDING

Avoid in first few weeks after delivery, particularly in preterm infants risk of profound neonatal hypotension; can be used in mothers breast-feeding older infants if essential but monitor infant’s blood pressure.

RENAI IMPAIRMENT

Reduce dose; max. initial dose 50 mg if eGFR above 40 mL/minute/1.73 m²; max. initial dose 25 mg daily (do not exceed 100 mg daily) if eGFR 20–40 mL/minute/1.73 m²; max. initial dose 12.5 mg daily (do not exceed 75 mg daily) if eGFR 10–20 mL/minute/1.73 m²; max. initial dose 6.25 mg daily (do not exceed 37.5 mg daily) if eGFR less than 10 mL/minute/1.73 m².
• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution.

Tablet
▶ Captopril (Non-proprietary)
Captopril 12.5 mg Captopril 12.5mg tablets | 56 tablet [P0M] £2.80 DT price = £2.44 | 100 tablet [P0M] £5.00
Captopril 25 mg Captopril 25mg tablets | 56 tablet [P0M] £4.52 DT price = £5.90 | 100 tablet [P0M] £8.07
Captopril 50 mg Captopril 50mg tablets | 56 tablet [P0M] £5.83 DT price = £7.24 | 100 tablet [P0M] £10.41
▶ Capoten (Bristol-Myers Squibb Pharmaceuticals Ltd)
Captopril 25 mg Capoten 25mg tablets | 28 tablet [P0M] £5.26
▶ Ecopace (AMCo)
Captopril 12.5 mg Ecopace 12.5mg tablets | 56 tablet [P0M] £0.48 DT price = £0.44
Captopril 25 mg Ecopace 25mg tablets | 56 tablet [P0M] £0.60 DT price = £0.56
Captopril 50 mg Ecopace 50mg tablets | 56 tablet [P0M] £0.72 DT price = £0.52

Oral solution
ELECTROLYTES: May contain Sodium
▶ Noyada (Martindale Pharmaceuticals Ltd)
Captopril 1 mg per 1 ml Noyada 5mg/5ml oral solution sugar-free | 100 ml [P0M] £98.21 DT price = £98.21
Captopril 5 mg per 1 ml Noyada 25mg/5ml oral solution sugar-free | 100 ml [P0M] £108.94 DT price = £108.94

Co-zidocapt
The properties listed below are those particular to the combination only. For the properties of the components please consider, captopril p. 159, hydrochlorothiazide p. 158.

• INDICATIONS AND DOSE
Mild to moderate hypertension in patients stabilised on the individual components in the same proportions
▶ BY MOUTH
Adult: (consult product literature)

• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
▶ Co-zidocapt (Non-proprietary)
Hydrochlorothiazide 12.5 mg, Captopril 25 mg Co-zidocapt 12.5mg/25mg tablets | 28 tablet [P0M] £11.00
Hydrochlorothiazide 25 mg, Captopril 50 mg Co-zidocapt 25mg/50mg tablets | 28 tablet [P0M] £14.00
▶ Capozone (Bristol-Myers Squibb Pharmaceuticals Ltd)
Hydrochlorothiazide 25 mg, Captopril 50 mg Capozone 25mg/50mg tablets | 30 tablet [P0M] £7.52

Prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction
▶ BY MOUTH
Adult (under close medical supervision): Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks

• SIDE-EFFECTS
▶ Common or very common Asthenia - blurred vision - depression - dyspnoea
▶ Rare Abnormal dreams - allergic alveolitis - exfoliative dermatitis - glossitis - gynaecomastia - pemphigus - pulmonary infiltrates - Raynaud’s syndrome - Stevens-Johnson syndrome - stomatitis - toxic epidermal necrolysis
▶ Very rare Gastro-intestinal angioedema

Breast feeding
Avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in mothers breast-feeding older infants if essential but monitor infant’s blood pressure.

Hepatic impairment
Enalapril is a prodrug and requires close monitoring in patients with hepatic impairment.

Renal impairment
Max. initial dose 2.5 mg daily if eGFR less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION Tablets may be crushed and suspended in water immediately before use.

• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Tablet
▶ Enalapril maleate (Non-proprietary)
Enalapril maleate 2.5 mg Enalapril 2.5mg tablets | 28 tablet [P0M] £3.89 DT price = £3.13
Enalapril maleate 5 mg Enalapril 5mg tablets | 28 tablet [P0M] £4.13 DT price = £3.87
Enalapril maleate 10 mg Enalapril 10mg tablets | 28 tablet [P0M] £5.64 DT price = £5.99
Enalapril maleate 20 mg Enalapril 20mg tablets | 28 tablet [P0M] £6.63 DT price = £1.40
▶ Innovace (Merck Sharp & Dohme Ltd)
Enalapril maleate 2.5 mg Innovace 2.5mg tablets | 28 tablet [P0M] £5.35 DT price = £3.13
Enalapril maleate 5 mg Innovace 5mg tablets | 28 tablet [P0M] £7.51 DT price = £10.87
Enalapril maleate 10 mg Innovace 10mg tablets | 28 tablet [P0M] £10.53 DT price = £0.99
Enalapril maleate 20 mg Innovace 20mg tablets | 28 tablet [P0M] £12.51 DT price = £1.40

Enalapril maleate
The properties listed below are those particular to the combination only. For the properties of the components please consider, enalapril maleate above, hydrochlorothiazide p. 158.

• INDICATIONS AND DOSE
Hypertension
▶ BY MOUTH
Adult: Initially 5 mg once daily, lower initial doses may be required when used in addition to diuretic or in renal impairment; maintenance 20 mg once daily; maximum 40 mg per day

Heart failure
▶ BY MOUTH
Adult (under close medical supervision): Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks

Enalapril with hydrochlorothiazide
The properties listed below are those particular to the combination only. For the properties of the components please consider, enalapril maleate above, hydrochlorothiazide p. 158.

• INDICATIONS AND DOSE
Mild to moderate hypertension in patients stabilised on the individual components in the same proportions
▶ BY MOUTH
Adult: (consult product literature)
Fosinopril sodium

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 10 mg daily for 4 weeks, then increased if necessary up to 40 mg daily, doses over 40 mg not shown to increase efficacy

**Congestive heart failure (adjunct) (under close medical supervision)**
- **BY MOUTH**
  - Adult: Initially 10 mg once daily, then increased if tolerated to 40 mg once daily, doses to be increased gradually

**SIDE-EFFECTS** Chest pain - musculoskeletal pain

**BREAST FEEDING** Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT** Fosinopril is a prodrug and requires close monitoring in patients with hepatic impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **Fosinopril sodium (Non-proprietary)**
    - Hydrochlorothiazide 12.5 mg, Enalapril maleate 20 mg
    - Tablet 20 mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [POM] £13.90 DT price = £19.98

Imidapril hydrochloride

**INDICATIONS AND DOSE**

**Essential hypertension**
- **BY MOUTH**
  - Adult: Initially 5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, doses to be increased at intervals of at least 3 weeks; maximum 20 mg per day
  - Elderly: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, doses to be increased at intervals of at least 3 weeks

**Essential hypertension in patients with heart failure, angina or cerebrovascular disease, or in renal or hepatic impairment**
- **BY MOUTH**
  - Adult: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, dose to be increased at intervals of at least 3 weeks; maximum 20 mg per day

**SIDE-EFFECTS** Blurred vision - bronchitis - confusion - depression - dry mouth - dyspnoea - glossitis - ileus - impotence - sleep disturbances - tinnitus

**BREAST FEEDING** Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT** Imidapril is a prodrug and requires close monitoring in patients with hepatic impairment.

**RENAL IMPAIRMENT** Initial dose 2.5 mg daily if eGFR 30–80 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Imidapril hydrochloride 5 mg Tanatril 5mg tablets | 28 tablet [POM] £6.40 DT price = £6.40
  - Imidapril hydrochloride 10 mg Tanatril 10mg tablets | 28 tablet [POM] £7.22 DT price = £7.22
  - Imidapril hydrochloride 20 mg Tanatril 20mg tablets | 28 tablet [POM] £8.67 DT price = £8.67

Lisinopril

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 2.5–5 mg once daily; usual maintenance 20 mg once daily; maximum 80 mg per day

**Hypertension, when used in addition to diuretic, in cardiac decompensation or in volume depletion**
- **BY MOUTH**
  - Adult: Initially 2–5 mg once daily; usual maintenance 20 mg once daily; maximum 80 mg per day

**Short-term treatment following myocardial infarction in haemodynamically stable patients—systolic blood pressure over 120 mmHg**
- **BY MOUTH**
  - Adult: Initially 5 mg, taken within 24 hours of myocardial infarction, followed by 5 mg, to be taken 24 hours after initial dose, then 10 mg, to be taken 24 hours after second dose, then 10 mg once daily for 6 weeks (or continued if heart failure), temporarily reduce maintenance dose to 5 mg and if necessary 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment; withdraw if prolonged hypotension occurs during treatment; systolic blood pressure less than 90 mmHg for more than 1 hour

**Short-term treatment following myocardial infarction in haemodynamically stable patients—systolic blood pressure 100–120 mmHg**
- **BY MOUTH**
  - Adult: Initially 2.5 mg once daily, maintenance 5 mg once daily, increase to maintenance dose only after at least 3 days of the initial dose, should not be started after myocardial infarction if systolic blood pressure less than 100 mmHg, temporarily reduce maintenance dose to 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment; withdraw if prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour)

**Renal complications of diabetes mellitus**
- **BY MOUTH**
  - Adult: Initially 2.5–5 mg once daily, adjusted according to response; usual dose 10–20 mg once daily

**Heart failure (adjunct) (under close medical supervision)**
- **BY MOUTH**
  - Adult: Initially 2.5 mg once daily; increased in steps of up to 10 mg at least every 2 weeks; maximum 35 mg per day
Lisinopril with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, lisinopril p. 161, hydrochlorothiazide p. 158.

INDICATIONS AND DOSE
Mild to moderate hypertension in patients stabilised on the individual components in the same proportions
- BY MOUTH
- Adult: (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Lisinopril (Non-proprietary)
  - Lisinopril 2.5 mg | Lisinopril 2.5mg tablets | 28 tablet [POM] £1.51 DT price = £0.77
  - Lisinopril 5 mg | Lisinopril 5mg tablets | 28 tablet [POM] £2.50 DT price = £0.74
  - Lisinopril 10 mg | Lisinopril 10mg tablets | 28 tablet [POM] £9.60 DT price = £0.78
  - Lisinopril 20 mg | Lisinopril 20mg tablets | 28 tablet [POM] £10.90 DT price = £0.85
  - Zestril (AstraZeneca UK Ltd)
    - Lisinopril 5 mg | Zestril 5mg tablets | 28 tablet [POM] £4.71 DT price = £0.74
    - Lisinopril 10 mg | Zestril 10mg tablets | 28 tablet [POM] £7.38 DT price = £0.78
    - Lisinopril 20 mg | Zestril 20mg tablets | 28 tablet [POM] £6.51 DT price = £0.85

Oral solution
- Lisinopril (Non-proprietary)
  - Lisinopril 1 mg per 1 ml | Lisinopril 5mg/5ml oral solution sugar free sugar-free | 150 ml [POM] £15.41 DT price = £15.41

Moexipril hydrochloride

INDICATIONS AND DOSE
Essential hypertension (monotherapy)
- BY MOUTH
- Adult: Initially 7.5 mg once daily, adjusted according to response; maintenance 7.5–15 mg once daily; maximum 30 mg per day
- Elderly: Initially 3.75 mg once daily, adjusted according to response; maintenance 7.5–15 mg once daily; maximum 30 mg per day

Essential hypertension when used in addition with nifedipine or other antihypertensive drug
- BY MOUTH
- Adult: Initially 3.75 mg once daily, adjusted according to response; maintenance 7.5–15 mg once daily; maximum 30 mg per day

CAUTIONS
Significant mitral valve stenosis

SIDE-EFFECTS
- Very rare
  - Numbness
- Frequency not known
  - Alopecia · angina · appetite · arrhythmias · blurred vision · cerebrovascular accident · confusion · depression · drowsiness · dry mouth · dyspepsia · flushing · hyperuricaemia · impotence · myocardial infarction · palpitation · pemphigus · sleep disturbances · Stevens-Johnson syndrome · toxic epidermal necrolysis · weight changes

BREAST FEEDING
Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

HEPATIC IMPAIRMENT
Initial dose 3.75 mg once daily. Moexipril is a prodrug and requires close monitoring in patients with hepatic impairment.

RENAL IMPAIRMENT
If eGFR less than 40 mL/minute/1.73 m², initial dose 3.75 mg once daily titrated to max. 15 mg once daily.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
No licensed medicines identified.

Perindopril arginine

INDICATIONS AND DOSE
Hypertension
- BY MOUTH
- Adult: Initially 5 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 10 mg per day
- Elderly: Initially 2.5 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 10 mg per day

Hypertension, if used in addition to diuretic, or in cardiac decompensation or volume depletion
- BY MOUTH
- Adult: Initially 2.5 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 10 mg per day
Perindopril arginine with indapamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, perindopril arginine p. 162, indapamide p. 158.

### INDICATIONS AND DOSE

**Hypertension not adequately controlled by perindopril alone**

- **BY MOUTH**
  - Elderly: Initially 2 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day

**Hypertension, if used in addition to diuretic, or in cardiac decompensation or volume depletion**

- **BY MOUTH**
  - Adult: Initially 2 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day

**Prophylaxis of cardiac events following myocardial infarction or revascularisation in stable coronary artery disease**

- **BY MOUTH**
  - Adult: Initially 2 mg once daily for at least 2 weeks, dose to be taken in the morning, then increased if tolerated to 4 mg once daily
  - Elderly: Initially 2 mg once daily for 1 week, then increased if tolerated to 4 mg once daily for 1 week, then increased if tolerated to 8 mg once daily

**SIDE-EFFECTS**

- Asthenia
- Mood disturbances
- Sleep disturbances

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 22

- Coversyl Arginine (Servier Laboratories Ltd)
  - Perindopril arginine 2.5 mg
    - Coversyl Arginine 2.5mg tablets | 30 tablet [PO] £4.43 DT price = £4.43
    - Coversyl Arginine 5mg tablets | 30 tablet [PO] £6.28 DT price = £6.26
  - Perindopril arginine 10 mg
    - Coversyl Arginine 10mg tablets | 30 tablet [PO] £10.65 DT price = £10.65

Perindopril arginine

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 4 mg once daily for 2 weeks, dose to be taken in the morning, then increased if tolerated to 8 mg once daily
  - Elderly: Initially 2 mg once daily for 1 week, then increased if tolerated to 4 mg once daily for 1 week, then increased if tolerated to 8 mg once daily

**SIDE-EFFECTS**

- Asthenia
- Mood disturbances
- Sleep disturbances

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 22

- Coversyl Arginine Plus (Servier Laboratories Ltd)
  - Indapamide 1.25 mg, Perindopril arginine 5 mg
    - Coversyl Arginine Plus 5mg/1.25mg tablets | 30 tablet [PO] £9.51 DT price = £9.51

Perindopril erbumine

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 4 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day

**Quinapril**

**INDICATIONS AND DOSE**

**Essential hypertension**

- **BY MOUTH**
  - Adult: Initially 10 mg once daily; maintenance 20–40 mg daily in up to 2 divided doses; maximum 80 mg per day
  - Elderly: Initially 2.5 mg once daily; maintenance 20–40 mg daily in up to 2 divided doses; maximum 80 mg per day

**Essential hypertension if used in addition to diuretic**

- **BY MOUTH**
  - Adult: Initially 2.5 mg once daily; maintenance 20–40 mg daily in up to 2 divided doses; maximum 80 mg per day
Heart failure (adjunct) (under close medical supervision)

▶ BY MOUTH
Adult: Initially 2.5 mg daily, increased if tolerated to 10–20 mg daily in 1–2 divided doses, doses to be increased gradually; maximum 40 mg per day

• SIDE-EFFECTS Asthenia · back pain · blurred vision · chest pain · depression · flatulence · impotence · insomnia · nervousness · oedema
• BREAST FEEDING Avoid in the first few weeks after delivery, particularly in preterm infants, due to the risk of profound neonatal hypotension; if essential, may be used in mothers breast-feeding older infants—the infant’s blood pressure should be monitored.
• HEPATIC IMPAIRMENT Quinapril is a prodrug and requires close monitoring in patients with hepatic impairment.
• RENAL IMPAIRMENT Max. initial dose 2.5 mg once daily if eGFR less than 40 mL/minute/1.73 m².

• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
Quinapril (as Quinapril hydrochloride) 5 mg Quinapril 5mg tablets | 28 tablet (PoM) £8.59 DT price = £8.57
Quinapril (as Quinapril hydrochloride) 10 mg Quinapril 10mg tablets | 28 tablet (PoM) £8.59 DT price = £8.57
Quinapril (as Quinapril hydrochloride) 20 mg Quinapril 20mg tablets | 28 tablet (PoM) £3.05 DT price = £1.55
Quinapril (as Quinapril hydrochloride) 40 mg Quinapril 40mg tablets | 28 tablet (PoM) £3.51 DT price = £2.02
Accupro (Pfizer Ltd)
Quinapril (as Quinapril hydrochloride) 5 mg Accupro 5mg tablets | 28 tablet (PoM) £6.60 DT price = £8.57
Quinapril (as Quinapril hydrochloride) 10 mg Accupro 10mg tablets | 28 tablet (PoM) £8.60 DT price = £8.57
Quinapril (as Quinapril hydrochloride) 20 mg Accupro 20mg tablets | 28 tablet (PoM) £10.79 DT price = £1.55
Quinapril (as Quinapril hydrochloride) 40 mg Accupro 40mg tablets | 28 tablet (PoM) £9.75 DT price = £2.02

Quinapril with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, quinapril p. 163, hydrochlorothiazide p. 158.

• INDICATIONS AND DOSE
Hypertension in patients stabilised on the individual components in the same proportions
▶ BY MOUTH
Adult: (consult product literature)

• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
Quinapril with hydrochlorothiazide (Non-proprietary)
Quinapril (as Quinapril hydrochloride) 10 mg,
Hydrochlorothiazide 12.5 mg Quinapril 10mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (PoM) £11.75 DT price = £11.75
Accretic (Pfizer Ltd)
Quinapril (as Quinapril hydrochloride) 10 mg,
Hydrochlorothiazide 12.5 mg Accretic 12.5mg/10mg tablets | 28 tablet (PoM) £11.75 DT price = £11.75

Ramipril

• INDICATIONS AND DOSE
Hypertension
▶ BY MOUTH
Adult: Initially 1.25–2.5 mg once daily, increased if necessary up to 10 mg once daily, dose to be increased at intervals of 2–4 weeks

Symptomatic heart failure (adjunct) (under close medical supervision)
▶ BY MOUTH
Adult: Initially 1.25 mg once daily, increased if tolerated to 10 mg daily, preferably taken in 2 divided doses, increase dose gradually at intervals of 1–2 weeks

Prophylaxis after myocardial infarction in patients with clinical evidence of heart failure (started at least 48 hours after infarction)
▶ BY MOUTH
Adult: Initially 2.5 mg twice daily for 3 days, then increased to 5 mg twice daily

Prophylaxis after myocardial infarction in patients with clinical evidence of heart failure (started at least 48 hours after infarction) when initial dose not tolerated
▶ BY MOUTH
Adult: 1.25 mg twice daily for 2 days, then increased to 2.5 mg twice daily, then increased to 5 mg twice daily, withdraw treatment if dose cannot be increased to 2.5 mg twice daily

Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or with diabetes mellitus and at least one additional risk factor for cardiovascular disease
▶ BY MOUTH
Adult: Initially 2.5 mg once daily for 1–2 weeks, then increased to 5 mg once daily for a further 2–3 weeks, then increased to 10 mg once daily

Nephropathy (consult product literature)
▶ BY MOUTH
Adult: Initially 1.25 mg once daily for 2 weeks, then increased to 2.5 mg once daily for a further 2 weeks, then increased if tolerated to 5 mg once daily

• SIDE-EFFECTS
Common or very common Bronchitis · dyspnoea · muscle cramps · stomatitis · syncope
Uncommon Angina · anxiety · arrhythmias · chest pain · decreased libido · depression · dry mouth · flushing · impotence · loss of appetite · myocardial infarction · nervousness · palpitations · peripheral oedema · sweating · tachycardia · visual disturbances
Rare Confusion · conjunctivitis · impaired hearing · onycholysis · tinnitus · tremor
Frequency not known Alopecia · cerebrovascular accident · erythema multiforme · glynaecomastia · hyperatraemia · pemphigoid exanthema · precipitation or exacerbation of Raynaud’s syndrome · skin reactions · sleep disturbance · Stevens-Johnson syndrome · toxic epidermal necrolysis

• BREAST FEEDING Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

• HEPATIC IMPAIRMENT Max. daily dose 2.5 mg. Ramipril is a prodrug and requires close monitoring in patients with hepatic impairment.

• RENAL IMPAIRMENT Max. daily dose 5 mg if eGFR 30–60 mL/minute/1.73 m²; max. initial dose 1.25 mg once daily (do not exceed 5 mg daily) if eGFR less than 30 mL/minute/1.73 m².
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Ramipril (Non-proprietary)**
  - Ramipril 1.25 mg: 28 tablet POM £5.25 DT price = £1.63
  - Ramipril 2.5 mg: 28 tablet POM £7.49 DT price = £0.98
  - Ramipril 5 mg: 28 tablet POM £10.40 DT price = £0.95
  - Ramipril 10 mg: 28 tablet POM £14.20 DT price = £1.06

- **Tratice (Sanofi)**
  - Ramipril 1.25 mg: 28 tablet POM £5.09 DT price = £1.63
  - Ramipril 2.5 mg: 7 tablet POM no price available | 28 tablet POM £7.22 DT price = £0.98
  - Ramipril 5 mg: 21 tablet POM no price available | 28 tablet POM £10.05 DT price = £0.95
  - Ramipril 10 mg: 7 tablet POM no price available | 28 tablet POM £13.68 DT price = £1.06

**Capsule**

- **Ramipril (Non-proprietary)**
  - Ramipril 1.25 mg: 28 capsule POM £1.80 DT price = £1.29
  - Ramipril 2.5 mg: 28 capsule POM £2.03 DT price = £1.49
  - Ramipril 5 mg: 28 capsule POM £2.05 DT price = £1.26
  - Ramipril 10 mg: 28 capsule POM £2.20 DT price = £1.29

**Oral solution**

- **Ramipril (Non-proprietary)**
  - Ramipril 500 microgram per 1 ml: 150 ml POM £96.00 DT price = £96.00

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**Ramipril with felodipine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ramipril p. 164, felodipine p. 150.

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**INDICATIONS AND DOSE**

**Hypertension in patients stabilised on the individual components in the same proportions**

- **BY MOUTH**
- Adult: (consult product literature)

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

- **CAUTIONARY AND ADVISORY LABELS. 25**
- **Triapin (Sanofi)**
  - Felodipine 2.5 mg, Ramipril 2.5 mg: Triapin 2.5mg/2.5mg modified-release tablets | 28 tablet POM £24.95
  - Felodipine 5 mg, Ramipril 5 mg: Triapin 5mg/5mg modified-release tablets | 28 tablet POM £16.13 DT price = £16.13

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**Trandolapril**

**INDICATIONS AND DOSE**

Mild to moderate hypertension

- **BY MOUTH**
- Adult: Initially 500 micrograms once daily, then increased to up to 4 mg once daily, doses to be increased gradually

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**Prophylaxis after myocardial infarction in patients with left ventricular dysfunction (starting as early as 3 days after infarction)**

- **BY MOUTH**
- Adult: Initially 500 micrograms once daily, then increased to up to 4 mg once daily, doses to be increased gradually

**SIDE-EFFECTS**


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**SIDE-EFFECTS, FURTHER INFORMATION**

- Symptomatic hypotension If symptomatic hypotension develops during titration, do not increase dose further; if possible, reduce dose of any adjunctive treatment and if this is not effective or feasible, reduce dose of trandolapril.

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**ANTIANGIOTENSIN SYSTEM > ANGIOTENSIN II RECEPTOR ANTAGONISTS**

**Angiotensin II receptor antagonists**

**CONTRA-INDICATIONS**

- The combination of an angiotensin-II receptor antagonist with aliskiren is contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m². The combination of an angiotensin-II receptor antagonist with aliskiren is contra-indicated in patients with diabetes mellitus

**CAUTIONS**

- Afro-Caribbean patients—particularly those with left ventricular hypertrophy (may not benefit from an angiotensin-II receptor antagonist) - aortic or mitral valve stenosis - elderly (lower initial doses may be appropriate) - hypertrophic cardiomyopathy - patients with a history of angioedema - patients with primary aldosteronism (may not benefit from an angiotensin-II receptor antagonist) - renal artery stenosis

**INTERACTIONS**

- Appendix 1 (angiotensin-II receptor antagonists)

**SIDE-EFFECTS**

- Hyperkalaemia - angioedema (may be delayed onset) - symptomatic hypotension including dizziness (particularly in patients with intravascular volume depletion, e.g. those taking high-dose diuretics)
Azilsartan medoxomil

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
    - **Adult**: Initially 40 mg once daily, increased if necessary up to 80 mg once daily
  - **Hypertension with intravascular volume depletion**
    - **BY MOUTH**
    - **Adult**: Initially 20–40 mg daily, increased if necessary up to 80 mg daily

- **CAUTIONS**
  - Heart failure

- **SIDE-EFFECTS**
  - **Common or very common** Diarrhoea, raised creatinine
  - **Very rare** Arthralgia, back pain, blood disorders, cough, hepatitis, hyponatraemia, myalgia, nausea, pruritus, rash, urticaria

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises monitor closely in mild to moderate impairment (no information available)

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution in severe impairment—no information available.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - **Edarbi** (Takeda UK Ltd)
      - Azilsartan medoxomil 20 mg: £16.80 DT price = £13.95
      - Azilsartan medoxomil 40 mg: £16.80 DT price = £13.95
      - Azilsartan medoxomil 80 mg: £19.95 DT price = £16.80

Eprosartan

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
    - **Adult**: 600 mg once daily

- **SIDE-EFFECTS**
  - **Common or very common** Headache, nausea, rhinitis, diarrhoea, malaise, vomiting

- **HEPATIC IMPAIRMENT**
  - Caution in mild or moderate impairment.

- **RENAL IMPAIRMENT**
  - Caution if eGFR less than 30 mL/minute/1.73 m²—limited experience.
MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eprosartan (Non-proprietary)</td>
<td></td>
</tr>
<tr>
<td>Eprosartan (as Eprosartan mesilate) 300 mg</td>
<td>Eprosartan 300mg tablets</td>
</tr>
<tr>
<td>Eprosartan (as Eprosartan mesilate) 400 mg</td>
<td>Eprosartan 400mg tablets</td>
</tr>
<tr>
<td>Eprosartan (as Eprosartan mesilate) 600 mg</td>
<td>Eprosartan 600mg tablets</td>
</tr>
<tr>
<td>Teveten (BGP Products Ltd)</td>
<td></td>
</tr>
<tr>
<td>Eprosartan (as Eprosartan mesilate) 300 mg</td>
<td>Tevoten 300mg tablets</td>
</tr>
<tr>
<td>Eprosartan (as Eprosartan mesilate) 600 mg</td>
<td>Tevoten 600mg tablets</td>
</tr>
</tbody>
</table>

SIDE-EFFECTS

- Common or very common: Fatigue, musculoskeletal pain, nausea, vomiting
- Uncommon: Chest pain, cough, diarrhoea, dyspepsia, flushing, sexual dysfunction, tachycardia
- Rare: Rash, urticaria
- Very rare: Arthralgia, cutaneous vasculitis, headache, hepatitis, myalgia, renal dysfunction, taste disturbance, tinnitus

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
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</thead>
<tbody>
<tr>
<td>Irbesartan (Non-proprietary)</td>
<td></td>
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<tr>
<td>Irbesartan 75 mg</td>
<td>Irbesartan 75mg tablets</td>
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<tr>
<td>Irbesartan 150 mg</td>
<td>Irbesartan 150mg tablets</td>
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<tr>
<td>Irbesartan 300 mg</td>
<td>Irbesartan 300mg tablets</td>
</tr>
<tr>
<td>Aprovel (Sanofi)</td>
<td></td>
</tr>
<tr>
<td>Irbesartan 75 mg</td>
<td>Aprovel 75mg tablets</td>
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<tr>
<td>Irbesartan 150 mg</td>
<td>Aprovel 150mg tablets</td>
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<tr>
<td>Irbesartan 300 mg</td>
<td>Aprovel 300mg tablets</td>
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</tbody>
</table>

Irbesartan with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, irbesartan above, hydrochlorothiazide p. 158.

INDICATIONS AND DOSE

Hypertension not adequately controlled with irbesartan alone

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan with hydrochlorothiazide (Non-proprietary)</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide 12.5 mg, Irbesartan 150 mg</td>
<td>CoAprovel 150mg/12.5mg tablets</td>
</tr>
<tr>
<td>Hydrochlorothiazide 25 mg, Irbesartan 300 mg</td>
<td>CoAprovel 300mg/25mg tablets</td>
</tr>
<tr>
<td>Hydrochlorothiazide 12.5 mg, Irbesartan 300 mg</td>
<td>CoAprovel 300mg/12.5mg tablets</td>
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</tbody>
</table>

Losartan potassium

INDICATIONS AND DOSE

Diabetic nephropathy in type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoAprovel (Sanofi)</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide 12.5 mg, Irbesartan 150 mg</td>
<td>CoAprovel 300mg/12.5mg tablets</td>
</tr>
</tbody>
</table>
**Hypertension with intravascular volume depletion**

- Adult 76 years and over: Initially 25 mg once daily for several weeks, then increased if necessary to 100 mg once daily
- Adult 18-75 years: Initially 25 mg once daily for several weeks, then increased if necessary up to 100 mg once daily

**CAUTIONS**
Severe heart failure

**SIDE-EFFECTS**
- Common or very common: Vertigo
- Uncommon: Angina, dyspnoea, gastro-intestinal disturbances, headache, malaise, oedema, palpitation, pruritus, rash, sleep disorders, urticaria
- Rare: Atrial fibrillation, cerebrovascular accident, hepatitis, paraesthesia, syncope
- Frequency not known: Anemia, anaphylaxis, arthralgia, cough, depression, erectile dysfunction, Henoch-Schönlein purpura, hyponatraemia, myalgia, pancreatitis, photosensitivity, renal impairment, rhabdomyolysis, thrombocytopenia, tinnitus, vasculitis

**HEPATIC IMPAIRMENT**
Consider dose reduction in mild to moderate impairment. Manufacturer advises avoid in severe impairment—no information available.

**PRESCRIBING AND DISPENSING INFORMATION**
Flavours of oral liquid formulations may include berry-citrus.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **Losartan potassium (Non-proprietary)**
  - Losartan potassium 12.5 mg: Losartan 12.5 mg tablets / 28 tablet (Pom) £30.00 DT price = £26.66
  - Losartan potassium 25 mg: Losartan 25 mg tablets / 28 tablet (Pom) £16.18 DT price = £0.81
  - Losartan potassium 50 mg: Losartan 50 mg tablets / 28 tablet (Pom) £12.80 DT price = £0.87
  - Losartan potassium 100 mg: Losartan 100 mg tablets / 28 tablet (Pom) £16.18 DT price = £1.04
- **Cozaar (Merck Sharp & Dohme Ltd)**
  - Losartan potassium 12.5 mg: Cozaar 12.5 mg tablets / 28 tablet (Pom) £8.09 DT price = £26.66
  - Losartan potassium 25 mg: Cozaar 25 mg tablets / 28 tablet (Pom) £16.18 DT price = £0.81
  - Losartan potassium 50 mg: Cozaar 50 mg tablets / 28 tablet (Pom) £12.80 DT price = £0.87
  - Losartan potassium 100 mg: Cozaar 100 mg tablets / 28 tablet (Pom) £16.18 DT price = £1.04

**Oral suspension**
- **Cozaar (Merck Sharp & Dohme Ltd)**
  - Losartan potassium 2.5 mg per 1 ml: Cozaar 2.5 mg/ml oral suspension sugar-free / 200 ml (Pom) £53.68 DT price = £53.68

**Losartan with hydrochlorothiazide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, losartan potassium p. 167, hydrochlorothiazide p. 158.

**INDICATIONS AND DOSE**
Hypertension not adequately controlled with losartan alone

- By mouth
- Adult: (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Losartan with hydrochlorothiazide (Non-proprietary)**
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 50 mg: Losartan 50 mg / Hydrochlorothiazide 12.5 mg tablets / 28 tablet (Pom) £13.75 DT price = £1.35
  - Hydrochlorothiazide 25 mg, Losartan potassium 100 mg: Losartan 100 mg / Hydrochlorothiazide 25 mg tablets / 28 tablet (Pom) £16.18 DT price = £1.63
- **Cozaar-Comp (Merck Sharp & Dohme Ltd)**
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 50 mg: Cozaar-Comp 50 mg / 12.5 mg tablets / 28 tablet (Pom) £12.80 DT price = £1.35
  - Hydrochlorothiazide 25 mg, Losartan potassium 100 mg: Cozaar-Comp 100 mg / 25 mg tablets / 28 tablet (Pom) £16.18 DT price = £1.63
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 100 mg: Cozaar-Comp 100 mg / 12.5 mg tablets / 28 tablet (Pom) £16.18 DT price = £1.63

**Olmesartan medoxomil**

**INDICATIONS AND DOSE**
Hypertension

- By mouth
- Adult: Initially 10 mg daily, increased if necessary to 20 mg daily; maximum 40 mg per day

**CONTRA-INDICATIONS**
Biliary obstruction

**SIDE-EFFECTS**
- Common or very common: Arthritis, chest pain, cough, fatigue, gastro-intestinal disturbances, haematuria, hypertriglyceridaemia, hyperuricaemia, influenza-like symptoms, musculoskeletal pain, peripheral oedema, pharyngitis, rhinitis, urinary-tract infection
- Uncommon: Angina, rash, vertigo
- Very rare: Headache, myalgia, pruritus, thrombocytopenia, urticaria

**HEPATIC IMPAIRMENT**
Dose should not exceed 20 mg daily in moderate impairment. Manufacturer advises avoid in severe impairment—no information available.

**RENAL IMPAIRMENT**
Max. 20 mg daily if eGFR less than 20 mL/minute/1.73 m². Avoid if eGFR less than 20 mL/minute/1.73 m².

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **Olmetec (Daichi Sankyo UK Ltd)**
  - Olmesartan medoxomil 10 mg: Olmetec 10 mg tablets / 28 tablet (Pom) £10.95 DT price = £10.95
  - Olmesartan medoxomil 20 mg: Olmetec 20 mg tablets / 28 tablet (Pom) £12.95 DT price = £12.95
  - Olmesartan medoxomil 40 mg: Olmetec 40 mg tablets / 28 tablet (Pom) £17.50 DT price = £17.50

**Olmesartan with amlodipine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil above, amlodipine p. 147.

**INDICATIONS AND DOSE**
Hypertension in patients stabilised on the individual components in the same proportions

- By mouth
- Adult: (consult product literature)
MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Sevikar** (Daichi Sankyo UK Ltd)
  - Amlodipine (as Amlodipine besilate) 5 mg, Olmesartan medoxomil 20 mg: Sevikar 20mg/5mg tablets | 28 tablet PoM £16.95
  - Amlodipine (as Amlodipine besilate) 10 mg, Olmesartan medoxomil 40 mg: Sevikar 40mg/10mg tablets | 28 tablet PoM £16.95
  - Amlodipine (as Amlodipine besilate) 5 mg, Olmesartan medoxomil 40 mg: Sevikar 40mg/5mg tablets | 28 tablet PoM £16.95

Olmesartan with amlodipine and hydrochlorothiazide
The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil p. 168, amlodipine p. 147, hydrochlorothiazide p. 158.

**INDICATIONS AND DOSE**
Hypertension in patients stabilised on the individual components in the same proportions, or for hypertension not adequately controlled with olmesartan and amlodipine
- **BY MOUTH**
- **Adult:** (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Sevikar HCT** (Daichi Sankyo UK Ltd)
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 20 mg: Sevikar HCT 20mg/5mg/12.5mg tablets | 28 tablet | £16.95
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 25 mg, Olmesartan medoxomil 40 mg: Sevikar HCT 40mg/5mg/25mg tablets | 28 tablet | £16.95
  - Amlodipine besilate 10 mg, Hydrochlorothiazide 25 mg, Olmesartan medoxomil 40 mg: Sevikar HCT 40mg/10mg/25mg tablets | 28 tablet | £16.95
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg: Sevikar HCT 40mg/5mg/12.5mg tablets | 28 tablet | £16.95
  - Amlodipine besilate 10 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg: Sevikar HCT 40mg/10mg/12.5mg tablets | 28 tablet | £16.95

Olmesartan with hydrochlorothiazide
The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil p. 168, hydrochlorothiazide p. 158.

**INDICATIONS AND DOSE**
Hypertension not adequately controlled with olmesartan alone
- **BY MOUTH**
- **Adult:** (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Olmetec Plus** (Daichi Sankyo UK Ltd)
  - Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 20 mg: Olmetec Plus 20mg/12.5mg tablets | 28 tablet PoM £12.95
  - Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg: Olmetec Plus 40mg/12.5mg tablets | 28 tablet PoM £17.50
  - Olmesartan medoxomil 20 mg, Hydrochlorothiazide 25 mg: Olmetec Plus 20mg/25mg tablets | 28 tablet PoM £12.95
  - Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg: Olmetec Plus 40mg/12.5mg tablets | 28 tablet PoM £17.50

**Telmisartan**

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
- **Adult:** Initially 20–40 mg once daily for at least 4 weeks, increased if necessary up to 80 mg once daily

**Prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease, or type 2 diabetes mellitus with target-organ damage**
- **BY MOUTH**
- **Adult:** 80 mg once daily

**SIDE-EFFECTS**
- **Common or very common** Arthralgia • back pain • chest pain • eczema • gastro-intestinal disturbances • influenza-like symptoms • leg cramps • myalgia • pharyngitis • sinusitis • urinary–tract infection
- **Uncommon** Abnormal vision • anxiety • dry mouth • flatulence • increased sweating • tendinitis–like symptoms • vertigo
- **Rare** Blood disorders • bradycardia • depression • dyspnoea • eosinophilia • increase in uric acid • insomnia • pruritus • rash • tachycardia
- **Frequency not known** Asthenia • syncope

**HEPATIC IMPAIRMENT**
20–40 mg once daily in mild or moderate impairment. Avoid in severe impairment or biliary obstruction.

**RENAL IMPAIRMENT** Manufacturer advises initial dose of 20 mg once daily in severe impairment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Telmisartan (Non-proprietary)**
  - Telmisartan 20 mg: Telmisartan 20mg tablets | 28 tablet | £10.55
  - Telmisartan 40 mg: Telmisartan 40mg tablets | 28 tablet | £10.07–£12.93
  - Telmisartan 80 mg: Telmisartan 80mg tablets | 28 tablet | £1.41–£16.15

- **Micardis** (Boehringer Ingelheim Ltd)
  - Telmisartan 20 mg: Micardis 20mg tablets | 28 tablet | £11.10
  - Telmisartan 40 mg: Micardis 40mg tablets | 28 tablet | £13.61
  - Telmisartan 80 mg: Micardis 80mg tablets | 28 tablet | £17.00

- **Tolura** (Consilient Health Ltd)
  - Telmisartan 20 mg: Tolura 20mg tablets | 28 tablet | £11.10
  - Telmisartan 40 mg: Tolura 40mg tablets | 28 tablet | £13.61
  - Telmisartan 80 mg: Tolura 80mg tablets | 28 tablet | £17.00
**Telmisartan with hydrochlorothiazide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, telmisartan p. 169, hydrochlorothiazide p. 158.

- **INDICATIONS AND DOSE**
  - Hypertension not adequately controlled by telmisartan alone
    - **BY MOUTH**
    - Adult: consult product literature

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Telmisartan with hydrochlorothiazide (Non-proprietary)
      - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
        - Tablets [Pom] £13.61
      - Hydrochlorothiazide 25 mg, Telmisartan 80 mg
        - Tablets [Pom] £16.15
      - Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg
        - Tablets [Pom] £16.15
    - Actelsar HCT (Actavis UK Ltd)
      - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
        - Tablets [Pom] £13.61
      - Hydrochlorothiazide 25 mg, Telmisartan 80 mg
        - Tablets [Pom] £17.00
      - Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg
        - Tablets [Pom] £17.00
    - MicardisPlus (Boehringer Ingelheim Ltd)
      - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
        - Tablets [Pom] £13.61
      - Hydrochlorothiazide 25 mg, Telmisartan 80 mg
        - Tablets [Pom] £17.00
      - Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg
        - Tablets [Pom] £17.00
    - Tolucomi (Consilient Health Ltd)
      - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
        - Tablets [Pom] £13.61
      - Hydrochlorothiazide 25 mg, Telmisartan 80 mg
        - Tablets [Pom] £17.00
      - Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg
        - Tablets [Pom] £17.00

**Valsartan**

- **INDICATIONS AND DOSE**
  - Hypertension
    - **BY MOUTH**
    - Adult: Initially 80 mg once daily, increased if necessary up to 320 mg daily, doses to be increased at intervals of 4 weeks
  - Hypertension with intravascular volume depletion
    - **BY MOUTH**
    - Adult: Initially 40 mg once daily, increased if necessary up to 320 mg daily, doses to be increased at intervals of 4 weeks
  - Heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used
    - Heart failure, in conjunction with an ACE inhibitor when a beta-blocker cannot be used (under expert supervision)
    - **BY MOUTH**
    - Adult: Initially 40 mg twice daily, increased to up to 160 mg twice daily, doses to be increased at intervals of at least 2 weeks

**Myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct)**

- **BY MOUTH**
  - Adult: Initially 20 mg twice daily, increased if necessary up to 160 mg twice daily, doses to be increased over several weeks if tolerated

- **CONTRA-INDICATIONS**
  - Biliary cirrhosis; cholestasis

- **SIDE-EFFECTS**
  - Common or very common
    - Renal impairment
  - Uncommon
    - Acute renal failure, cough, fatigue, gastrointestinal disturbance, headache, syncope
  - Frequency not known
    - Hypersensitivity reactions; myalgia, neuropenia, pruritus, rash, serum sickness, thrombocytopenia, vasculitis
  - **HEPATIC IMPAIRMENT**
    - Max. dose 80 mg daily in mild to moderate impairment. Avoid in severe hepatic impairment.
  - **RENAL IMPAIRMENT**
    - Use with caution if eGFR less than 10 mL/minute/1.73 m²—no information available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

- **Tablet**
  - Valsartan (Non-proprietary)
    - Valsartan 40 mg
      - Tablets [Pom] £5.00
    - Valsartan 80 mg
      - Tablets [Pom] £6.69
    - Valsartan 160 mg
      - Tablets [Pom] £14.69
  - Capsule
    - Valsartan 40 mg
      - Capsules [Pom] £3.80
    - Valsartan 80 mg
      - Capsules [Pom] £4.00
    - Valsartan 160 mg
      - Capsules [Pom] £17.50
  - Oral solution
    - Diovan (Novartis Pharmaceuticals UK Ltd)
      - Valsartan 3 mg per 1 ml
        - Oral solution [Pom] £2.20

Combinations available: *Amlodipine with valsartan*, p. 148

**Valsartan with hydrochlorothiazide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, valsartan above, hydrochlorothiazide p. 158.

- **INDICATIONS AND DOSE**
  - Hypertension not adequately controlled by valsartan alone
    - **BY MOUTH**
    - Adult: consult product literature

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Valsartan with hydrochlorothiazide (Non-proprietary)
      - Hydrochlorothiazide 12.5 mg, Valsartan 80 mg
        - Tablets [Pom] £13.97
      - Hydrochlorothiazide 25 mg, Valsartan 160 mg
        - Tablets [Pom] £18.41
Hydrochlorothiazide 12.5 mg, Valsartan 160 mg | Valsartan 160mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet | £18.41 DT price = £2.42
- Co-Diovan (Novartis Pharmaceuticals UK Ltd)
Hydrochlorothiazide 12.5 mg, Valsartan 80 mg | Co-Diovan 80mg/12.5mg tablets | 28 tablet | £16.76 DT price = £7.97
Hydrochlorothiazide 25 mg, Valsartan 160 mg | Co-Diovan 160mg/25mg tablets | 28 tablet | £22.09 DT price = £10.60
Hydrochlorothiazide 12.5 mg, Valsartan 160 mg | Co-Diovan 160mg/12.5mg tablets | 28 tablet | £22.09 DT price = £2.42

DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
- Renin inhibitors inhibit renin directly; renin converts angiotensinogen to angiotensin I.

**Aliskiren**

- **DRUG ACTION** Renin inhibitors inhibit renin directly; renin converts angiotensinogen to angiotensin I.

**INDICATIONS AND DOSE**
- Essential hypertension either alone or in combination with other antihypertensives
  - **BY MOUTH**
  - Adult: 150 mg once daily, increased if necessary to 300 mg once daily

**CONTRA-INDICATIONS** Concomitant treatment with an ACE inhibitor or an angiotensin-II receptor antagonist in patients with an eGFR less than 60 mL/minute/1.73 m² - concomitant treatment with an ACE inhibitor or an angiotensin-II receptor antagonist in patients with diabetes mellitus, hereditary angioedema, idiopathic angioedema

**CAUTIONS** Combination treatment with an ACE inhibitor - combination treatment with an angiotensin-II receptor antagonist - concomitant use of diuretics (first doses may cause hypotension - initiate with care) - history of angioedema - moderate to severe congestive heart failure - patients at risk of renal impairment - salt depletion (first doses may cause hypotension - initiate with care) - volume depletion (first doses may cause hypotension - initiate with care)

**CAUTIONS, FURTHER INFORMATION**
- Concomitant use of drugs affecting the renin-angiotensin system
- Combination therapy with two drugs affecting the renin-angiotensin system (ACE inhibitors, angiotensin-II receptor antagonists, and aliskiren) is not recommended due to an increased risk of hyperkalaemia, hypotension, and renal impairment, compared to use of a single drug.
- Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor with an angiotensin-II receptor antagonist. There is some evidence that the benefits of combination use of an ACE inhibitor with candesartan or valsartan may outweigh the risks in selected patients with heart failure for whom other treatments are unsuitable, however, the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparing diuretic is not recommended. For patients currently taking combination therapy, the need for continued combined therapy should be reviewed. If combination therapy is considered essential, it should be carried out under specialist supervision, with close monitoring of blood pressure, renal function, and electrolytes (particularly potassium); monitoring should be considered at the start of treatment, then monthly, and also after any change in dose or during intercurrent illness.

**INTERACTIONS**
- **Appendix 1 (aliskiren).** peripheral oedema, cough, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Rare: Anaemia, angioedema, erythema
- Frequency not known: Liver disorders, nausea, vertigo, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- If diarrhoea severe or persistent discontinue treatment.
- **PREGNANCY** Manufacturer advises avoid—no information available; other drugs acting on the renin-angiotensin system have been associated with fetal malformations and neonatal death.
- **BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.
- **RENAL IMPAIRMENT** Avoid if eGFR is less than 30 mL/minute/1.73 m² - no information available. Use with caution in renal artery stenosis - no information available. Monitor plasma-potassium concentration in renal impairment.
- **MONITORING REQUIREMENTS** Monitor patients with a history of angioedema closely during treatment.
- **NATIONAL FUNDING/ACESS DECISIONS**
- Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (January 2010) that aliskiren (Rasilez®) is not recommended for use within NHS Scotland.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21**
- Rasilez (Novartis Pharmaceuticals UK Ltd)
  - Aliskiren (as Aliskiren hemifumarate) 150 mg Rasilez 150mg tablets | 28 tablet | £28.51 DT price = £28.51
  - Aliskiren (as Aliskiren hemifumarate) 300 mg Rasilez 300mg tablets | 28 tablet | £34.27 DT price = £34.27

**VASODILATORS VS VASODILATOR ANTIHYPERTENSIVES**

**Hydralazine hydrochloride**

**INDICATIONS AND DOSE**
- Moderate to severe hypertension (adjunct)
  - **BY MOUTH**
  - Adult: Initially 25 mg twice daily, increased if necessary up to 50 mg twice daily
- Heart failure (with long acting nitrate) (initiated in hospital or under specialist supervision)
  - **BY MOUTH**
  - Adult: Initially 25 mg 3-4 times a day, subsequent doses to be increased every 2 days if necessary; usual maintenance 50–75 mg 4 times a day
- Hypertensive emergencies (including during pregnancy)

**HYPERTENSION WITH RENAL COMPLICATIONS**

**BY INTRAVENOUS INFUSION**
- Adult: Initially 200–300 micrograms/minute; usual maintenance 50–150 micrograms/minute
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, to be diluted with 10 mL sodium chloride 0.9%; dose may be repeated after 20–30 minutes

**CONTRA-INDICATIONS** Acute porphyrias p. 930 · cor pulmonale · dissecting aortic aneurysm · high output heart failure · idiopathic systemic lupus erythematosus · myocardial insufficiency due to mechanical obstruction · severe tachycardia

**CAUTIONS** Cerebrovascular disease · coronary artery disease (may provoke angina, avoid by myocardial
infarction until stabilised) - occasionally blood pressure reduction too rapid even with low parenteral doses

- **INTERACTIONS** → Appendix 1 (hydralazine).
- **SIDE-EFFECTS**
  - Rare: Rash
  - Frequency not known: Abnormal liver function - agitation - anorexia - anxiety - arthralgia - blood disorders - dizziness - dysphonia - fever - fluid retention - flushing - gastro-intestinal disturbances - haematuria - haemolytic anaemia - headache - hypotension - increased lacrimation - jaundice - leucopenia - myalgia - nasal congestion - palpitiation - paraesthesia - peripheral neuritis - polynephritis - proteinuria - raised plasma creatinine - systemic lupus erythematosus - like syndrome after long-term therapy with over 100 mg daily (or less in women and in slow acetylator individuals) - tachycardia - thrombocytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**
The incidence of side-effects is lower if the dose is kept below 100 mg daily, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.

- **PREGNANCY** Neonatal thrombocytopenia reported, but risk should be balanced against risk of uncontrolled maternal hypertension. Manufacturer advises avoid before third trimester.

- **BREAST FEEDING** Present in milk but not known to be harmful. Monitor infant in breast-feeding.

- **HEPATIC IMPAIRMENT** Reduce dose.

- **RENAL IMPAIRMENT** Reduce dose if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS** Manufacturer advises test for antinuclear factor and for proteinuria every 6 months and check acetylator status before increasing dose above 100 mg daily, but evidence of clinical value unsatisfactory.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Apresoline®) give continuously in Sodium chloride 0.9%. Suggested infusion volume 500 mL.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **EXCIPIENTS:** May contain Gluten, propylene glycol
  - Hydralazine hydrochloride (Non-proprietary)
    - Hydralazine hydrochloride 10 mg: Apo-Hydralazine 10mg tablets | 100 tablet (£PO) no price available
    - Hydralazine hydrochloride 25 mg: Hydralazine 25mg tablets | 56 tablet (£PO) £8.25 DT price = £7.15 | 84 tablet (£PO) £14.00
    - Hydralazine hydrochloride 50 mg: Hydralazine 50mg tablets | 56 tablet (£PO) £15.46 DT price = £13.93
  - Apresoline (AmCo)
    - Hydralazine hydrochloride 25 mg: Apresoline 25mg tablets | 84 tablet (£PO) £3.38

**Powder for solution for injection**

- **Hydralazine hydrochloride (Non-proprietary)**
  - Hydralazine hydrochloride 20 mg: Hydralazine 20mg powder for concentrate for solution for injection ampoules | 5 ampoule (£PO) £64.50
  - Apresoline (AmCo)
    - Hydralazine hydrochloride 20 mg: Apresoline 20mg powder for solution for injection ampoules | 5 ampoule (£PO) £11.09

**Minoxidil**

- **INDICATIONS AND DOSE**
  - Severe hypertension, in addition to a diuretic and a beta-blocker
    - By mouth
    - Adult: Initially 5 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg, increased at intervals of at least 3 days, seldom necessary to exceed 50 mg daily; maximum 100 mg per day
    - Elderly: Initially 2.5 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg, increased at intervals of at least 3 days, seldom necessary to exceed 50 mg daily; maximum 100 mg per day

- **CONTRA-INDICATIONS** Phaeochromocytoma

- **CAUTIONS** Acute porphyrias p. 930 - after myocardial infarction (until stabilised) - angina

- **INTERACTIONS** → Appendix 1 (vasodilator antihypertensives).

- **SIDE-EFFECTS** Breast tenderness - gastro-intestinal disturbances - hypertrichosis - peripheral oedema - rashes - reversible rise in creatinine and blood urea nitrogen - sodium retention - tachycardia - water retention - weight gain

- **PREGNANCY** Avoid—possible toxicity including reduced placental perfusion. Neonatal hirsutism reported.

- **BREAST FEEDING** Present in milk but not known to be harmful.

- **RENAL IMPAIRMENT** Use with caution in significant impairment.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Loniten** (Pfizer Ltd)
  - Minoxidil 2.5 mg: Loniten 2.5mg tablets | 60 tablet (£PO) £8.88 DT price = £8.88
  - Minoxidil 5 mg: Loniten 5mg tablets | 60 tablet (£PO) £15.83 DT price = £15.83
  - Minoxidil 10 mg: Loniten 10mg tablets | 60 tablet (£PO) £30.68 DT price = £30.68

4.1a Hypertension associated with phaeochromocytoma

Other drugs used for Hypertension associated with phaeochromocytoma: Propranolol hydrochloride, p. 142

**VASODILATORS** → PERIPHERAL VASODILATORS

**Phenoxybenzamine hydrochloride**

- **INDICATIONS AND DOSE**
  - Hypertension in phaeochromocytoma
    - By mouth
    - Adult: Initially 10 mg daily, increased in steps of 10 mg daily until hypertension controlled or treatment not tolerated; maintenance 1–2 mg/kg daily in 2 divided doses

- **CONTRA-INDICATIONS** During recovery period after myocardial infarction (usually 3–4 weeks) - history of cerebrovascular accident

- **CAUTIONS** Avoid contact with skin (risk of contact sensitisation) - avoid in acute porphyrias p. 930 - carcinogenic in animals - cerebrovascular disease - congestive heart failure - elderly - severe ischaemic heart disease

- **SIDE-EFFECTS**
  - Rare: Gastro-intestinal disturbances
  - Frequency not known: Inhibition of ejaculation - lassitude - miosis - nasal congestion - postural hypotension (with dizziness and marked compensatory tachycardia)

- **PREGNANCY** Hypotension may occur in newborn.
4.1b Hypertensive crises

Other drugs used for Hypertensive crises
Hydralazine hydrochloride, p. 171 • Labetalol hydrochloride, p. 140

ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING

Guanethidine monosulfate

- INDICATIONS AND DOSE
  Hypertensive crisis (but no longer recommended)
  - BY INTRAMUSCULAR INJECTION
    - Adult: 10–20 mg, dose may be repeated after 3 hours if necessary

- CONTRA-INDICATIONS
  Heart failure • phaeochromocytoma

- CAUTIONS
  Asthma • cerebral arteriosclerosis • coronary arteriosclerosis • history of peptic ulceration

- INTERACTIONS
  Appendix 1 (adrenergic neurone blockers)

- SIDE-EFFECTS
  Diarrhoea • drowsiness • failure of ejaculation • fluid retention • headache • nasal congestion • postural hypotension

- PREGNANCY
  Postural hypotension and reduced uteroplacental perfusion. Should not be used to treat hypertension in pregnancy.

- REMOVAL OF DRUG
  The drug should be washed off by intravenous infusion of sodium nitroprusside at a rate of 500 ng/kg/minute, or by infusion of a loop diuretic.

- HANDLING AND STORAGE
  Solution for injection

- CONTRA-INDICATIONS
  Angina • coronary insufficiency • evidence of coronary artery disease • history of myocardial infarction • hypotension

- CAUTIONS
  Elderly • gastritis • peptic ulcer

- INTERACTIONS
  Appendix 1 (alpha-blockers).

- SIDE-EFFECTS
  Acute or prolonged hypotension • angina • arrhythmias • chest pain • diarrhoea • dizziness • flushing • nasal congestion • nausea • postural hypotension • tachycardia • vomiting

- PREGNANCY
  Use with caution • may cause marked decrease in maternal blood pressure with resulting fetal anoxia.

- BREAST FEEDING
  Manufacturer advises avoid — no information available.

- RENAL IMPAIRMENT
  Manufacturer advises caution — no information available.

- MONITORING REQUIREMENTS
  Monitor blood pressure and heart rate.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.
Overdose
Side-effects caused by excessive plasma concentration of the cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, marked metabolic acidosis (discontinue and give antidote, see cyanide in Emergency treatment of poisoning p. 1204).

- **PREGNANCY** Avoid prolonged use—potential for accumulation of cyanide in fetus.
- **BREAST FEEDING** No information available. Caution advised due to thiocyanate metabolite.
- **HEPATIC IMPAIRMENT** Use with caution. Avoid in hepatic failure—cyanide or thiocyanate metabolites may accumulate.
- **RENAL IMPAIRMENT** Avoid prolonged use—cyanide or thiocyanate metabolites may accumulate.
- **MONITORING REQUIREMENTS** Monitor blood pressure (including intra-arterial blood pressure) and blood-cyanide concentration, and if treatment exceeds 3 days, also blood thiocyanate concentration.
- **TREATMENT CESSATION** Avoid sudden withdrawal—terminate infusion over 15–30 minutes.
- **DIRECTIONS FOR ADMINISTRATION** For continuous intravenous infusion in Glucose 5%, infuse via infusion device to allow precise control. For further details, consult product literature.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Powder and solvent for solution for infusion**
    - Sodium nitroprusside (Non-proprietary)
    - Sodium nitroprusside dihydrate 50 mg Sodium nitroprusside 50mg powder and solvent for solution for infusion vials | 1 vial | no price available

4.1c Pulmonary hypertension

**Other drugs used for Pulmonary hypertension**
Epoprostenol, p. 109 - Sildenafil, p. 744 - Tadalafil, p. 746

**ANTITHROMBOTIC DRUGS > PROSTAGLANDINS, CARDIOVASCULAR**

**Iloprost**

- **INDICATIONS AND DOSE**
  - **Idiopathic or familial pulmonary arterial hypertension (initiated under specialist supervision)**
    - **BY INHALATION OF NEBULISED SOLUTION**
    - Adult: Initially 2.5 micrograms for 1 dose, increased to 5 micrograms for 1 dose, increased if tolerated to 5 micrograms 6–9 times a day, adjusted according to response; reduced if not tolerated to 2.5 micrograms 6–9 times a day, reduce to lower maintenance dose if high dose not tolerated

- **CONTRA-INDICATIONS** Conditions which increase risk of haemorrhage - congenital or acquired valvular defects of the myocardium - decompensated cardiac failure (unless under close medical supervision) - pulmonary veno-occlusive disease - severe arrhythmias - unstable angina - within 5 months of cerebrovascular events - within 6 months of myocardial infarction

- **CAUTIONS** Acute pulmonary infection - chronic obstructive pulmonary disease - Hypotension (do not initiate if systolic blood pressure below 85 mmHg) - severe asthma - unstable pulmonary hypertension with advanced right heart failure

- **INTERACTIONS** → Appendix 1 (iloprost).

**SIDE-EFFECTS**
- **Common or very common** Chest pain - cough - diarrhoea - dyspnoea - haemorrhage - headache - hypotension - jaw pain - nausea - oral irritation - rash - throat pain - vomiting
- **Frequency not known** Bronchospasm - taste disturbance - thrombocytopenia - wheezing
- **PREGNANCY** Use if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Initially 2.5 micrograms at intervals of 3–4 hours (max. 6 times daily), adjusted according to response (consult product literature). Elimination reduced.
- **DIRECTIONS FOR ADMINISTRATION** For inhaled treatment, to minimise accidental exposure use only with nebulisers listed in Ventavis® product literature in a well ventilated room.
- **PRESCRIBING AND DISPENSING INFORMATION** Delivery characteristics of nebuliser devices may vary—only switch devices under medical supervision.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
  - The Scottish Medicines Consortium has advised (November 2005) that iloprost (Ventavis®) is accepted for restricted use within NHS Scotland in patients in whom bosentan is ineffective or not tolerated, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Nebuliser liquid**
    - Ventavis (Bayer Plc)
    - Iloprost (as Iloprost trometamol) 10 microgram per 1 ml Ventavis 10micrograms/ml nebuliser solution 1ml ampoules | 30 ampoule | £400.19 | 168 ampoule | £2,241.08

**ENDOTHELIN RECEPTOR ANTAGONISTS**

**Ambrisentan**

- **INDICATIONS AND DOSE**
  - **Pulmonary arterial hypertension (initiated under specialist supervision)**
    - **BY MOUTH**
    - Adult: 5 mg once daily, increased if necessary to 10 mg once daily

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Max. 5 mg daily with concomitant ciclosporin.

- **CONTRA-INDICATIONS** Idiopathic pulmonary fibrosis
- **CAUTIONS** Not to be initiated in significant anaemia
- **INTERACTIONS** → Appendix 1 (ambrisentan).
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain - anaemia - chest pain - constipation - diarrhoea - dizziness - dyspnoea - epistaxis - flushing - headache - heart failure - hypotension - malaise - nausea - palpititation - peripheral oedema - upper respiratory tract disorders - vomiting
  - **Uncommon** Autoimmune hepatitis - hepatic injury - syncope

- **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment and ensure effective contraception during treatment. Monthly pregnancy tests advised.
- **PREGNANCY** Avoid (teratogenic in animal studies).
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Avoid in severe impairment.
- **RENAL IMPAIRMENT** Use with caution if eGFR less than 30 mL/minute/1.73 m².
Pulmonary hypertension

**MONITORING REQUIREMENTS**
- Monitor haemoglobin concentration or haematocrit after 1 month and 3 months of starting treatment, and periodically thereafter (reduce dose or discontinue treatment if significant decrease in haemoglobin concentration or haematocrit observed).
- Monitor liver function before treatment, and monthly thereafter—discontinue if liver enzymes raised significantly or if symptoms of liver impairment develop.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (October 2008) that ambrisentan (Volibris®) should be prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Tracleer (Actelion Pharmaceuticals UK Ltd) Ambrisentan 62.5 mg Tracleer 62.5mg tablets | 36 tablet [POM] £1,510.21 Ambrisentan 125 mg Tracleer 125mg tablets | 36 tablet [POM] £1,510.21

**Macitentan**

**INDICATIONS AND DOSE**
Pulmonary arterial hypertension (initiated under specialist supervision)
- **BY MOUTH**
  - Adult: Initially 6.25 mg twice daily for 4 weeks, then increased to 12.5 mg twice daily (max. per dose 250 mg); maximum 500 mg per day

**Bosentan**

**INDICATIONS AND DOSE**
Pulmonary arterial hypertension (initiated under specialist supervision)
- **BY MOUTH**
  - Adult: Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily

**MEDICATIONS**
- Pulmonary arterial hypertension (initiated under specialist supervision)
  - **BY MOUTH**
    - Adult: Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily (max. per dose 250 mg); maximum 500 mg per day

**INTERACTIONS**
- Common or very common Anaemia · bronchitis · headache · hypotension · upper respiratory-tract disorders · urinary-tract infection
- Frequency not known Leucopenia · thrombocytopenia
- Conception and contraception Manufacturer advises exclude pregnancy before treatment and ensure effective contraception during and for one month after stopping treatment. Monthly pregnancy tests advised.
- Pregnancy Toxicity in animal studies.
- Breast feeding Manufacturer advises avoid—present in milk in animal studies.
- Hepatic impairment Do not initiate if serum transaminases exceed 3 times upper limit of normal. Avoid in moderate and severe impairment.
- Renal impairment Manufacturer advises caution in severe impairment and avoid in patients undergoing dialysis (no information available). In renal impairment consider monitoring blood pressure (risk of hypotension).
- Monitoring requirements
  - Monitor liver function before treatment, then monthly thereafter (discontinue if unexplained persistent raised serum transaminases or signs of hepatic injury—can restart on advice on hepatologist if liver function tests return to normal and no hepatic injury).
  - Monitor haemoglobin concentration before treatment and then as indicated.
- Patient and carer advice Patient card should be provided.
  - Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as dark urine, nausea, vomiting, fatigue, abdominal pain, or pruritus develop.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (March 2014) that macitentan (Opsumit®) should be initiated and prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Opsumit (Actelion Pharmaceuticals UK Ltd) Macitentan 10 mg Opsumit 10mg tablets | 30 tablet [POM] £2,306.00
GUANYLATE CYCLASE STIMULATORS

Riociguat

**INDICATIONS AND DOSE**
Chronic thromboembolic pulmonary hypertension that is recurrent or persistent following surgery, or is inoperable (initiated under specialist supervision) | Monotherapy or in combination with an endothelin receptor antagonist for idiopathic or hereditary pulmonary arterial hypertension, or pulmonary arterial hypertension associated with connective tissue disease (initiated under specialist supervision)

**BY MOUTH**
- Adult: Initially 1 mg 3 times a day for 2 weeks, increased in steps of 0.5 mg 3 times a day, dose to be increased every 2 weeks, increased up to 2.5 mg 3 times a day (max. per dose 2.5 mg 3 times a day), increase up to maximum dose only if systolic blood pressure ≥ 95 mmHg and no signs of hypotension, if treatment interrupted for 3 or more days, restart at 1 mg three times daily for 2 weeks and titrate as before, during titration, reduce dose by 0.5 mg three times daily if systolic blood pressure falls below 95 mmHg and patient shows signs of hypotension
- Titrate dose cautiously in moderate to severe renal impairment. Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m²—limited information available.

**DIRECTIONS FOR ADMINISTRATION**
Tablets may be crushed and mixed with water or soft foods and swallowed immediately.

**PATIENT AND CARER ADVICE**
Smoking cessation advised (response possibly reduced). Patients should inform prescriber if smoking started or stopped during treatment; dose adjustment may be necessary.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (November 2014) that riociguat (Adempas *) is accepted for restricted use within NHS Scotland for the treatment of chronic thromboembolic pulmonary hypertension in patients for whom a phosphodiesterase type-5 inhibitor is inappropriate, not tolerated, or ineffective, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Adempas (Merck Sharp & Dohme Ltd)▼
  - Riociguat 500 microgram tablets | 42 tablet  | £36
  - Riociguat 1 mg tablets | 42 tablet  | £997.36
  - Riociguat 1.5 mg tablets | 42 tablet  | £997.36
  - Riociguat 2 mg tablets | 42 tablet  | £997.36
  - 84 tablet  | £1,994.72
  - Riociguat 2.5 mg tablets | 84 tablet  | £1,994.72

**4.2 Hypotension and shock**

**Sympathomimetics**

**Inotropic sympathomimetics**

**Shock**
Shock is a medical emergency associated with a high mortality. The underlying causes of shock such as haemorrhage, sepsis, or myocardial insufficiency should be corrected. The profound hypotension of shock must be treated promptly to prevent tissue hypoxia and organ failure. Volume replacement is essential to correct the hypovolaemia associated with haemorrhage and sepsis but may be detrimental in cardiogenic shock. Depending on haemodynamic status, cardiac output may be improved by the use of sympathomimetic inotropes such as adrenaline/epinephrine p. 211, dobutamine p. 210 or dopamine hydrochloride p. 177. In septic shock, when fluid replacement and inotropic support fail to maintain blood pressure, the vasoconstrictor noradrenaline/norepinephrine p. 178 may be considered. In cardiogenic shock peripheral resistance is frequently high and to raise it further may worsen myocardial performance and exacerbate tissue ischaemia.

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

See also advice on the management of anaphylactic shock in Antihistamines, allergen immunotherapy and allergic emergencies p. 259.

**Vasoconstrictor sympathomimetics**
Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors to...
constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed.

The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney.

Spinal and epidural anaesthesia may result in sympathetic block with resultant hypotension. Management may include intravenous fluids (which are usually given prophylactically), oxygen, elevation of the legs, and injection of a pressor drug such as ephedrine hydrochloride p. 254. As well as constricting peripheral vessels ephedrine hydrochloride also accelerates the heart rate (by acting on beta receptors). Use is made of this dual action of ephedrine hydrochloride to manage associated bradycardia (although intravenous injection of atropine sulfate p. 1179 may also be required if bradycardia persists).

**SYMPATHOMIMETICS**

### Dopamine hydrochloride

**DRUG ACTION** Dopamine is a cardiac stimulant which acts on beta receptors in cardiac muscle, and increases contractility with little effect on rate.

**INDICATIONS AND DOSE**

- **Cardiogenic shock in infarction or cardiac surgery**  
  - **BY INTRAVENOUS INFUSION**  
    - Adult: Initially 2–5 micrograms/kg/minute

**CONTRA-INDICATIONS** Phaeochromocytoma · tachyarrhythmia

**CAUTIONS** Correct hypovolaemia · hyperthyroidism · low dose in shock due to acute myocardial infarction

**INTERACTIONS**  
  - Appendix 1 (sympathomimetics).

**SIDE-EFFECTS**

- **Common or very common** Chest pain · dyspnoea · headache · hypotension · nausea · palpitation · tachycardia · vasoconstriction · vomiting
- **Uncommon** Bradycardia · gangrene · hypertension · mydriasis
- **Rare** Fatal ventricular arrhythmias

**PREGNANCY** No evidence of harm in animal studies—manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** May suppress lactation—not known to be harmful.

**DIRECTIONS FOR ADMINISTRATION** Dopamine concentrate for intravenous infusion to be diluted before use.

For **intravenous infusion** give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to max. concentration of 3.2 mg/mL; incompatible with bicarbonate.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

  **Solution for infusion**

  - **Dopamine hydrochloride (Non-proprietary)**
    - Dopamine hydrochloride 40 mg per 1 ml Dopamine 200mg/5ml solution for infusion ampoules | 5 ampoule | £19.42–£20.00 | 10 ampoule | £39.04
    - Dopamine 200mg/5ml concentrate for solution for infusion ampoules | 10 ampoule | no price available
    - Dopamine hydrochloride 160 mg per 1 ml Dopamine 800mg/5ml solution for infusion ampoules | 10 ampoule | £34.00

**SYMPATHOMIMETICS**

### Metaraminol

**INDICATIONS AND DOSE**

- **Acute hypotension**
  - **BY INTRAVENOUS INFUSION**
    - Adult: 15–100 mg, adjusted according to response

**Emergency treatment of acute hypotension**

- **INICALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 0.5–5 mg, then (by intravenous infusion) 15–100 mg, adjusted according to response

**CONTRA-INDICATIONS** Hypertension

**CAUTIONS** Cirrhosis · coronary vascular thrombosis · diabetes mellitus · elderly · extravasation at injection site may cause necrosis · following myocardial infarction · hypercapnia · hyperthyroidism · hypoxia · mesenteric vascular thrombosis · peripheral vascular thrombosis · Prinzmetal’s variant angina · uncorrected hypovolaemia

**CAUTIONS, FURTHER INFORMATION**

- Hypertensive response Metaraminol has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure.

**INTERACTIONS**  
  - Appendix 1 (sympathomimetics).

**SIDE-EFFECTS** Angle-closure glaucoma · anorexia · anxiety · arrhythmias · bradycardia · confusion · dyspnoea · fatal ventricular arrhythmia reported in Laennec’s cirrhosis · headache · hypertension · hypoxia · insomnia · nausea · palpitation · peripheral ischaemia · psychosis · tachycardia · tremor · urinary retention · vomiting · weakness

**PREGNANCY** May reduce placental perfusion—manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises caution—no information available.

**MONITORING REQUIREMENTS** Monitor blood pressure and rate of flow frequently.

**DIRECTIONS FOR ADMINISTRATION** For **intravenous infusion** (Aramine ®), give continuously or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Suggested volume 500 mL.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

  **Solution for injection**

  - **Metaraminol (Non-proprietary)**
    - Metaraminol (as Metaraminol tartrate) 10 mg per 1 ml Metaraminol 10mg/1ml solution for injection ampoules | 10 ampoule | £31.97

**Midodrine hydrochloride**

**DRUG ACTION** Midodrine hydrochloride is a pro-drug of desglymidodrine. Desglymidodrine is a sympathomimetic agent, which acts on peripheral alpha-adrenergic receptors to increase arterial resistance, resulting in an increase in blood pressure.

**INDICATIONS AND DOSE**

- **Severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate**
  - **BY MOUTH**
    - Adult: Initially 2.5 mg 3 times a day, increased if necessary up to 10 mg 3 times a day, dose to be increased at weekly intervals, according to blood pressure measurements; usual...
178  Blood pressure conditions

**Noradrenaline/norepinephrine**

- **INDICATIONS AND DOSE**
  - **Acute hypotension**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 0.16–0.33 mL/minute, adjusted according to response, to be given via central venous catheter, of a solution containing noradrenaline 40 micrograms(base)/mL.

- **DOSE EQUIVALENCE AND CONVERSION**
  - 1 mg of noradrenaline base is equivalent to 2 mg of noradrenaline acid tartrate. **Doses expressed as the base.**

- **CONTRA-INDICATIONS**
  - Hypertension
  - **CAUTIONS**
    - Coronary vascular thrombosis - diabetes mellitus - elderly - extravasation at injection site may cause necrosis - following myocardial infarction - hypercapnia - hyperthyroidism - hypoxia - mesenteric vascular thrombosis - peripheral vascular thrombosis - Prinzmetal's variant angina - uncorrected hypovolaemia

- **INTERACTIONS**
  - Appendix 1 (sympathomimetics).

- **SIDE-EFFECTS**
  - Rare
  - Common or very common

- **Further Information**
  - Systolic hypertension.
  - Noradrenaline/norepinephrine.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion.

### Solution for infusion

- Noradrenaline/norepinephrine (Non-proprietary)
  - Noradrenaline (as Noradrenaline acid tartrate) 1 mg per 1 mL Noradrenaline (Norepinephrine) 4mg/4mL concentrate for solution for infusion ampoules | 10 ampoule (POM) £44.00
  - Noradrenaline (base) 8mg/8mL concentrate for solution for infusion ampoules | 10 ampoule (PBS) £116.00
  - Noradrenaline (base) 2mg/2mL solution for infusion ampoules | 5 ampoule (POM) £12.00 (Hospital only)
  - Noradrenaline (base) 4mg/4mL solution for infusion ampoules | 5 ampoule (POM) £22.00 (Hospital only)
  - Noradrenaline (base) 4mg/4mL concentrate for solution for infusion ampoules | 10 ampoule (POM) £58.00
  - Noradrenaline (Norepinephrine) 2mg/2mL concentrate for solution for infusion ampoules | 5 ampoule (POM) £11.00

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion.

| Tablet | Noradrenaline hydrochloride 2.5 mg | Bramox 2.5mg tablets | 100 tablet (POM) | £5.05 DT price + £5.05
| Tablet | Noradrenaline hydrochloride 5 mg | Bramox 5mg tablets | 100 tablet (POM) | £7.05 DT price + £7.05

### CAUTIONS

Atherosclerotic cardiovascular disease (especially with symptoms of intestinal angina or claudication of the legs) - autonomic dysfunction - elderly (manufacturer recommends cautious dose titration) - prostate disorders

### INTERACTIONS

- Appendix 1 (sympathomimetics).

### SIDE-EFFECTS

- Rare
- Common or very common

### Further Information

- Systolic hypertension
- Noradrenaline/norepinephrine

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion.
Phenylephrine hydrochloride

**INDICATIONS AND DOSE**

**Acute hypotension**

- By subcutaneous injection, or by intramuscular injection
  - Adult: Initially 2–5 mg, followed by 1–10 mg, after at least 15 minutes if required
  - By slow intravenous injection
  - Adult: 100–500 micrograms, repeated as necessary after at least 15 minutes
  - By intravenous infusion
  - Adult: Initially up to 180 micrograms/minute, reduced to 30–60 micrograms/minute, adjusted according to response

**CONTRA-INDICATIONS**  Hypertension  •  severe hyperthyroidism

**CAUTIONS**  Coronary disease  •  coronary vascular thrombosis  •  diabetes  •  elderly  •  extravasation at injection site may cause necrosis  •  following myocardial infarction  •  hypercapnia  •  hyperthyroidism  •  hypoxia  •  mesenteric vascular thrombosis  •  peripheral vascular thrombosis  •  Prinzmetal’s variant angina  •  susceptibility to angle-closure glaucoma  •  uncorrected hypovolaemia

**INTERACTIONS**  → Appendix 1 (sympathomimetics). Phenylephrine may interact with systemically administered monoamine-oxidase inhibitors.

**SIDE-EFFECTS**  Angle-closure glaucoma  •  anorexia  •  anxiety  •  arrhythmias  •  bradycardia (also reflex bradycardia)  •  confusion  •  dyspnoea  •  headache  •  hypertension  •  hypoxia  •  insomnia  •  nausea  •  palpitation  •  peripheral ischaemia  •  psychosis  •  tachycardia  •  tremor  •  urinary retention  •  vomiting  •  weakness

**PREGNANCY**  Avoid if possible; malformations reported following use in first trimester; fetal hypoxia and bradycardia reported in late pregnancy and labour.

**MONITORING REQUIREMENTS**

Contra-indicated in hypertension—monitor blood pressure and rate of flow frequently.

**DIRECTIONS FOR ADMINISTRATION**  For intravenous infusion give intermittently in Glucose 5% or Sodium chloride 0.9%. Dilute 10 mg in 500 mL infusion fluid.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- Phenylephrine hydrochloride (Non-proprietary)
  - Phenylephrine hydrochloride (as Phenylephrine hydrochloride) 50 microgram per 1 ml
  - Phenylephrine 500 micrograms/10ml solution for injection pre-filled syringes  | 1 pre-filled disposable injection [P] £15.00  | 10 pre-filled disposable injection [P] £150.00
  - Phenylephrine hydrochloride 100 microgram per 1 ml
  - Phenylephrine 1mg/10ml solution for injection ampoules  | 10 ampoule [P] £40.00
  - Phenylephrine hydrochloride 10 mg per 1 ml
  - Phenylephrine 10mg/1ml solution for injection ampoules  | 10 ampoule [P] £99.12

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**5 Heart failure**

**Heart failure**

**Drugs treatment**

Drug treatment of heart failure associated with a reduced left ventricular ejection fraction (left ventricular systolic dysfunction) is covered below; optimal management of heart failure with a preserved left ventricular ejection fraction has not been established.

The treatment of chronic heart failure aims to relieve symptoms, improve exercise tolerance, reduce the incidence of acute exacerbations, and reduce mortality. An ACE inhibitor, titrated to a ‘target dose’ (or the maximum tolerated dose if lower), together with a beta-blocker, form the basis of treatment for all patients with heart failure due to left ventricular systolic dysfunction.

An ACE inhibitor is generally advised for patients with asymptomatic left ventricular systolic dysfunction or symptomatic heart failure. An angiotensin-II receptor antagonist may be a useful alternative for patients who, because of side-effects such as cough, cannot tolerate ACE inhibitors; a relatively high dose of the angiotensin-II receptor antagonist may be required to produce benefit. Candesartan cilexetil p. 166 or valsartan p. 170 may be given under specialist supervision as adjuncts to an ACE inhibitor in the treatment of heart failure when other treatments are unsuitable; the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparking diuretic is not recommended. The combination of valsartan with sacubitril p. 181, an angiotensin-II receptor antagonist with a neprilysin inhibitor, may be a suitable alternative for those patients already stabilised on an ACE inhibitor or angiotensin-II receptor antagonist.

The beta-blockers bisoprolol fumarate p. 144 and carvedilol p. 139 are of value in any grade of stable heart failure due to left ventricular systolic dysfunction; nebivolol p. 146 is licensed for stable mild to moderate heart failure in patients over 70 years. Beta-blocker treatment should be started by those experienced in the management of heart failure, at a very low dose and titrated very slowly over a period of weeks or months. Symptoms may deteriorate initially, calling for adjustment of concomitant therapy.

The aldosterone antagonist spironolactone p. 180 can be added to an ACE inhibitor and a beta-blocker in patients who continue to remain symptomatic (particularly in those with moderate to severe heart failure); low doses of spironolactone reduce symptoms and mortality in these patients. If spironolactone cannot be used, eplerenone p. 180 may be considered for the management of heart failure after an acute myocardial infarction with evidence of left ventricular systolic dysfunction, or for chronic mild heart failure with left ventricular systolic dysfunction. Close monitoring of serum creatinine, eGFR, and potassium is necessary, particularly following any change in treatment or any change in the patient’s clinical condition.

Patients who cannot tolerate an ACE inhibitor or an angiotensin-II receptor antagonist, or in whom they are contra-indicated, may be given isosorbide dinitrate p. 208 with hydralazine hydrochloride p. 171 but this combination may be poorly tolerated. The combination of isosorbide dinitrate and hydralazine hydrochloride may be considered in addition to standard therapy with an ACE inhibitor and a beta-blocker in patients who continue to remain symptomatic (particularly in patients of African or Caribbean origin who have moderate to severe heart failure).

Digoxin p. 103 improves symptoms of heart failure and exercise tolerance and reduces hospitalisation due to acute exacerbations but it does not reduce mortality. Digoxin is reserved for patients with worsening or severe heart failure.
due to left ventricular systolic dysfunction who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker in combination with either an aldosterone antagonist, candesartan cilexetil, or isosorbide dinitrate with hydralazine and hydrochloride.

Patients with fluid overload should also receive either a loop or a thiazide diuretic (with salt or fluid restriction where appropriate). A thiazide diuretic may be of benefit in patients with mild heart failure and good renal function; however, thiazide diuretics are ineffective in patients with poor renal function (eGFR less than 30 mL/minute/1.73 m²) and a loop diuretic is preferred. If diuresis with a single diuretic is insufficient, a combination of a loop diuretic and a thiazide diuretic may be tried; addition of metolazone p. 220 may also be considered but the resulting diuresis may be profound and care is needed to avoid potentially dangerous electrolyte disturbances.

### Other drugs used for Heart failure


### DIURETICS > POTASSIUM-SPARING DIURETICS > ALDOSTERONE ANTAGONISTS

#### Co-flumacnptone

The properties listed below are those particular to the combination only. For the properties of the components please consider, spironolactone below.

- **INDICATIONS AND DOSE**
  - **Congestive heart failure**
    - **Adult:** Initially 100/100 mg daily; maintenance 25/25–200/200 mg daily, maintenance dose not recommended because spironolactone generally given in lower dose

- **LESS SUITABLE FOR PRESCRIBING**
  - Co-flumacnptone tablets are less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **Eplerenone (Non-proprietary)**
    - Eplerenone 25 mg Eplerenone 25 mg tablets | 28 tablet POM £42.72 DT price = £6.06
    - Eplerenone 50 mg Eplerenone 50 mg tablets | 28 tablet POM £42.72 DT price = £7.21
    - **Inspra (Pfizer Ltd)**
      - Eplerenone 25 mg Inspra 25 mg tablets | 28 tablet POM £42.72 DT price = £6.06
      - Eplerenone 50 mg Inspra 50 mg tablets | 28 tablet POM £42.72 DT price = £7.21

#### Eplerenone

- **INDICATIONS AND DOSE**
  - Adjunct in stable patients with left ventricular ejection fraction <40% with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event) | Adjunct in chronic mild heart failure with left ventricular ejection fraction <30%
  - **BY MOUTH**
    - Adult: Initially 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment

- **CONTRA-INDICATIONS**
  - Hyperkalaemia

- **CAUTIONS**
  - Elderly

- **INTERACTIONS**
  - Common or very common: Azolectin, constipation, cough, diarrhoea, dizziness, hyperkalaemia, hypotension, muscle spasm, musculoskeletal pain, nausea, pruritus, rash, renal impairment, syncope

  **SIDE-EFFECTS**
  - Common: Arterial thrombosis, atrial fibrillation, back pain, cholecytitis, dehydration, dyslipidaemia, eosinophilia, epidermal growth factor receptor decreased, flatulence, gynaecomastia, headache, hyperglycaemia, hypoaesthesia, hyponatraemia, hypothyroidism, insomnia, malaise, pharyngitis, postural hypotension, pyelonephritis, sweating, tachycardia, vomiting

  **Frequency not known**
  - Angioedema

- **PREGNANCY**
  - Manufacturer advises caution—no information available.

- **BREAST FEEDING**
  - Manufacturer advises use only if potential benefit outweighs risk.

- **HEPATIC IMPAIRMENT**
  - Avoid in severe impairment.

- **RENAL IMPAIRMENT**
  - Initially 25 mg on alternate days if eGFR 30–60 mL/minute/1.73 m², adjust dose according to serum-potassium concentration—consult product literature. Avoid if eGFR less than 30 mL/minute/1.73 m². Increased risk of hyperkalaemia in renal impairment—close monitoring required.

- **MONITORING REQUIREMENTS**
  - Monitor plasma-potassium concentration before treatment, during initiation, and when dose changed.

#### Spironolactone

- **INDICATIONS AND DOSE**
  - **Oedema | Ascites in cirrhosis of the liver**
    - **BY MOUTH**
      - Adult: 100–400 mg daily, adjusted according to response

  - **Malignant ascites**
    - **BY MOUTH**
      - Adult: Initially 100–200 mg daily, then increased if necessary to 400 mg daily, maintenance dose adjusted according to response

  - **Nephrotic syndrome**
    - **BY MOUTH**
      - Adult: 100–200 mg daily

  - **Oedema in congestive heart failure**
    - **BY MOUTH**
      - Adult: Initially 100 mg daily, alternatively initially 25–200 mg daily, dose may be taken as a single dose or divided doses, maintenance dose adjusted according to response
Moderate to severe heart failure (adjunct)

- **BY MOUTH**
- **Adult:** Initially 25 mg once daily, then adjusted according to response to 50 mg once daily

Resistant hypertension (adjunct)

- **BY MOUTH**
- **Adult:** 25 mg once daily

Primary hyperaldosteronism in patients awaiting surgery

- **BY MOUTH**
- **Adult:** 100–400 mg daily, may be used for long-term maintenance if surgery inappropriate, use lowest effective dose

- **UNLICENSED USE** Resistant hypertension (adjunct) unlicensed indication.
- **CONTRA-INDICATIONS** Addison’s disease · anuria · hyperkalaemia
- **CAUTIONS** Acute porphyrias p. 930 · elderly · potential metabolic products carcinogenic in rodents
- **INTERACTIONS** → Appendix 1 (diuretics).

Potassium supplements must not be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

- **SIDE-EFFECTS** Acute renal failure · agranulocytosis · alopecia · benign breast tumour · breast pain · changes in libido · confusion · dizziness · drowsiness · electrolyte disturbances · gastro-intestinal disturbances · gynaecomastia · hepatotoxicity · hyperkalaemia (discontinue) · hypertrichosis · hyperuricaemia · hyponatraemia · leg cramps · leucopenia · malaise · menstrual disturbances · rash · Stevens-Johnson syndrome · thrombocytopenia

- **PREGNANCY** Use only if potential benefit outweighs risk—feminisation of male fetus in animal studies.
- **BREAST FEEDING** Metabolites present in milk, but amount probably too small to be harmful.
- **RENAL IMPAIRMENT** Avoid in acute renal insufficiency or severe impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).
- **MONITORING REQUIREMENTS** Monitor electrolytes—discontinue if hyperkalaemia occurs (in severe heart failure monitor potassium and creatinine 1 week after initiation and after any dose increase, monthly for first 3 months, then every 3 months for 1 year, and then every 6 months).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Table

| Tablet | CAUTIONARY AND ADVISORY LABELS | Spironolactone (Non-proprietary) | Spironolactone 25 mg Spironolactone 25mg tablets | 28 tablet | £1.95 DT price = £1.26 | Spironolactone 50 mg Spironolactone 50mg tablets | 28 tablet | £4.99 DT price = £1.79 | Spironolactone 100 mg Spironolactone 100mg tablets | 28 tablet | £6.24 DT price = £2.16 | 30 tablet | £7.78 | Aldactone (Pfizer Ltd) | Aldactone 25 mg Aldactone 25mg tablets | 100 tablet | £8.89 | Aldactone 50 mg Aldactone 50mg tablets | 100 tablet | £17.78 | Aldactone 100 mg Aldactone 100mg tablets | 28 tablet | £9.96 DT price = £2.16 | 100 tablet | £35.56 |

### DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

- **ANGIOTENSIN II RECEPTOR ANTAGONISTS**

#### Valsartan with sacubitril

The properties listed below are those particular to the combination only. For the properties of the components please consider, valsartan p. 170.

- **DRUG ACTION** Sacubitril (a prodrug) inhibits the breakdown of natriuretic peptides resulting in varied effects including increased diuresis, natriuresis, and vasodilatation.

- **INDICATIONS AND DOSE**

Symptomatic chronic heart failure with reduced ejection fraction (in patients not currently taking an ACE inhibitor or angiotensin II receptor antagonist, or stabilised on low doses of either of these agents)

- **BY MOUTH**
- **Adult:** Initially 26/24 mg twice daily for 3–4 weeks, increased if tolerated to 51/49 mg twice daily for 3–4 weeks, then increased if tolerated to 103/97 mg twice daily

**Symptomatic chronic heart failure with reduced ejection fraction (in patients currently stabilised on an ACE inhibitor or angiotensin II receptor antagonist)**

- **BY MOUTH**
- **Adult:** Initially 51/49 mg twice daily for 2–4 weeks, increased if tolerated to 103/97 mg twice daily, consider a starting dose of 26/24 mg if systolic blood pressure less than 110 mmHg

**DOSE EQUIVALENCE AND CONVERSION**

Entresto® tablets contain valsartan and sacubitril; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of valsartan and sacubitril respectively. Valsartan, in this formulation, is more bioavailable than other tablet formulations—26 mg, 51 mg, and 103 mg valsartan is equivalent to 40 mg, 80 mg and 160 mg, respectively. Furthermore, note that the 26/24 mg, 51/49 mg and 103/97 mg strengths are sometimes referred to as a total of both drug strengths, that is, 50 mg, 100 mg and 200 mg, respectively.

- **CONTRA-INDICATIONS** Concomitant use of ACE inhibitor (separate administration by 36 hours) · systolic blood pressure less than 100 mmHg
- **INTERACTIONS** → Appendix 1 (angiotensin-II receptor antagonists, sacubitril)
- **SIDE-EFFECTS**

- **Common or very common** Anaemia · diarrhoea · gastritis · hypoglycaemia · hypokalaemia · nausea · vertigo
- **PREGNANCY** Manufacturer advises avoid—toxicity with sacubitril in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises starting dose of 26/24 mg twice daily in moderate impairment. Contra-indicated in severe impairment.
- **RENAI IMPAIRMENT** Manufacturer recommends a starting dose of 26/24 mg twice daily if eGFR less than 30 mL/minute/1.73m². Also consider this starting dose if eGFR 30 to 60 mL/minute/1.73m².
● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (April 2016) NICE TA388

Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in adults:

- with New York Heart Association class II to IV symptoms
- a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of an ACE inhibitor or angiotensin II receptor antagonist.

www.nice.org.uk/ta388

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Entresto (Novartis Pharmaceuticals UK Ltd)
- Sacubitril 24 mg, Valsartan 26 mg Entresto 24mg/26mg tablets | 28 tablet £45.78 DT price = £45.78
- Sacubitril 49 mg, Valsartan 51 mg Entresto 49mg/51mg tablets | 28 tablet £45.78 | 56 tablet £91.56 DT price = £91.56
- Sacubitril 97 mg, Valsartan 103 mg Entresto 97mg/103mg tablets | 56 tablet £91.56 DT price = £91.56

PHOSPHODIESTERASE TYPE-3 INHIBITORS

Enoximone

● DRUG ACTION

Enoximone is a phosphodiesterase type-3 inhibitor that exerts most effect on the myocardium; it has positive inotropic properties and vasodilator activity.

● INDICATIONS AND DOSE

Congestive heart failure where cardiac output reduced and filling pressures increased

- BY SLOW INTRAVENOUS INJECTION
  - Adult: Initially 0.5–1 mg/kg, rate not exceeding 12.5 mg/minute, then 500 micrograms/kg every 30 minutes until satisfactory response or total of 3 mg/kg given; maintenance, initial dose of up to 3 mg/kg may be repeated every 3–6 hours as required
- BY INTRAVENOUS INFUSION
  - Adult: Initially 90 micrograms/kg/minute, dose to be given over 10–30 minutes, followed by 5–20 micrograms/kg/minute, dose to be given as either a continuous or intermittent infusion; maximum 24 mg/kg per day

● CAUTIONS

Heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction

● INTERACTIONS → Appendix 1 (phosphodiesterase type-3 inhibitors).

● SIDE-EFFECTS

Chills · diarrhoea · ectopic beats · fever · headache · hypotension · insomnina · nausea · oliguria · supraventricular arrhythmias (more likely in patients with pre-existing arrhythmias) · upper and lower limb pain · urinary retention · ventricular tachycardia (more likely in patients with pre-existing arrhythmias) · vomiting

● PREGNANCY

Manufacturer advises use only if potential benefit outweighs risk.

● BREAST FEEDING

Manufacturer advises caution—no information available.

● HEPATIC IMPAIRMENT

Dose reduction may be required.

● RENAL IMPAIRMENT

Consider dose reduction.

● MONITORING REQUIREMENTS

Monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count and hepatic enzymes.

Milrinone

● DRUG ACTION

Milrinone is a phosphodiesterase type-3 inhibitor that exerts most effect on the myocardium; it has positive inotropic properties and vasodilator activity.

● INDICATIONS AND DOSE

Short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy (not immediately after myocardial infarction) Acute heart failure, including low output states following heart surgery

- INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 50 micrograms/kg, given over 10 minutes, followed by (by intravenous infusion) 375–750 nanograms/kg/minute usually given following surgery for up to 12 hours or in congestive heart failure for 48–72 hours; maximum 1.13 mg/kg per day

● CONTRA-INDICATIONS

Severe hypovolaemia

● CAUTIONS

Correct hypokalaemia · heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction

● INTERACTIONS → Appendix 1 (phosphodiesterase type-3 inhibitors).

● SIDE-EFFECTS

Common or very common · Ectopic beats · headache · hypotension · supraventricular arrhythmias (more likely in patients with pre-existing arrhythmias) · ventricular tachycardia

- Uncommon
  - Chest pain · hypokalaemia · thrombocytopenia · tremor · ventricular fibrillation
  - Very rare
    - Anaphylaxis · bronchospasm · rash

● PREGNANCY

Manufacturer advises use only if potential benefit outweighs risk.

● BREAST FEEDING

Manufacturer advises avoid—no information available.

● RENAL IMPAIRMENT

Reduce dose and monitor response if eGFR less than 50 mL/minute/1.73 m²—consult product literature for details.

● MONITORING REQUIREMENTS

Monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count and hepatic enzymes.

● DIRECTIONS FOR ADMINISTRATION

Avoid extravasation.

For intravenous injection, may be given either undiluted or diluted before use.

For intravenous infusion (Primacor®) give continuously in Glucose 5% or Sodium chloride 0.9%; dilute to a suggested concentration of 200 micrograms/mL.
6 Hyperlipidaemia

Lipid-regulating drugs

Primary and secondary prevention of cardiovascular disease

Preventative measures should be taken in individuals with a high risk of developing cardiovascular disease (primary prevention) and to prevent recurrence of events in those with established cardiovascular disease (secondary prevention).

Primary prevention

Individuals at high risk of developing cardiovascular disease include those who have diabetes mellitus, chronic kidney disease (eGFR < 60 mL/minute/1.73 m²) and/or albuminuria, and those with familial hypercholesterolaemia. The risk also increases with age; those aged 85 years and over are at particularly high risk, especially if they smoke or have hypertension. Preventative measures are also required for other individuals who are considered to be at high risk of developing atherothrombotic cardiovascular disease based on risk estimated using risk calculators (see Risk calculators); those with a 10-year risk of cardiovascular disease of 10% or more should benefit most from drug treatment. Patients with a 10-year cardiovascular risk of less than 10% may benefit from an assessment of their lifetime risk (using the JBS3 tool—see Risk calculators for more detail), discussion on the impact of lifestyle interventions and, if necessary, drug therapy.

Risk calculators

Risk assessment calculators are recommended by both NICE (clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease) and JBS3 (Joint British Societies’ consensus recommendations for the prevention of cardiovascular disease 2014). They should not be used in patients at high cardiovascular risk. Both calculators are unevaluated for assessing risk in those aged 85 years and over, and NICE advises against using a risk assessment tool in those with type 1 diabetes mellitus.

The QRISK® 2 risk calculator www.qrisk.org/ is recommended by NICE clinical guideline 181, and the JBS3 risk calculator www.jbs3risk.com/pages/risk_calculator.htm is endorsed by JBS3. Both tools assess cardiovascular risk—coronary heart disease (angina and myocardial infarction), stroke, and transient ischaemic attack, on the basis of lipid profile, systolic blood pressure, gender, age, ethnicity, smoking status, BMI, chronic kidney disease, diabetes mellitus, atrial fibrillation, treated hypertension, rheumatoid arthritis, or a family history of premature cardiovascular disease. Risk assessment tools underestimate risk in patients with additional risk due to existing conditions or medication, such as:

- serious mental disorder
- autoimmune disorders such as systemic lupus erythematosus and other systemic inflammatory disorders
- antiretroviral treatment
- medication causing dyslipidaemia as a side-effect e.g. antipsychotics, corticosteroids, or immunosuppressants
- triglyceride concentration > 4.5 mmol/litre

Cardiovascular disease risk is also underestimated in those who are already taking antihypertensive or lipid-regulating drugs, and in those who have recently stopped smoking.

Severe obesity (BMI > 40 kg/m²) also increases cardiovascular risk; the need for further treatment of risk...
Cardiovascular system

factors in patients below the cardiovascular risk threshold for treatment should be based on clinical judgement.

**Preventative measures for primary prevention**

All patients at high risk of cardiovascular disease should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation.

Offer a statin as first-line drug treatment if lifestyle modifications are inappropriate or ineffective (see also Statins for the prevention of cardiovascular disease). Lipid-regulating drug treatment must be combined with advice on diet and lifestyle measures, and where appropriate, treatment of comorbidities and secondary causes of dyslipidaemia.

**Secondary prevention**

Statins should be offered to all patients, including the elderly, with cardiovascular disease such as those with coronary heart disease (including history of angina or acute myocardial infarction), occlusive arterial disease (including peripheral vascular disease, non- haemorrhagic stroke, or transient ischaemic attacks).

**Preventative measures for secondary prevention**

Patients should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation, however, initiation of lipid-regulating drug treatment should not be delayed to manage modifiable risk factors, and must be combined with advice on diet and lifestyle measures, and where appropriate, treatment of co-morbidities and secondary causes of dyslipidaemia.

**Statins for the prevention of cardiovascular disease**

A statin reduces the risk of cardiovascular disease events, and is the drug of first choice for primary and secondary prevention of cardiovascular disease. Before starting treatment with statins, secondary causes of dyslipidaemia should be addressed; these include uncontrolled diabetes mellitus, hepatic disease, nephrotic syndrome, and excessive alcohol consumption. Patients with hypothyroidism should receive adequate thyroid replacement therapy (before assessing the requirement for lipid-regulating treatment if for primary prevention) because correcting hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.

For the purpose of reducing cardiovascular risk, NICE Clinical Guideline 181 (NICE clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease) defines statins by the percentage reduction in LDL-cholesterol they achieve:

For **primary prevention**, NICE Clinical Guideline 181 recommends that atorvastatin p. 191 a high-intensity statin (when prescribed at a dose of at least 20 mg/day), should be offered to those with a 10-year risk of cardiovascular disease of 10% or more; patients aged 85 years and over may benefit from atorvastatin to reduce the risk of non-fatal myocardial infarction. For **secondary prevention**, atorvastatin is also recommended. Patients taking a low- or medium-intensity statin should discuss the benefits and risks of switching to a high-intensity statin at their next medication review.

A statin should be considered for all adults with type 1 diabetes mellitus, particularly those aged 40 years and over, or who have had diabetes for more than 10 years, or who have established nephropathy, or other risk factors for cardiovascular disease. JBS3 recommendations (Joint British Societies’ consensus recommendations for the prevention of cardiovascular disease (JBS3) 2014) in diabetes mellitus differ in certain respects from NICE Clinical Guideline 181 (NICE clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease)—see JBS3 recommendations for further details. In type 2 diabetes, assess level of risk using the risk calculator and treat for primary prevention if necessary.

Total cholesterol, HDL-cholesterol, and non-HDL cholesterol concentrations should be checked 3 months after starting treatment with a high intensity statin. NICE Clinical Guideline 181 recommends aiming for a reduction in non-HDL cholesterol concentration greater than 40%; JBS3 recommends a target non-HDL cholesterol concentration below 2.5 mol/litre. If these are not achieved, ensure lifestyle modifications are optimised and consider increasing the dose of the statin if started on less than atorvastatin 80 mg and the patient is judged to be at higher risk because of comorbidities, risk score or, using clinical judgement.

**Fibrates** should not be routinely used for primary or secondary prevention. Nicotinic acid p. 190, bile acid sequestrants, and omega-3 fatty acid compounds are not recommended for primary or secondary prevention.

**Hypercholesterolaemia, hypertriglyceridaemia, and familial hypercholesterolaemia**

A statin is also the drug of first choice for treating hypercholesterolaemia and moderate hypertriglyceridaemia. Severe hyperlipidaemia not adequately controlled with a maximal dose of a statin may require the use of an additional lipid-regulating drug such as ezetimibe p. 187; such treatment should generally be supervised by a specialist.

A number of conditions, some familial, are characterised by very high LDL-cholesterol concentration, high triglyceride concentration, or both. Fenofibrate p. 188 may be added to statin therapy if triglycerides remain high even after the LDL-cholesterol concentration has been reduced adequately; nicotinic acid may also be used to further lower triglyceride or LDL-cholesterol concentration.

Combination of a statin with a fibrate or with nicotinic acid carries an increased risk of side-effects (including rhabdomyolysis) and should be used under specialist supervision; monitoring of liver function and creatine kinase should also be considered. The concomitant administration of gemfibrozil with a statin increases the risk of rhabdomyolysis considerably—this combination should not be used.

A statin is recommended for all patients with familial hypercholesterolaemia. A ‘high-intensity’ statin (as defined in NICE Clinical Guideline 71, August 2008. Identification and management of familial hypercholesterolaemia) e.g. rosuvastatin p. 193 (initiated by a specialist) or atorvastatin p. 191 should be considered in order to achieve the recommended reduction in LDL-cholesterol concentration of greater than 50% from baseline; a ‘high-intensity’ statin is one that produces a greater LDL-cholesterol reduction than simvastatin 40 mg. Patients with heterozygous familial hypercholesterolaemia who have contra-indications to, or are intolerant of, statins should receive ezetimibe. The combination of a statin and ezetimibe can be considered if a statin alone fails to provide adequate control (or if intolerance limits dose titration), and when a switch to an alternative statin is being considered. Patients for whom statins and ezetimibe are inappropriate, should be referred to a specialist for the consideration of treatment with a bile acid sequestrant, nicotinic acid, or a fibrate.
The prescribing of drug therapy in homozygous familial hypercholesterolaemia should be undertaken in a specialist centre.

### Reduction in low-density lipoprotein cholesterol

<table>
<thead>
<tr>
<th>Therapy intensity</th>
<th>Drug</th>
<th>Daily dose (reduction in LDL cholesterol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-intensity</td>
<td>Atorvastatin</td>
<td>20mg (43%) 40mg (49%) 80mg (55%)</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
<td>10mg (43%) 20mg (48%) 40mg (53%)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>80mg (42%)</td>
</tr>
<tr>
<td>Medium-intensity</td>
<td>Atorvastatin</td>
<td>10mg (37%)</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
<td>80mg (33%)</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
<td>5mg (38%)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>20mg (32%) 40mg (37%)</td>
</tr>
<tr>
<td>Low-intensity</td>
<td>Fluvastatin</td>
<td>20mg (21%) 40mg (27%)</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>10mg (20%) 20mg (24%) 40mg (29%)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>10mg (27%)</td>
</tr>
</tbody>
</table>

Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

### Statins

Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration.

**Alirocumab**

Alirocumab p. 195 is licensed for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to dietary measures. It can be used in combination with a statin, or with a statin and other lipid-regulating drugs, in patients unable to achieve their LDL-cholesterol treatment goals with the maximum tolerated dose of a statin. It can also be used alone or in combination with other lipid-regulating drugs if a statin is contra-indicated or not tolerated.

**Bile acid sequestrants**

Bile acid sequestrants effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia. Treatment with bile acid sequestrants may be appropriate under specialist supervision if statins and ezetimibe are inappropriate, and when LDL-cholesterol is severely raised, for example in familial hypercholesterolaemia.

**Fibrates**

Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mol/litre or in those who cannot tolerate a statin (specialist use).

**Lomitapide**

Lomitapide p. 195 is licensed as an adjunct to dietary measures and other lipid-regulating drugs for the treatment of homozygous familial hypercholesterolaemia.

### Nicotinic acid group

The value of nicotinic acid is limited by its side-effects, especially vasodilatation.

Nicotinic acid is used by specialists in combination with a statin if the statin alone cannot adequately control dyslipidaemia (raised LDL-cholesterol, triglyceridaemia, and low HDL-cholesterol).

Acipimox p. 190 seems to have fewer side-effects than nicotinic acid but may be less effective in its lipid-regulating capabilities.

### Omega-3 fatty acid compounds

There is no evidence that omega-3 fatty acid compounds reduce the risk of cardiovascular disease.

### Other drugs used for Hyperlipidaemia

- **Inositol nicotinate**, p. 221

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**Bile acid sequestrants**

- **DRUG ACTION** Bile acid sequestrants act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma.

- **CAUTIONS** Interference with the absorption of fat-soluble vitamins (supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged).

- **SIDE-EFFECTS** Constipation - diarrhoea - gastro-intestinal discomfort - hypertriglyceridaemia (aggravation) - hypoprothrombinaemia associated with vitamin K deficiency - increased risk of bleeding - nausea - vomiting

- **PREGNANCY** Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

- **BREAST FEEDING** Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

**Coleselam hydrochloride**

- **INDICATIONS AND DOSE**
  - **Primary hypercholesterolaemia as an adjunct to dietary measures (monotherapy)**
    - **BY MOUTH**
    - Adult: 3.75 g daily in 1–2 divided doses; maximum 4.375 g per day
  - **Primary hypercholesterolaemia as an adjunct to dietary measures, in combination with a statin**
  - **Primary and familial hypercholesterolaemia, in combination with ezetimibe, either with or without a statin**
    - **BY MOUTH**
    - Adult: 2.5–3.75 g daily in 1–2 divided doses, may be taken at the same time as the statin and ezetimibe

- **CONTRA-INDICATIONS** Biliary obstruction - bowel obstruction

- **CAUTIONS** Gastro-intestinal motility disorders - inflammatory bowel disease - major gastro-intestinal surgery

- **INTERACTIONS** Appendix 1 (colesenlam).

- **SIDE-EFFECTS** Headache - myalgia

- **HEPATIC IMPAIRMENT** Manufacturer advises caution.
Colestyramine hydrochloride

**INDICATIONS AND DOSE**

Hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures

- **BY MOUTH**
  - Adult: Initially 4 g daily, increased in steps of 4 g every week; increased to 12–24 g daily in 1–4 divided doses, adjusted according to response; maximum 36 g per day

Pruritus associated with partial biliary obstruction and primary biliary cirrhosis

- **BY MOUTH**
  - Adult: 4–8 g once daily

Diarrhoea associated with Crohn’s disease, ileal resection, vagotomy, diabetic vagal neuropathy, and radiation

- **BY MOUTH**
  - Adult: 8 g 3 times a day for 11 days; reduced to 4 g 3 times a day, dose should only be reduced if not tolerated

Accelerated elimination of teriflunomide

- **BY MOUTH**
  - Adult: 8 g 3 times a day for 11 days

**SIDE-EFFECTS**

- Rare: Intestinal obstruction
- Frequency not known: Hyperchloraemic acidosis (on prolonged use)

**DIRECTIONS FOR ADMINISTRATION**

The contents of each sachet should be mixed with at least 100 mL of water or other suitable liquid such as fruit juice, skimmed milk; alternatively it can be mixed with thin soups, cereals, yoghurt, or pulpy fruits ensuring at least 100 mL of liquid is provided.

Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption.

**PATIENT AND CARER ADVICE**

Patient counselling on administration is advised for colestyramine powder (avoid other drugs at same time).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Colestipol hydrochloride (Non-proprietary)
    - Colestipol hydrochloride 1 gram
      - Colestit 1g tablets | 120 tablet [POM] no price available
  - Granules
    - Colestipol hydrochloride 5 gram
      - Colestit 5g granules sachets plain sugar-free | 30 sachet [POM] £15.05
      - Colestit Orange 5g granules sachets sugar-free | 30 sachet [POM] £15.05

- **Powder**
  - Colestipol hydrochloride (Non-proprietary)
    - Colestipol hydrochloride anhydrous 4 gram
      - Colestipol 4g oral powder sachets | 50 sachet [POM] no price available
    - Colestipol hydrochloride 4g oral powder sachets sugar free sugar-free | 50 sachet [POM] £24.46–£30.00 DT price + £2.61
    - Questran (Bristol-Myers Squibb Pharmaceuticals Ltd)
      - Colestipol anhydrous 4 gram
        - Questran 4g oral powder sachets | 50 sachet [POM] £10.76

**CONTRA-INDICATIONS**

Complete biliary obstruction (not likely to be effective)

**INTERACTIONS**

- Appendix 1 (colestipol)
- Appendix 1 (colestyramine)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
LIPID MODIFYING DRUGS > CHOLESTEROL ABSORPTION INHIBITORS

**Ezetimibe**

**DRUG ACTION** Ezetimibe inhibits the intestinal absorption of cholesterol. If used alone, it has a modest effect on lowering LDL-cholesterol, with little effect on other lipoproteins.

**INDICATIONS AND DOSE**
Adjust to dietary measures and statin treatment in primary hypercholesterolaemia > Adjunct to dietary measures and statin in homozygous familial hypercholesterolaemia > Primary hypercholesterolaemia (if statin inappropriate or not tolerated) > Adjunct to dietary measures in homozygous sitosterolaemia

**BY MOUTH**
Adult: 10 mg daily

**INTERACTIONS** > Appendix 1 (ezetimibe).
There is an increased risk of rhabdomyolysis if ezetimibe is used in combination with a statin.

**SIDE-EFFECTS**
- **Common or very common** Fatigue - gastro-intestinal disturbances - headache - myalgia
- **Rare** Anaphylaxis - angioedema - arthralgia - hepatitis - hypersensitivity reactions - rash
- **Very rare** Cholecystitis - cholelithiasis - myopathy - pancreatitis - raised creatine kinase - rhabdomyolysis - thrombocytopenia

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Avoid in moderate and severe impairment—may accumulate.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (February 2016) NICE TA385
This guidance should be used with NICE’s guidelines on cardiovascular disease: risk assessment and reduction, including lipid modification and familial hypercholesterolaemia: identification and management (see Lipid-regulating drugs p. 183).

Ezetimibe, alone, is recommended as an option for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia in adult patients in whom initial statin therapy is contra-indicated, or who are intolerant of initial statin therapy.

Ezetimibe, in combination with initial statin therapy, is also recommended as an option for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia in adult patients when:
- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and
- a change from initial statin therapy to an alternative statin is being considered.

When prescribing ezetimibe in combination with statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

www.nice.org.uk/TA385

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Ezetrol** (Merck Sharp & Dohme Ltd)
  - **Ezetimibe 10 mg** Ezetrol 10mg tablets 28 tablet (BNF) £26.31 DT price = £26.31

Combinations available: **Simvastatin with ezetimibe**, p. 194

LIPID MODIFYING DRUGS > FIBRATES

**Bezafibrate**

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE**
Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated > Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
Adult: 200 mg 3 times a day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**
Adult: 400 mg once daily, modified-release dose form is not appropriate in patients with renal impairment.

**CONTRA-INDICATIONS** Gall bladder disease • hypoalbuminaemia • nephrotic syndrome • photosensitivity to fibrates

**CAUTIONS** Correct hypothyroidism before initiating treatment.

**INTERACTIONS** > Appendix 1 (fibrates).
Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

**SIDE-EFFECTS**
- **Common or very common** Abdominal distension - anorexia - diarrhoea - nausea
- **Uncommon** Alopecia - cholesterol - dizziness - erectile dysfunction - headache - myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis)—special risk in renal impairment • photosensitivity reactions • pruritus • rash • renal failure • urticaria
- **Rare** Pancreatitis - peripheral neuropathy
- **Very rare** Anaemia - gallstones - increased platelet count - interstitial lung disease - leucopenia - pancytopenia - Stevens-Johnson syndrome - thrombocytopenic purpura - toxic epidermal necrolysis

**PREGNANCY** Manufacturers advise avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Avoid in severe liver disease.

**RENAI IMPAIRMENT** Reduce dose to 400 mg daily if eGFR 40–60 mL/minute/1.73 m². Reduce dose to 200 mg every 1–2 days if eGFR 15–40 mL/minute/1.73 m². Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

Avoid immediate-release preparations if eGFR less than 15 mL/minute/1.73 m².

Avoid modified-release preparations if eGFR less than 60 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Consider monitoring of liver function and creatine kinase when fibrates used in combination with a statin.
**Ciprofibrate**

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE**

Adjucent to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia. Adjunct to statin in mixed hyperlipidaemia if triglycerides and HDL-cholesterol inadequately controlled in patients at high cardiovascular risk.

- **BY MOUTH USING CAPSULES**
  - **Adult:** Initially 200 mg daily, then increased if necessary to 267 mg daily, maximum 200 mg daily with concomitant statin, 200 mg capsules not appropriate for use in renal impairment, 267 mg capsules not appropriate for initial dose titration, or in renal impairment.
  - **BY MOUTH USING TABLETS**
  - **Adult:** 160 mg daily, tablets not appropriate in renal impairment.

**CONTRA-INDICATIONS** Gall bladder disease · hypoaalbuminaemia · nephrotic syndrome · photosensitivity to fibrates

**CAUTIONS** Correct hypothyroidism before initiating treatment.

**INTERACTIONS** Appendices 1 (fibrates). Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

**SIDE-EFFECTS**

- **Common or very common** Abdominal distension · anorexia · diarrhoea · nausea
- **Uncommon** Alopecia · cholestasis · dizziness · erectile dysfunction · headache · myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis) — special risk in renal impairment · photosensitivity reactions · pruritus · rash · renal failure · urticaria
- **Rare** Pancreatitis · peripheral neuropathy
- **Very rare** Anaemia · gallstones · increased platelet count · interstitial lung disease · leucopenia · pancreatitis · Stevens-Johnson syndrome · thrombocytopenic purpura · toxic epidermal necrolysis
- **Frequency not known** Pneumonitis · pulmonary fibrosis
- **PREGNANCY** Manufacturers advise avoid — toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid — present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment.

**PRESCRIBING AND DISPENSING INFORMATION** Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bezafibrate (Non-proprietary)</strong></td>
<td>Bezafibrate 200 mg Bezafibrate 400 mg modified-release tablets</td>
</tr>
<tr>
<td><strong>Bezalip (Teva UK Ltd)</strong></td>
<td>Bezafibrate 200 mg Bezalip 200 mg tablets</td>
</tr>
<tr>
<td><strong>Bezafibrate (Non-proprietary)</strong></td>
<td>Bezafibrate 400 mg Bezafibrate 400 mg modified-release tablets</td>
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<tr>
<td><strong>Bezalip Mono (Teva UK Ltd)</strong></td>
<td>Bezafibrate 400 mg Bezalip Mono 400 mg modified-release tablets</td>
</tr>
<tr>
<td><strong>Fibraxate XL (Sandoz Ltd)</strong></td>
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<tr>
<td><strong>Fibraxate XL 400 mg</strong></td>
<td>Fibraxate XL 400 mg tablets</td>
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</tbody>
</table>

**INTERACTIONS**

- **Liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised).**
- **Consider monitoring liver function and creatine kinase when fibrates used in combination with a statin.**

**PRESCRIBING AND DISPENSING INFORMATION** Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
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<tr>
<td><strong>Fibraxate XL (Sandoz Ltd)</strong></td>
<td>Fibraxate 400 mg Fibraxate 400 mg tablets</td>
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<tr>
<td><strong>Fibraxate 400 mg</strong></td>
<td>Fibraxate 400 mg tablets</td>
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</table>

**Fenofibrate**

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE**

Adjucent to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia. Adjunct to statin in mixed hyperlipidaemia if triglycerides and HDL-cholesterol inadequately controlled in patients at high cardiovascular risk.

- **BY MOUTH USING CAPSULES**
  - **Adult:** Initially 200 mg daily, then increased if necessary to 267 mg daily, maximum 200 mg daily with concomitant statin, 200 mg capsules not appropriate for use in renal impairment, 267 mg capsules not appropriate for initial dose titration, or in renal impairment.
  - **BY MOUTH USING TABLETS**
  - **Adult:** 160 mg daily, tablets not appropriate in renal impairment.

**CONTRA-INDICATIONS** Gall bladder disease · pancreatitis (unless due to severe hypertriglyceridaemia) · photosensitivity to ketoprofen

**CAUTIONS** Correct hypothyroidism before initiating treatment.

**INTERACTIONS** Appendices 1 (fibrates). Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

**SIDE-EFFECTS**

- **Common or very common** Abdominal distension · anorexia · diarrhoea · nausea
- **Uncommon** Alopecia · cholestasis · dizziness · erectile dysfunction · headache · myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis) — special risk in renal impairment · photosensitivity reactions · pruritus · rash · renal failure · urticaria
- **Rare** Pancreatitis · peripheral neuropathy
- **Very rare** Anaemia · gallstones · increased platelet count · interstitial lung disease · leucopenia · pancytopenia · Stevens-Johnson syndrome · thrombocytopenic purpura · toxic epidermal necrolysis
- **Frequency not known** Pneumonitis · pulmonary fibrosis
- **PREGNANCY** Manufacturers advise avoid — toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid — present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT** Reduce dose to 100 mg on alternate days in moderate impairment. Avoid in severe impairment. Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

**MONITORING REQUIREMENTS**

- **Liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised).**
- **Consider monitoring liver function and creatine kinase when fibrates used in combination with a statin.**

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE**

Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia. Adjunct to statin in mixed hyperlipidaemia if triglycerides and HDL-cholesterol inadequately controlled in patients at high cardiovascular risk.

- **BY MOUTH USING CAPSULES**
  - **Adult:** Initially 200 mg daily, then increased if necessary to 267 mg daily, maximum 200 mg daily with concomitant statin, 200 mg capsules not appropriate for use in renal impairment, 267 mg capsules not appropriate for initial dose titration, or in renal impairment.
  - **BY MOUTH USING TABLETS**
  - **Adult:** 160 mg daily, tablets not appropriate in renal impairment.

**CONTRA-INDICATIONS** Gall bladder disease · pancreatitis (unless due to severe hypertriglyceridaemia) · photosensitivity to ketoprofen

**CAUTIONS** Correct hypothyroidism before initiating treatment.

**INTERACTIONS** Appendices 1 (fibrates). Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

**SIDE-EFFECTS**

- **Common or very common** Abdominal distension · anorexia · diarrhoea · nausea
- **Uncommon** Alopecia · cholestasis · dizziness · erectile dysfunction · headache · myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis) — special risk in renal impairment · pancreatitis · photosensitivity reactions · pruritus · pulmonary embolism · rash · renal failure · urticaria
- **Rare** Pancreatitis · peripheral neuropathy
- **Very rare** Anaemia · gallstones · increased platelet count · interstitial lung disease · leucopenia · pancytopenia ·
Stevens-Johnson syndrome • thrombocytopenic purpura • toxic epidermal necrolysis

- Frequency not known Interstitial pneumopathies
- PREGNANCY Avoid—embryotoxicity in animal studies.
- BREAST FEEDING Manufacturers advise avoid—no information available.
- HEPATIC IMPAIRMENT Avoid.
- RENAL IMPAIRMENT Reduce dose to 134 mg daily if eGFR less than 60 mL/minute/1.73 m². Reduce dose to 67 mg daily if eGFR less than 20 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m².

Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

- MONITORING REQUIREMENTS
  - Liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised).
  - Consider monitoring liver function and creatine kinase when fibrates used in combination with a statin.

- PRESCRIBING AND DISPENSING INFORMATION Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21

- Fenofibrate (Non-proprietary)
  - Fenofibrate micronised 160 mg Fenofibrate micronised 160 mg tablets | 28 tablet (£0.66 DT price = £6.69)
  - Supralip (BGP Products Ltd)

- Fenofibrate micronised 160 mg Supralip 160 mg tablets | 28 tablet (£0.66 DT price = £6.69)

**Capsule**

CAUTIONARY AND ADVISORY LABELS 21

- Fenofibrate (Non-proprietary)
  - Fenofibrate micronised 67 mg Fenofibrate micronised 67 mg capsules | 90 capsule (£0.22 DT price = £22.61)
  - Fenofibrate micronised 200 mg Fenofibrate micronised 200 mg capsules | 28 capsule (£0.65 DT price = £17.83)
  - Fenofibrate micronised 267 mg Fenofibrate micronised 267 mg capsules | 28 capsule (£0.65 DT price = £17.83)

- Lipantil Micro (BGP Products Ltd)
  - Fenofibrate micronised 67 mg Lipantil Micro 67 capsules | 90 capsule (£0.22 DT price = £22.61)
  - Fenofibrate micronised 200 mg Lipantil Micro 200 capsules | 28 capsule (£0.65 DT price = £17.83)
  - Fenofibrate micronised 267 mg Lipantil Micro 267 capsules | 28 capsule (£0.65 DT price = £17.83)

Combinations available: Simvastatin with fenofibrate, p. 195

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**Gemfibrozil**

- **DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

- **INDICATIONS AND DOSE**
  - Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated
  - Adjunct to diet and other appropriate measures in primary hypercholesterolaemia if statin contra-indicated or not tolerated
  - Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia
  - Adjunct to diet and other appropriate measures in primary prevention of cardiovascular disease in men with hyperlipidaemias if statin contra-indicated or not tolerated

- **CONTRA-INDICATIONS** History of gall-bladder or biliary tract disease including gallstones • photosensitivity to fibrates

- **CAUTIONS** Correct hypothyroidism before initiating treatment • elderly

- **INTERACTIONS** → Appendix 1 (fibrates).

The combination of gemfibrozil and a statin should preferably be avoided; high risk of muscle effects (especially rhabdomyolysis).

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain • constipation • diarrhoea • dyspepsia • eczema • fatigue • flatulence • headache • nausea • rash • vertigo • vomiting
  - Uncommon Atrial fibrillation
  - Rare Hepatitis • paraesthesia • alopecia • anaemia • angioedema • appendicitis • blurred vision • bone-marrow suppression • cholestatic jaundice • depression • disturbances in hepatic function • dizziness • drowsiness • eosinophilia • exfoliative dermatitis • leucopenia • myalgia • myasthenia • myopathy • myositis accompanied by increase in creatine kinase (discontinue if raised significantly) • pancreatitis • photosensitivity • pruritus • sexual dysfunction • thrombocytopenia • urticaria

- **PREGNANCY** Manufacturers advise avoid unless essential—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Avoid.

- **RENAL IMPAIRMENT** Initially 900 mg daily if eGFR 30–80 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

- **MONITORING REQUIREMENTS**
  - Monitor blood counts for first year.
  - Monitor liver-function (discontinue treatment if abnormalities persist).
  - Consider monitoring creatine kinase if used in combination with a statin.

- **PRESCRIBING AND DISPENSING INFORMATION** Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).
LIPID MODIFYING DRUGS > NICOTINIC ACID DERIVATIVES

Acipimox

- **INDICATIONS AND DOSE**
  Adjunct or alternative treatment in hyperlipidaemias of types IIb and IV in patients who have not responded adequately to other lipid-regulating drugs such as a statin or fibrate, and lifestyle changes (including diet, exercise, and weight reduction)
  - **BY MOUTH**
    - Adult: 250 mg 2–3 times a day

- **CONTRA-INDICATIONS**
  Peptic ulcer

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain, dyspepsia, flushing, headache, malaise, urticaria
  - Uncommon Anaphylactoid reaction, arthralgia, bronchospasm, erythema, myalgia, myositis, pruritus, rash
  - Frequency not known Diarrhoea, dry eyes, vasodilatation

- **PREGNANCY**
  Manufacturer advises avoid—no information available.

- **BREAST FEEDING**
  Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT**
  Reduce dose to 250 mg 1–2 times daily if eGFR 30–60 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  Monitor hepatic and renal function.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  Cautionary and Advisory Labels 22
  - Lopid (Pfizer Ltd)
    - Gemfibrozil 300 mg Lopid 300mg capsules | 100 capsule PoM £31.76 DT price = £31.76

LIPID MODIFYING DRUGS > STATINS

Statins

- **DRUG ACTION**
  Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver.

- **CAUTIONS**
  Elderly: high alcohol intake - history of liver disease - hypothyroidism - patients at increased risk of muscle toxicity, including myopathy or rhabdomyolysis (e.g. those with a personal or family history of muscular disorders, previous history of muscular toxicity and a high alcohol intake)

- **INTERACTIONS**
  Appendix 1 (nicotinic acid).

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain, dyspepsia, flushing, headache, hypophosphataemia, increase in uric acid, palpitation, peripheral oedema, prolonged prothrombin time, reduced platelet count—shortness of breath, tachycardia
  - Rare Hypotension, insomnia, myalgia, myasthenia, myopathy, reduced glucose tolerance, rhinitis, syncope
  - Very rare Anorexia, rhabdomyolysis, visual disturbance

- **BREAST FEEDING**
  Present in milk—avoid.

- **HEPATIC IMPAIRMENT**
  Avoid in severe impairment. Discontinue if severe abnormalities in liver function tests. Manufacturer advises monitor liver function in mild to moderate hepatic impairment.

- **RENAI IMPAIRMENT**
  Manufacturer advises use with caution—no information available.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, modified-release tablet, capsule

  **Capsule**
  - Nicotinic acid (Non-proprietary)
    - Nicotinic acid 500 mg Solgar Niacin 500mg capsules | 100 capsule no price available

Nicotinic acid

- **DRUG ACTION**
  In doses of 1.5 to 3 g daily, it lowers both cholesterol and triglyceride concentrations by inhibiting synthesis; it also increases HDL-cholesterol.

- **INDICATIONS AND DOSE**
  Adjunct to statin in dyslipidaemia or used alone if statin not tolerated
  - **BY MOUTH**
    - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  Active peptic ulcer disease - arterial bleeding

- **CAUTIONS**
  Acute myocardial infarction - diabetes mellitus - gout - history of peptic ulceration - unstable angina

- **INTERACTIONS**
  Appendix 1 (nicotinic acid).
INTERACTIONS  Appendix 1 (statins).
There is an increased incidence of myopathy if a statin is given with a fibrate (the combination of a statin and gemfibrozil should preferably be avoided), with lipid-lowering doses of nicotinic acid, with fusicid acid (risk of rhabdomyolysis—the combination of a statin and fusidic acid should be avoided); temporarily discontinue statin and restart 7 days after last fusidic acid dose), or with drugs that increase the plasma-statin concentration, such as macrolide antibiotics, imidazole and triazole antifungals, and ciclosporin; close monitoring of liver function and, if muscular symptoms occur, of creatine kinase is necessary.

SIDE-EFFECTS

- Rare Hepatitis, jaundice
- Very rare Hepatic failure, interstitial lung disease, lupus erythematosus-like reactions, pancreatitis
- Frequency not known Alopecia, altered liver function tests, amenorrhea, arthralgia, asthma, depression, dizziness, fatigue, gastro-intestinal disturbances, headache, hyperglicaemia, hypersensitivity reactions, may be associated with the development of diabetes mellitus (particularly in those already at risk of the condition), myalgia, myopathy, myositis, paroaesthesia, peripheral neuropathy, pruritus, rash, rhabdomyolysis, sexual dysfunction, sleep disturbance, thrombocytopenia, urticaria, visual disturbance

SIDE-EFFECTS, FURTHER INFORMATION

- Muscle effects The risk of myopathy, myositis, and rhabdomyolysis associated with statin use is rare. Although myalgia has been reported commonly in patients receiving statins, muscle toxicity truly attributable to statin use is rare. Muscle toxicity can occur with all statins, however the likelihood increases with higher doses.

If muscular symptoms or raised creatine kinase occur during treatment, other possible causes (e.g. vigorous physical activity, hypothyroidism, infection, recent trauma, and drug or alcohol addiction) should be excluded before statin therapy is implicated, particularly if statin treatment has previously been tolerated for more than 3 months. When a statin is suspected to be the cause of myopathy, and creatine kinase concentration is markedly elevated (more than 5 times upper limit of normal), or if muscular symptoms are severe, treatment of statin should be discontinued. If symptoms resolve and creatine kinase concentrations return to normal, the statin should be reintroduced at a lower dose and the patient monitored closely; an alternative statin should be prescribed if unacceptable side-effects are experienced with a particular statin. Statins should not be discontinued in the event of small, asymptomatic elevations of creatine kinase. Routine monitoring of creatine kinase is unnecessary in asymptomatic patients.

Statins should not be discontinued if there is an increase in the blood-glucose concentration or HbA\textsubscript{1c} as the benefits continue to outweigh the risks.

- Interstitial lung disease If patients develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention.

CONCEPTION AND CONTRACEPTION Adequate contraception is required during treatment and for 1 month afterwards.

PREGNANCY Statins should be avoided in pregnancy (discontinue 3 months before attempting to conceive) as congenital anomalies have been reported and the decreased synthesis of cholesterol possibly affects fetal development.

HEPATIC IMPAIRMENT Statins should be used with caution in those with a history of liver disease. Avoid in active liver disease or when there are unexplained persistent elevations in serum transaminases.

MONITORING REQUIREMENTS

Before starting treatment with statins, at least one full lipid profile (non-fasting) should be measured, including total cholesterol, HDL-cholesterol, non-HDL-cholesterol (calculated as total cholesterol minus HDL-cholesterol), and triglyceride concentrations, thyroid-stimulating hormone, and renal function should also be assessed.

Liver function There is little information available on a rational approach to liver-function monitoring; however, NICE suggests that liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity (NICE clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease).

Those with serum transaminases that are raised, but less than 3 times the upper limit of the reference range, should not be routinely excluded from statin therapy. Those with serum transaminases of more than 3 times the upper limit of the reference range should discontinue statin therapy.

Creatine kinase Before initiation of statin treatment, creatine kinase concentration should be measured in patients who have had persistent, generalised, unexplained muscle pain (whether associated or not with previous lipid-regulating drugs); if the concentration is more than 5 times the upper limit of normal, a repeat measurement should be taken after 7 days. If the repeat concentration remains above 5 times the upper limit, statin treatment should not be started; if concentrations are still raised but less than 5 times the upper limit, the statin should be started at a lower dose.

Diabetes Patients at high risk of diabetes mellitus should have fasting blood-glucose concentration or HbA\textsubscript{1c} checked before starting statin treatment, and then repeated after 3 months.

PATIENT AND CARER ADVICE Advise patients to report promptly unexplained muscle pain, tenderness, or weakness.

Atorvastatin

INDICATIONS AND DOSE

Primary hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures | Combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures

- BY MOUTH
  - Adult: Usual dose 10 mg once daily; increased if necessary up to 80 mg once daily, dose to be increased at intervals of at least 4 weeks

Heterozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures | Homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures

- BY MOUTH
  - Adult: Initially 10 mg once daily, then increased to 40 mg once daily, dose to be increased at intervals of at least 4 weeks; maximum 80 mg per day

Primary prevention of cardiovascular events in patients at high risk of a first cardiovascular event

- BY MOUTH
  - Adult: 20 mg once daily, dose can be increased if necessary
Secondary prevention of cardiovascular events

- **BY MOUTH**
  - Adult: 80 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
Reduced dose required (max. 10 mg daily) with concomitant ciclosporin, or tipranavir combined with ritonavir—seek specialist advice.

Maximum dose of 40 mg once daily when combined with anion-exchange resin for heterozygous familial hypercholesterolaemia.

- **UNLICENSED USE** Not licensed for use in secondary prevention of cardiovascular events.
  - Starting dose of 20 mg once daily is not licensed for the primary prevention of cardiovascular events.

**CAUTIONS**

- **SIDE-EFFECTS**
  - Common or very common Back pain · epistaxis · hyperglycaemia · nasopharyngitis · pharyngeolaryngeal pain
  - Uncommon Anorexia · blurred vision · chest pain · hypoglycaemia · malaise · neck pain · peripheral oedema · pyrexia · tinnitus · weight gain
  - Rare Cholestasis · Stevens-Johnson syndrome · toxic epidermal necrolysis
  - **Very rare** Gynaecomastia · hearing loss

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT** In chronic kidney disease, for primary and secondary prevention of cardiovascular events [unlicensed starting dose in primary prevention; unlicensed in secondary prevention], initially 20 mg once daily, increased if necessary (on specialist advice if eGFR < 30 mL/minute/1.73 m²); max. 80 mg once daily.

- **PATIENT AND CARER ADVICE** Patient counselling is advised for atorvastatin tablets (muscle effects).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Atorvastatin (Non-proprietary)**
  - Atorvastatin (as Atorvastatin calcium trihydrate) 10 mg | 28 tablet (Pfizer Ltd) £13.00 DT price = £13.80
  - Atorvastatin (as Atorvastatin calcium trihydrate) 20 mg | 28 tablet (Pfizer Ltd) £24.64 DT price = £26.40
  - Atorvastatin (as Atorvastatin calcium trihydrate) 40 mg | 28 tablet (Pfizer Ltd) £49.57

- **Lipitor (Pfizer Ltd)**
  - Atorvastatin (as Atorvastatin calcium trihydrate) 10 mg Lipitor 10mg chewable tablets sugar-free | 30 tablet (Pfizer Ltd) £13.80
  - Atorvastatin (as Atorvastatin calcium trihydrate) 20 mg Lipitor 20mg chewable tablets sugar-free | 30 tablet (Pfizer Ltd) £26.40

**Fluvastatin**

- **INDICATIONS AND DOSE**
  - Adjunct to diet in primary hypercholesterolaemia or combined (mixed) hyperlipidaemia (types IIa and IIb)
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Adult: Initially 20–40 mg daily, dose to be taken in the evening, increased if necessary up to 80 mg daily in 2 divided doses, dose to be adjusted at intervals of at least 4 weeks
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Adult: 80 mg daily

- **SIDE-EFFECTS**
  - Very rare Vasculitis

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT** Manufacturer advises doses above 40 mg daily should be initiated with caution if eGFR less than 30 mL/minute/1.73 m².

- **PATIENT AND CARER ADVICE** Patient counselling is advised for fluvastatin tablets/capsules (muscle effects).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2004) that fluvastatin is accepted for restricted use for the secondary prevention of coronary events after percutaneous coronary angioplasty; if the patient has previously been receiving another statin, then there is no need to change the statin.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 25**

- **Fluvastatin (Non-proprietary)**
  - Fluvastatin (as Fluvastatin sodium) 80 mg Lipstatin 80mg modified-release tablets | 28 tablet (Novartis Pharmaceuticals UK Ltd) no price available DT price = £19.20
  - Dorisyn XL (Aspire Pharma Ltd)
    - Fluvastatin (as Fluvastatin sodium) 80 mg Dorisyn XL 80mg tablets | 28 tablet (Pfizer Ltd) £19.20 DT price = £19.20
  - Lescol XL (Novartis Pharmaceuticals UK Ltd)
    - Fluvastatin (as Fluvastatin sodium) 80 mg Lescol XL 80mg tablets | 28 tablet (Pfizer Ltd) £19.20 DT price = £19.20
  - Luvinsta XL (Actavis UK Ltd)
    - Fluvastatin (as Fluvastatin sodium) 80 mg Luvinsta XL 80mg tablets | 28 tablet (Pfizer Ltd) £19.20 DT price = £19.20
  - Nandovar XL (Sandoz Ltd)
    - Fluvastatin (as Fluvastatin sodium) 80 mg Nandovar XL 80mg tablets | 28 tablet (Pfizer Ltd) £16.32 DT price = £19.20
Pravastatin sodium

- **INDICATIONS AND DOSE**

  Adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemias in patients who have not responded adequately to dietary control
  - **BY MOUTH**
    - Adult: 10–40 mg daily, dose to be taken at night, dose to be adjusted at intervals of at least 4 weeks

  Prevention of cardiovascular events in patients with previous myocardial infarction or unstable angina
  - **BY MOUTH**
    - Adult: 40 mg daily, dose to be taken at night

  Reduction of hyperlipidaemia in patients receiving immunosuppressive therapy following solid-organ transplantation
  - **BY MOUTH**
    - Adult: Initially 20 mg daily, then increased if necessary up to 40 mg daily, dose to be taken at night, close medical supervision is required if dose is increased to maximum dose

- **SIDE-EFFECTS**

  - Uncommon Abnormal urination • dysuria • nocturia • urinary frequency
  - Very rare Fulminant hepatic necrosis

- **BREAST FEEDING**

  Manufacturer advises avoid—small amount of drug present in breast milk.

- **RENAL IMPAIRMENT**

  Manufacturer advises initial dose of 10 mg once daily in moderate to severe impairment.

- **PATIENT AND CARER ADVICE**

  Patient counselling is advised for pravastatin tablets (muscle effects).

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

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**Rosuvastatin**

- **INDICATIONS AND DOSE**

  Primary hypercholesterolaemia (type IIA including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIB), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures
  - **BY MOUTH**
    - Adult 18–69 years: Initially 5–10 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased at intervals of at least 4 weeks
    - Adult (patients of Asian origin): Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased at intervals of at least 4 weeks
    - Adult 70 years and over: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased at intervals of at least 4 weeks

  Primary hypercholesterolaemia (type IIA including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIB), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures and who have risk factors for myopathy or rhabdomyolysis
  - **BY MOUTH**
    - Adult: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased at intervals of at least 4 weeks

  Severe primary hypercholesterolaemia (type IIA including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIB), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures, in patients with high cardiovascular risk (under expert supervision)
  - **BY MOUTH**
    - Adult: Initially 5–10 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased at intervals of at least 4 weeks

  Prevention of cardiovascular events in patients at high risk of a first cardiovascular event
  - **BY MOUTH**
    - Adult 18–69 years: 20 mg once daily
    - Adult (patients of Asian origin): Initially 5 mg once daily, then increased if necessary up to 20 mg once daily
    - Adult 70 years and over: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily

  Prevention of cardiovascular events in patients at high risk of a first cardiovascular event and with risk factors for myopathy or rhabdomyolysis
  - **BY MOUTH**
    - Adult: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily

  **DOSE ADJUSTMENTS DUE TO INTERACTIONS**

  Initially 5 mg once daily with concomitant fibrate increased if necessary up to max. 20 mg daily. For dose adjustments with concomitant atazanavir, clopidogrel, darunavir, dronedarone, eltorbopag, ezetimibe, itraconazole, lopinavir, or tipranavir, consult product literature. Maximum dose 5 mg with concomitant ombitasvir, paritaprevir, and ritonavir given with dasabuvir, but maximum 10 mg daily with concomitant ombitasvir, paritaprevir, and ritonavir given without dasabuvir.

- **CAUTIONS**

  Patients of Asian origin
Simvastatin

**INDICATIONS AND DOSE**

Primary hypercholesterolaemia, or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures

- **BY MOUTH**
  - Adult: 10–20 mg once daily, then increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

Homozgyous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures

- **BY MOUTH**
  - Adult: Initially 40 mg once daily, then increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus

- **BY MOUTH**
  - Adult: Initially 20–40 mg once daily, increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Max. 10 mg daily with concomitant bezafibrate or ciprofibrate.

Max. 20 mg daily with concomitant amiodarone, verapamil, diltiazem, amiodipine, or ranolazine.

Max. 40 mg daily with concomitant lomitapide.

**SIDE-EFFECTS**

- Rare: Anaemia
- Frequency not known: Tendinopathy

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**RENA L IMPAIRMENT**

Doses above 10 mg daily should be used with caution if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Patient counselling is advised for simvastatin tablets/oral suspension (muscle effects).

**EXCEPTIONS TO LEGAL CATEGORY**

Simvastatin 10 mg tablets can be sold to the public to reduce risk of first coronary event in individuals at moderate risk of coronary heart disease (approx. 10–15% risk of major event in 10 years), max. daily dose 10 mg and pack size of 28 tablets; treatment should form part of a programme to reduce risk of coronary heart disease.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Simvastatin (Non-proprietary)**
  - Simvastatin 10 mg: Simvastatin 10 mg tablets | 28 tablet | £18.00 DT price = £0.67
  - Simvastatin 20 mg: Simvastatin 20 mg tablets | 28 tablet | £29.60 DT price = £0.76
  - Simvastatin 40 mg: Simvastatin 40 mg tablets | 28 tablet | £23.60 DT price = £0.84
  - Simvastatin 80 mg: Simvastatin 80 mg tablets | 28 tablet | £29.61 DT price = £1.68

- **Zocor** (Merck Sharp & Dohme Ltd)
  - Simvastatin 10 mg: Zocor 10 mg tablets | 28 tablet | £18.03 DT price = £0.67
  - Simvastatin 20 mg: Zocor 20 mg tablets | 28 tablet | £29.69 DT price = £0.76
  - Simvastatin 40 mg: Zocor 40 mg tablets | 28 tablet | £29.69 DT price = £0.84
  - Simvastatin 80 mg: Zocor 80 mg tablets | 28 tablet | £29.69 DT price = £1.68

**Oral suspension**

**EXCIPIENTS:** May contain Propylene glycol

- **Simvastatin (Non-proprietary)**
  - Simvastatin 4 mg per 1 ml: Simvastatin 20 mg/5 ml oral suspension sugar free sugar-free | 150 ml | £119.40 DT price = £119.40
  - Simvastatin 8 mg per 1 ml: Simvastatin 40 mg/5 ml oral suspension sugar free sugar-free | 150 ml | £162.40 DT price = £162.40

Simvastatin with ezetimibe

The properties listed below are those particular to the combination only. For the properties of the components please consider, simvastatin above, ezetimibe p. 187.

**INDICATIONS AND DOSE**

Homozgyous familial hypercholesterolaemia, primary hypercholesterolaemia, and mixed hyperlipidaemia in patients over 10 years stabilised on the individual components in the same proportions, or for patients not adequately controlled by statin alone

- **BY MOUTH**
  - Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Inegy** (Merck Sharp & Dohme Ltd)
  - Ezetimibe 10 mg, Simvastatin 20 mg: Inegy 10 mg/20 mg tablets | 28 tablet | £33.42 DT price = £33.42
  - Ezetimibe 10 mg, Simvastatin 40 mg: Inegy 10 mg/40 mg tablets | 28 tablet | £38.98 DT price = £38.98
  - Ezetimibe 10 mg, Simvastatin 80 mg: Inegy 10 mg/80 mg tablets | 28 tablet | £41.21 DT price = £41.21
Simvastatin with fenofibrate

The properties listed below are those particular to the combination only. For the properties of the components please consider, simvastatin p. 194, fenofibrate p. 188.

### INDICATIONS AND DOSE

Adjunct to diet and exercise in mixed dyslipidaemia, when LDL-cholesterol levels are adequately controlled with the corresponding dose of simvastatin monotherapy (in patients at high cardiovascular risk)

- **By mouth**
  - Adult: 20/145 mg once daily, alternatively 40/145 mg once daily, dose should be based on previous simvastatin monotherapy dose

### CAUTIONS

History of pulmonary embolism

### SIDE-EFFECTS

- Common or very common Gastroenteritis
- Uncommon Dermatitis - eczema

### RENAL IMPAIRMENT

Manufacturer advises avoid if eGFR less than 60 mL/minute/1.73 m²; use with caution if eGFR 60–89 mL/minute/1.73 m².

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

**EXCIPIENTS:** May contain Butylated hydroxyanisole, lecithin
- **Cholib (BGP Products Ltd)**
  - Simvastatin 20 mg, Fenofibrate 145 mg Cholib 145mg/20mg tablets | 30 tablet (POM) £7.71 DT price + £7.71
  - Simvastatin 40 mg, Fenofibrate 145 mg Cholib 145mg/40mg tablets | 30 tablet (POM) £8.33 DT price + £8.33

### LIPID MODIFYING DRUGS

**Alirocumab**

24-Oct-2016

**DRUG ACTION**

Alirocumab binds to a pro-protein involved in the regulation of LDL receptors on liver cells; receptor numbers are increased, which results in increased uptake of LDL-cholesterol from the blood.

**INDICATIONS AND DOSE**

Primary hypercholesterolaemia or mixed dyslipidaemia in patients who have not responded adequately to other measures (in combination with a statin, or with a statin and other lipid-lowering therapies, or with other lipid-lowering therapies or alone if a statin contraindicated or not tolerated)

- **By subcutaneous injection**
  - Adult: 75–150 mg every 2 weeks, adjusted according to response, to be administered into the thigh, abdomen or upper arm, dose adjustments should be made at 4-weekly intervals

**INTERACTIONS**

Appendix 1 (alirocumab)

**SIDE-EFFECTS**

- Common or very common Oropharyngeal pain - rhinorrhea
- Rare Eczema (discoid) - urticaria
- Frequency not known Vasculitis

**PREGNANCY**

Manufacturer advises avoid unless clinical condition requires treatment—maternal toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises with caution in severe impairment—no information available.

**RENAL IMPAIRMENT**

Manufacturer advises with caution in severe impairment—no information available.

**HANDLING AND STORAGE**

Manufacturer advises store in a refrigerator (2–8 °C)—consult product literature for further information regarding storage outside refrigerator.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016) NICE TA393
  - Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:
    - low-density lipoprotein cholesterol (LDL-C) concentrations are persistently above the thresholds specified in the NICE documentation and
    - the manufacturer provides alirocumab with the discount agreed in the patient access scheme.

- Patients whose treatment was started before this guidance was published should continue treatment until they and their clinician consider it appropriate to stop.

- **www.nice.org.uk/TA393**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (Aug 2016) that alirocumab (Praluent®) is accepted for restricted use within NHS Scotland for treatment of primary hypercholesterolaemia or mixed dyslipidaemia (alone or in combination with other lipid lowering therapies, as specified within it’s license), for specialist use only and only in patients at high cardiovascular risk as follows:

- patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥5.0mmol/L, for primary prevention of cardiovascular events, or
- patients with HeFH and LDL-C ≥3.5mmol/L, for secondary prevention of cardiovascular events, or
- patients at high risk due to previous cardiovascular events and LDL-C ≥4.0mmol/L, or
- patients with recurrent/polyvascular disease and LDL-C ≥3.5mmol/L.

This advice is contingent upon the continuing availability of the Patient Access Scheme (PAS) in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Polysorbates

- **Praluent (Sanofi)**
  - **Alirocumab 75 mg per 1 ml** Praluent 75mg/1ml solution for injection pre-filled disposable injection (POM) £168.00 | 2 pre-filled disposable injection (POM) £336.00
  - **Alirocumab 150 mg per 1 ml** Praluent 150mg/1ml solution for injection pre-filled disposable injection (POM) £168.00 | 2 pre-filled disposable injection (POM) £336.00

**Lomitapide**

2016

**DRUG ACTION**

Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP), reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids such as cholesterol and triglycerides.

**INDICATIONS AND DOSE**

Adjunct to dietary measures and other lipid-regulating drugs with or without low-density lipoprotein apheresis in homozygous familial hypercholesterolaemia (under expert supervision)

- **By mouth**
  - Adult: Initially 5 mg daily for 2 weeks, dose to be taken at least 2 hours after evening meal, then increased if necessary to 10 mg daily, for at least 4 weeks, then increased to 20 mg daily for at least 4 weeks, then increased in steps of 20 mg daily, adjusted at intervals of at least 4 weeks; maximum 60 mg per day

**Appendix 1**

- Lomitapide was published should continue treatment until they and their clinician consider it appropriate to stop.

- **www.nice.org.uk/TA393**

- Scottish Medicines Consortium (SMC) Decisions

  - The Scottish Medicines Consortium has advised (Aug 2016) that alirocumab (Praluent®) is accepted for restricted use within NHS Scotland for treatment of primary hypercholesterolaemia or mixed dyslipidaemia (alone or in combination with other lipid lowering therapies, as specified within it’s license), for specialist use only and only in patients at high cardiovascular risk as follows:

  - patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥5.0mmol/L, for primary prevention of cardiovascular events, or
  - patients with HeFH and LDL-C ≥3.5mmol/L, for secondary prevention of cardiovascular events, or
  - patients at high risk due to previous cardiovascular events and LDL-C ≥4.0mmol/L, or
  - patients with recurrent/polyvascular disease and LDL-C ≥3.5mmol/L.

  - This advice is contingent upon the continuing availability of the Patient Access Scheme (PAS) in NHS Scotland or a list price that is equivalent or lower.

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**

    - **EXCIPIENTS:** May contain Polysorbates

      - **Praluent (Sanofi)**

        - **Alirocumab 75 mg per 1 ml** Praluent 75mg/1ml solution for injection pre-filled disposable injection (POM) £168.00 | 2 pre-filled disposable injection (POM) £336.00
        - **Alirocumab 150 mg per 1 ml** Praluent 150mg/1ml solution for injection pre-filled disposable injection (POM) £168.00 | 2 pre-filled disposable injection (POM) £336.00

- **Lomitapide**

  - **DRUG ACTION**

    - Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP), reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids such as cholesterol and triglycerides.

  - **INDICATIONS AND DOSE**

    - Adjunct to dietary measures and other lipid-regulating drugs with or without low-density lipoprotein apheresis in homozygous familial hypercholesterolaemia (under expert supervision)

      - **By mouth**

        - Adult: Initially 5 mg daily for 2 weeks, dose to be taken at least 2 hours after evening meal, then increased if necessary to 10 mg daily, for at least 4 weeks, then increased to 20 mg daily for at least 4 weeks, then increased in steps of 20 mg daily, adjusted at intervals of at least 4 weeks; maximum 60 mg per day
### CONTRA-INDICATIONS
Significant or chronic bowel disease

### CAUTIONS
Concomitant use of hepatotoxic drugs - lomitapide can interfere with the absorption of fat-soluble nutrients and supplementation of vitamin E and fatty acids is required - patients over 65 years

### INTERACTIONS
→ Appendix 1 (lomitapide).

### SIDE-EFFECTS

- **Common or very common**
  - Bloating
  - Abdominal pain
  - Appetite changes
  - Constipation
  - Diarrhoea
  - Dizziness
  - Dyspepsia
  - Ecchymosis
  - Erythematous rash
  - Flatulence
  - Gastr-o-oesophageal reflux disease
  - Gastroenteritis
  - Haemorrhoids
  - Headache
  - Hepatic steatosis
  - Hepatomegaly
  - Hypokalaemia
  - Leucopenia
  - Malaise
  - Migraine
  - Muscle spasms
  - Nausea
  - Neutropenia
  - Raised serum transaminases
  - Tenesmus
  - Vomiting
  - Weight loss

- **Uncommon**
  - Abnormal gait
  - Anaemia
  - Arthralgia
  - Chest pain
  - Drowsiness
  - Dry mouth
  - Dry skin
  - Eye swelling
  - Gastro-intestinal haemorrhage
  - Haematemesis
  - Haematuria
  - Hyperbilirubinaemia
  - Joint swelling
  - Myalgia
  - Pain in extremities
  - Paraesthesia
  - Proteinuria
  - Pyrexia
  - Sweating
  - Vertigo

### SIDE-EFFECTS, FURTHER INFORMATION
Reduce dose if serum transaminases raised during treatment (consult product literature).

### CONCEPTION AND CONTRACEPTION
Manufacturer advises exclude pregnancy before treatment and ensure effective contraception used.

### PREGNANCY
Avoid teratogenicity and embryotoxicity in animal studies.

### BREAST FEEDING
Manufacturer advises avoid no information available.

### HEPATIC IMPAIRMENT
Reduce dose if serum transaminases raised during treatment (consult product literature). Max. 40 mg daily in mild impairment. Avoid in moderate to severe impairment, or if unexplained persistent abnormal liver function tests.

### RENAL IMPAIRMENT
Max. 40 mg daily in end-stage renal disease.

### MONITORING REQUIREMENTS
- Monitor liver function tests before treatment, then at least monthly and before each dose increase for first year, then at least every 3 months and before each dose increase thereafter.
- Screen for hepatic steatosis and fibrosis before treatment, then annually thereafter.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Capsule
- **Lojuxta** (Aegerion Pharmaceuticals Ltd)
  - Lomitapide 5 mg Lojuxta 5 mg capsules | 28 capsule [POM] £17.765.00
  - Lomitapide 10 mg Lojuxta 10 mg capsules | 28 capsule [POM] £17.765.00
  - Lomitapide 20 mg Lojuxta 20 mg capsules | 28 capsule [POM] £17.765.00

#### Omega-3-acid ethyl esters

- **INDICATIONS AND DOSE**
  - **Adjunct to diet and statin in type IIb or III hypertriglyceridaemia**
  - **Adjunct to diet in type IV hypertriglyceridaemia**
    - **BY MOUTH**
    - **Adult:** Initially 2 capsules daily, dose to be taken with food, increased if necessary to 4 capsules daily

- **Adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months**
  - **BY MOUTH**
  - **Adult:** 1 capsule daily, dose to be taken with food

- **CAUTIONS**
  - Anticoagulant treatment (bleeding time increased) - haemorrhagic disorders

- **SIDE-EFFECTS**
  - **Common or very common**
    - Dyspepsia
    - Nausea
  - **Uncommon**
    - Abdominal pain
    - Dizziness
    - Gastritis
    - Taste disturbances
  - **Rare**
    - Acne
    - Headache
    - Hepatic disorders
    - Hyperglycaemia
    - Rash
  - **Very rare**
    - Gastro-intestinal haemorrhage
    - Hypotension
    - Increased white cell count
    - Nasal dryness
    - Urticaria

- **PREGNANCY**
  - Manufacturers advise use only if potential benefit outweighs risk — no information available.

- **BREAST FEEDING**
  - Manufacturers advise avoid — no information available.

- **HEPATIC IMPAIRMENT**
  - Monitor liver function in hepatic impairment.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**
  The Scottish Medicines Consortium has advised (November 2002) that omega-3-acid ethyl esters are not recommended for use within NHS Scotland for the treatment of hypertriglyceridaemia.

- **MEDICINAL FORMS**
  - **Capsule**
    - There can be variation in the licensing of different medicines containing the same drug.

- **Cautionary and Advisory Labels 21**
  - **Omega-3-acid ethyl esters (Non-proprietary)**
    - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
      - 460 mg Eicosapentaenoic acid 460 mg | Docosahexaenoic acid 380 mg capsules | 28 capsule £14.24 DT price = £14.24 | 100 capsule [POM] £50.86
    - Dualtis (BGP Products Ltd)
      - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
        - 460 mg Dualtis 1000 mg capsules | 28 capsule [P] £11.37 DT price = £14.24
    - Nebbaro (Zentiva)
      - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
        - 460 mg Nebbaro 1000 mg capsules | 28 capsule [P] £8.48 DT price = £14.24
    - Omacor (BGP Products Ltd)
      - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
        - 460 mg Omacor capsules | 28 capsule [P] £14.24 DT price = £14.24 | 100 capsule [POM] £50.84
    - Omega 3 (Glenmark Generics (Europe) Ltd, Alissa Healthcare Research Ltd)
      - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
        - 460 mg Omega 3-acid-ethyl esters 1000 mg capsules | 28 capsule [POM] £56.00 DT price = £14.24 | 100 capsule [POM] £21.00
    - PrestyloN (Teva UK Ltd)
      - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
        - 460 mg Prestylon 1 g capsules | 28 capsule [POM] £10.68 DT price = £14.24 | 100 capsule [POM] £38.13
    - Teromeg (AMCo)
      - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid
        - 460 mg Teromeg 1000 mg capsules | 28 capsule [POM] £11.39 DT price = £14.24 | 100 capsule [POM] £40.67
7 Myocardial ischaemia

Stable angina

Overview

It is important to distinguish stable angina from unstable angina. Stable angina usually results from atherosclerotic plaques in the coronary arteries that restrict blood flow and oxygen supply to the heart; it is often precipitated by exertion and relieved by rest. Treatment involves management of acute anginal pain, and long-term management to prevent angina attacks and to reduce the risk of cardiovascular events.

Management

Acute attacks of stable angina should be managed with sublingual glyceryl trinitrate p. 207 which can be taken immediately before performing activities that are known to bring on an attack. If attacks occur more than twice a week, regular drug therapy is required and should be introduced in a step-wise manner according to response.

Patients with stable angina should be given a beta-blocker or a calcium-channel blocker. In those with left-ventricular dysfunction, beta-blocker treatment should be started at a very low dose and titrated very slowly over a period of weeks or months. If a beta-blocker or a calcium-channel blocker alone fails to control symptoms adequately, a combination of a beta-blocker and a dihydropyridine calcium-channel blocker (e.g. amiodipine p. 147, felodipine p. 150, modified-release nifedipine p. 153) should be used; if this combination is not appropriate due to intolerance of, or contra-indication to, either beta-blockers or calcium-channel blockers, addition of a long-acting nitrate, ivabradine p. 200, nicorandil p. 201, or ranolazine p. 199 can be considered.

For those patients in whom both beta-blockers and calcium-channel blockers are not tolerated or are contra-indicated, monotherapy with a long-acting nitrate, ivabradine, nicorandil, or ranolazine should be considered.

Response to treatment should be assessed every 2–4 weeks after initiating or changing drug therapy; the drug should be titrated (according to symptom control) to the maximum tolerated dose. Consider referring the patient to a specialist if a combination of two drugs fails to control symptoms. Addition of a third antianginal drug should only be considered if symptom control is not achieved with two drugs and the patient is either due to undergo a revascularisation procedure, or a revascularisation procedure is considered inappropriate. See the use of antiplatelet drugs in patients undergoing coronary stenting.

For long-term prevention of cardiovascular events, see Prevention of cardiovascular events.

Antianginal drugs

Nitrates, calcium-channel blockers, and potassium channel activators (use in adults only) have a vasodilating and, consequently, blood pressure lowering effect. Vasodilators can act in heart failure by arteriolar dilatation which reduces both peripheral vascular resistance and left ventricular pressure, thus resulting in improved cardiac output. They can also cause venous dilatation which results in dilatation of capacitance vessels, increase of venous pooling, and diminution of venous return to the heart (decreasing left ventricular end-diastolic pressure).

Nicorandil, a potassium-channel activator with a nitrate component, has both arterial and venous vasodilating properties and is licensed for the prevention and long-term treatment of angina. Nicorandil has similar efficacy to other antianginal drugs in controlling symptoms; it may produce additional symptomatic benefit in combination with other antianginal drugs [unlicensed indication].

Ivabradine lowers the heart rate by its action on the sinus node. It is licensed for the treatment of angina in patients who are in normal sinus rhythm in combination with a beta-blocker, or when beta-blockers are contra-indicated or not tolerated. Ivabradine, in combination with standard therapy including a beta-blocker (unless contra-indicated or not tolerated), is also licensed for mild to severe stable chronic heart failure in patients who are in sinus rhythm.

Ranolazine is licensed as adjunctive therapy in patients who are inadequately controlled or intolerant of first-line antianginal drugs.

Other drugs used for Myocardial ischaemia


ANTITHROMBOTIC DRUGS > ANTIPLATELET DRUGS

Cangrelor

- **DRUG ACTION** Cangrelor is a direct P2Y12 platelet receptor antagonist that blocks adenosine diphosphate induced platelet activation and aggregation.

- **INDICATIONS AND DOSE** In combination with aspirin for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral P2Y12 inhibitor (e.g. clopidogrel, prasugrel, ticagrelor) prior to the PCI procedure and in whom oral therapy with a P2Y12 inhibitor is not suitable (under expert supervision).
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - **Adult:** Initially 30 micrograms/kg, to be given as a bolus dose, followed immediately by (by intravenous infusion) 4 micrograms/kg/minute, start treatment before percutaneous coronary intervention and continue infusion for at least 2 hours or for the duration of intervention if longer; maximum duration of infusion 4 hours

- **CONTRA-INDICATIONS** Active bleeding - history of stroke - history of transient ischaemic attack - patients at increased risk of bleeding (e.g. impaired haemostasis, irreversible coagulation disorders, major surgery or trauma, uncontrolled severe hypertension)

- **CAUTIONS** Disease states associated with increased bleeding risk

- **INTERACTIONS** Caution with concomitant use of drugs that increase risk of bleeding

- **SIDE-EFFECTS**
  - **Common or very common** Dyspnoea - ecchymosis - haematemesis - haemorrhage (including gastro-intestinal and intracranial)
  - **Uncommon** Acute renal failure - cardiac tamponade - epistaxis - haemoptysis - rash - retroperitoneal haemorrhage (fatalities reported) - urticaria
  - **Rare** Anaemia - bruising - thrombocytopenia
  - **Very rare** Menorrhagia

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.
Eptifibatide

**INDICATIONS AND DOSE**
In combination with aspirin and unfractionated heparin for the prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 24 hours (specialist use only)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 180 micrograms/kg, then (by intravenous infusion) 2 micrograms/kg/minute for up to 72 hours (up to 96 hours if percutaneous coronary intervention during treatment)

**CONTRA-INDICATIONS**
- Abnormal bleeding within 30 days
  - aneurysm
  - arteriovenous malformation or aneurysm
  - haemorrhagic diathesis
  - history of haemorrhagic stroke
  - increased INR
  - increased prothrombin time
  - intracranial disease
  - major surgery or severe trauma within 6 weeks
  - neoplasm
  - severe hypertension
  - stroke within last 30 days
  - thrombocytopenia

- **CAUTIONS**
  Discontinue if emergency cardiac surgery necessary
  - discontinue if intra-aortic balloon pump necessary
  - discontinue if thrombolytic therapy necessary
  - risk of bleeding
  - discontinue immediately if uncontrolled serious bleeding

- **INTERACTIONS**
  Caution with concomitant drugs that increase risk of bleeding—discontinue immediately if uncontrolled serious bleeding

**SIDE-EFFECTS**
- **Common or very common**
  - Bleeding manifestations
  - Bradycardia
  - Chest pain
  - Fever
  - Headache
  - Hypotension
  - Nausea
  - Puncture site pain
  - Thrombocytopenia
  - Vomiting
- **Rare**
  - Adult respiratory distress
  - Cardiac tamponade
  - Hypersensitivity reactions

**PREGNANCY**
Manufacturer advises use only if potential benefit outweighs risk—no information available.

**RENAL IMPAIRMENT**
Avoid in severe liver disease—increased risk of bleeding.

**HEPATIC IMPAIRMENT**
Avoid in severe liver disease—increased risk of bleeding.

**ANTITHROMBOTIC DRUGS**

**GLYCOPROTEIN IIb/IIIa INHIBITORS**

**Abciximab**

**INDICATIONS AND DOSE**
Prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention
(specialist use only)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 250 micrograms/kg, to be given over 1 minute, then (by intravenous infusion) 125 nanograms/kg/minute (max. per dose 10 micrograms/minute), to be started 10–60 minutes before percutaneous coronary intervention and continue for 12 hours

**SHORT-TERM PREVENTION OF MYOCARDIAL INFARCTION IN PATIENTS WITH UNSTABLE ANGINA NOT RESPONDING TO CONVENTIONAL TREATMENT AND WHO ARE SCHEDULED FOR PERCUTANEOUS CORONARY INTERVENTION (SPECIALIST USE ONLY)**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 250 micrograms/kg, to be given over 1 minute, then (by intravenous infusion) 125 nanograms/kg/minute (max. per dose 10 micrograms/minute), to be started up to 24 hours before possible percutaneous coronary intervention and continue infusion for 12 hours after intervention

**CONTRA-INDICATIONS**
- Active internal bleeding
  - arteriovenous malformation or aneurysm
  - haemorrhagic diathesis
  - hypertensive retinopathy
  - intracranial neoplasm
  - intracranial or intraspinal surgery or trauma within last 2 months
  - major surgery within last 2 months
  - severe hypertension
  - stroke within last 2 years
  - thrombocytopenia
  - vasculitis

**CAUTIONS**
Discontinue if uncontrollable serious bleeding occurs or emergency cardiac surgery needed (consult product literature for details of procedures to minimise bleeding—elderly

**INTERACTIONS**
Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- **Common or very common**
  - Back pain
  - Bleeding manifestations
  - Bradycardia
  - Chest pain
  - Fever
  - Headache
  - Hypotension
  - Nausea
  - Puncture site pain
  - Thrombocytopenia
  - Vomiting
- **Rare**
  - Adult respiratory distress
  - Cardiac tamponade
  - Hypersensitivity reactions

**PREGNANCY**
Manufacturer advises use only if potential benefit outweighs risk—no information available.

**RENAL IMPAIRMENT**
Avoid in severe liver disease—increased risk of bleeding.

**HEPATIC IMPAIRMENT**
Avoid in severe liver disease—increased risk of bleeding.
**RENAL IMPAIRMENT** Reduce infusion to 1 microgram/kg/minute if eGFR 30–50 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**
- Measure baseline prothrombin time, activated partial thromboplastin time, platelet count, haemoglobin, haematocrit and serum creatinine.
- Monitor haemoglobin, haematocrit and platelets within 6 hours after start of treatment, then at least once daily.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Integrilin** (GlaxoSmithKline UK Ltd)
  - Eptifibatide 2 mg per 1 ml Integrilin 20mg/10ml solution for injection vials | 1 vial (POM) £13.61 (Hospital only)

**Solution for infusion**
- **Integrilin** (GlaxoSmithKline UK Ltd)
  - Eptifibatide 750 microgram per 1 ml Integrilin 75mg/100ml solution for infusion vials | 1 vial (POM) £42.79 (Hospital only)

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**Tirofiban**

**INDICATIONS AND DOSE**
In combination with unfractionated heparin, aspirin, and clopidogrel for prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI) and with last episode of chest pain within 12 hours (with angiography planned for 4–48 hours after diagnosis) (initiated under specialist supervision)

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 400 nanograms/kg/minute for 30 minutes, then 100 nanograms/kg/minute for at least 48 hours (continue during and for 12–24 hours after percutaneous coronary intervention), maximum duration of treatment 108 hours

In combination with unfractionated heparin, aspirin, and clopidogrel for prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI) and with last episode of chest pain within 12 hours (with angiography within 4 hours of diagnosis) (initiated under specialist supervision)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 25 micrograms/kg, to be given over 3 minutes at start of percutaneous coronary intervention, then (by intravenous infusion) 150 nanograms/kg/minute for 12–24 hours, maximum duration of treatment 48 hours

In combination with unfractionated heparin, aspirin, and clopidogrel for reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction (STEMI) intended for primary percutaneous coronary intervention (PCI) (initiated under specialist supervision)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 25 micrograms/kg, to be given over 3 minutes at start of percutaneous coronary intervention, then (by intravenous infusion) 150 nanograms/kg/minute for 12–24 hours, maximum duration of treatment 48 hours

**CONTRA-INDICATIONS** Abnormal bleeding within 30 days · history of aneurysm · history of arteriovenous malformation · history of haemorrhagic stroke · history of intracranial disease · history of neoplasm · increased INR · increased prothrombin time · severe hypertension · stroke within 30 days · thrombocytopenia

**CAUTIONS** Active peptic ulcer (within 3 months) · acute pericarditis · anaemia · aortic dissection · cardiogenic shock · discontinue if intra-aortic balloon pump necessary · discontinue if thrombolytic therapy necessary · discontinue immediately if serious or uncontrollable bleeding occurs · discontinue if emergency cardiac surgery necessary · elderly · faecal occult blood · haematuria · haemorrhagic retinopathy · low body-weight · major surgery within 3 months (avoid if within 6 weeks) · organ biopsy or lithotripsy within last 2 weeks · puncture of non-compressible vessel within 24 hours · risk of bleeding (within 3 months) · severe heart failure · severe trauma within 5 months (avoid if within 6 weeks) · traumatic or protracted cardiopulmonary resuscitation within last 2 weeks · uncontrolled severe hypertension · vasculitis

**INTERACTIONS** → Appendix 1 (tirofiban), Concomitant drugs that increase risk of bleeding (including within 48 hours of thrombolytic administration).

**SIDE-EFFECTS** Bleeding manifestations · fever · headache · nausea · reversible thrombocytopenia

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Caution in mild to moderate liver disease. Avoid in severe liver disease—increased risk of bleeding.

**RENAL IMPAIRMENT** Use half normal dose if eGFR less than 30 mL/minute/1.73 m². Increased risk of bleeding. Monitor carefully if eGFR less than 60 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Monitor platelet count, haemoglobin and haematocrit before treatment, 2–6 hours after start of treatment and then at least once daily.

**DIRECTIONS FOR ADMINISTRATION** For *intravenous infusion* (Aggrastat®), give continuously in Glucose 5% or Sodium chloride 0.9%. Withdraw 50 mL infusion fluid from 250 mL bag and replace with 50 mL tirofiban concentrate (250 micrograms/mL) to give a final concentration of 50 micrograms/mL.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

**ELECTROLYTES:** May contain Sodium
- **Tirofiban (Non-proprietary)**
  - Tirofiban (as Tirofiban hydrochloride) 50 microgram per 1 ml Tirofiban 12.5mg/250ml infusion bags | 1 bag (POM) £160.72 (Hospital only)
- **Aggrastat** (Correvio GmbH)
  - Tirofiban (as Tirofiban hydrochloride) 50 microgram per 1 ml Aggrastat 12.5mg/250ml infusion bags | 1 bag (POM) no price available (Hospital only)

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium
- **Aggrastat** (Correvio GmbH)
  - Tirofiban (as Tirofiban hydrochloride) 250 microgram per 1 ml Aggrastat 12.5mg/50ml concentrate for solution for infusion vials | 1 vial (POM) no price available (Hospital only)

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**PIPERAZINE DERIVATIVES**

**Ranolazine**

**INDICATIONS AND DOSE**
As adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line antianginal therapies

- **BY MOUTH**
  - Adult: Initially 375 mg twice daily for 2–4 weeks, then increased to 500 mg twice daily, then adjusted according to response to 750 mg twice daily; reduced if not tolerated to 375–500 mg twice daily
Cardiovascular system

**CONTRA-INDICATIONS**
- Selective Sinus Node Inhibitors

**MEDICINAL FORMS**
- Renal impairment: Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².
- Hepatic impairment: Use with caution in mild impairment; avoid in moderate and severe impairment.

**SIDE-EFFECTS**
- Common or very common: Asthenia, constipation, dizziness, headache, nausea, vomiting.
- Uncommon: Abdominal pain, anorexia, anxiety, chromatia, confusion, cough, dehydration, drowsiness, dry mouth, dyspepsia, dyspnea, dysuria, epistaxis, flatulence, haematuria, hallucination, hot flush, hypoaesthesia, hypotension, insomnia, joint swelling, lethargy, muscle cramp, pain in extremities, peripheral oedema, prolonged QT interval, pruritus, sweating, syncope, tinnitus, tremor, visual disturbance, weight loss.
- Rare: Allergic dermatitis, amnesia, angioedema, cold extremities, erectile dysfunction, erode duodenitis, impaired hearing, loss of consciousness, pancreatitis, parosmia, rash, renal failure, throat tightness, urticaria.

**PREGNANCY**
- Manufacturer advises avoid unless essential—no information available.

**BREAST FEEDING**
- Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT**
- Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**
- Patient alert card to be provided.

**NATIONAL FUNDING/ACCESS DECISIONS**
- Scottish Medicines Consortium (SMC) Decisions
  - The Scottish Medicines Consortium has advised (October 2012) that ranolazine (Ranexa®) is not recommended for use within NHS Scotland.

**INTERACTIONS**
- Appendix 1 (ranolazine).

**SIDE-EFFECTS**
- Common or very common: Atrial fibrillation or other arrhythmias (treatment ineffective); elderly, in angiina, consider stopping if there is no or limited symptom improvement after 3 months; intraventricular conduction defects—mild to moderate hypotension (avoid if severe); retinitis pigmentosa.

**SIDE-EFFECTS**
- Common or very common: Atrial fibrillation—blurred vision; bradycardia—dizziness; first-degree heart block—headache; parohemia—ventricular extrasystoles; visual disturbances.
- Uncommon: Angioedema, constipation, diarhoea, dyspnoea, eosinophilia, hyperuricaemia, muscle cramps, nausea, palpitations, raised plasma-creatinine concentration; rash; supraventricular extrasystoles; vertigo.
- Very rare: Second and third-degree heart block, sick sinus syndrome.

**PREGNANCY**
- Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**
- Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
- Manufacturer advises use with caution if eGFR less than 15 mL/minute/1.73 m²—no information available.

**MONITORING REQUIREMENTS**
- Monitor regularly for atrial fibrillation (consider benefits and risks of continued treatment if atrial fibrillation occurs).
- Monitor for bradycardia, especially after any dose increase, and discontinue if resting heart rate persistently below 50 beats per minute or continued symptoms of bradycardia despite dose reduction.

**NATIONAL FUNDING/ACCESS DECISIONS**
- NICE technology appraisals (TAs)
  - Ivabradine for the treatment of chronic heart failure (November 2012) NICE TA267
Ivabradine, in combination with standard therapy including a beta-blocker (unless contra-indicated or not tolerated), an ACE inhibitor, and an aldosterone antagonist, is an option for treating mild to severe stable chronic heart failure in patients who:
- have a left ventricular ejection fraction of ≤ 35%, and
- are in sinus rhythm with a heart rate of ≥75 beats per minute
Ivabradine should be initiated only by a heart failure specialist after 4 weeks of stable optimal standard therapy; monitoring and dose titration should be carried out by a heart failure specialist, or a GP with special interest in heart failure, or by a heart failure specialist nurse. www.nice.org.uk/TA267

**Scottish Medicines Consortium (SMC) Decisions**
- The Scottish Medicines Consortium has advised (September 2012) that ivabradine (Procoralan®) is accepted for restricted use within NHS Scotland in accordance with its licensed indication for heart failure only if resting heart rate remains ≥75 beats per minute despite optimal standard therapy.

**SELECTIVE SINUS NODE IF INHIBITORS**

**Ivabradine**

**INDICATIONS AND DOSE**
- Treatment of angina in patients in normal sinus rhythm
  - By mouth
  - Adult: Initially 5 mg twice daily for 3–4 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute
  - Elderly: Initially 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute

**Mild to severe chronic heart failure**
- By mouth
  - Adult: Initially 5 mg twice daily for 2 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute

**CONTRA-INDICATIONS**
- Acute myocardial infarction, cardiogenic shock, congenital QT syndrome, do not initiate for angina if heart rate below 70 beats per minute, do not initiate for chronic heart failure if heart rate below 75 beats per minute, immediately after cerebrovascular accident, patients dependent on pacemaker, second- and third-degree heart block, severe hypotension, sick-sinus syndrome, sino-atrial block, unstable angina, unstable or acute heart failure.

**INTERACTIONS**
- Appendix 1 (ivabradine).
Acute coronary syndromes

Overview

Acute coronary syndromes encompass a spectrum of conditions which include unstable angina, and myocardial infarction with or without ST-segment elevation. Patients with different acute coronary syndromes may present similarly; definitive diagnosis is made on the basis of clinical presentation, ECG changes, and measurement of biochemical cardiac markers.

Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)

These are related acute coronary syndromes that fall between the classifications of stable angina and ST-segment elevation myocardial infarction (STEMI). They usually occur as a result of atheromatous plaque rupture, and are often characterised by stable angina that suddenly worsens, recurring or prolonged angina at rest, or new onset of severe angina. Patients with unstable angina have no evidence of myocardial necrosis, whereas in NSTEMI, myocardial necrosis (less significant than with STEMI) will be evident. There is a risk of progression to STEMI or sudden death, particularly in patients who experience pain at rest.

Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)

These conditions are managed similarly; the aims of management are to provide supportive care and pain relief during the acute attack and to prevent further cardiac events and death. For advice on the management of patients with acute ST-segment elevation myocardial infarction (STEMI), see below.

Initial management

Oxygen should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hypoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

Nitrate(s) are used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 207 is not effective, intravenous or buccal glyceryl trinitrate or intravenous isosorbide dinitrate p. 208 is given. If pain continues, diamorphine hydrochloride p. 423 or morphine p. 429 can be given by slow intravenous injection; an antiemetic such as metoclopramide hydrochloride p. 403 should also be given.

Aspirin p. 114 (chewed or dispersed in water) is given for its antiplatelet effect. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel p. 115 should also be given. Prasugrel p. 203 is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance). Ticagrelor p. 204 is also an alternative to clopidogrel (see NICE guidance). Patients should also receive either heparin (unfractionated) p. 125, a low molecular weight heparin, or fondaparinux sodium p. 119.

Patients without contra-indications should receive beta-blockers which should be continued indefinitely. In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, diltiazem hydrochloride p. 148 or verapamil hydrochloride p. 155 can be given.

The glycoprotein IIb/IIIa inhibitors eptifibatide p. 198 (in combination with heparin (unfractionated) and aspirin) and tirofiban p. 199 (in combination with heparin (unfractionated), aspirin, and clopidogrel) can be used for unstable angina or for NSTEMI in patients at a high risk of either myocardial infarction or death.

7.1 Acute coronary syndromes

Nicorandil

Nicorandil (Non-proprietary)

Nicorandil 10 mg | 60 tablet | £7.71
DT price = £2.33
Nicorandil 20 mg | 60 tablet | £14.64
DT price = £4.54
Ikerol (Zeneca)

Nicorandil 10 mg | 60 tablet | £7.71 DT price = £2.33
Nicorandil 20 mg | 60 tablet | £14.64 DT price = £4.54
In intermediate- and high-risk patients, abciximab p. 198 or eptifibatide (in combination with heparin [unfractionated] and aspirin), or tirofiban (in combination with heparin [unfractionated], aspirin, and clopidogrel) can also be used in patients undergoing percutaneous coronary intervention, to reduce the immediate risk of vascular occlusion. In intermediate- and high-risk patients in whom early intervention is planned, bivalirudin p. 127 can be considered as an alternative to the combination of a glycoprotein IIb/IIIa inhibitor plus a heparin.

Revascularisation procedures are often appropriate for patients with unstable angina or NSTEMI; see Antiplatelet drugs p. 113 for the use of antiplatelet drugs in patients undergoing coronary stenting.

**Long-term management**

The need for long-term angina treatment or for coronary angiography should be assessed. Most patients will require standard angina treatment to prevent recurrence of symptoms.

**ST-segment elevation myocardial infarction (STEMI)**

This is an acute coronary syndrome where atheromatous plaque rupture leads to thrombosis and myocardial ischaemia, with irreversible necrosis of the heart muscle, often leading to long-term complications. STEMI can also occasionally occur as a result of coronary spasm or embolism, arteritis, spontaneous thrombosis, or sudden severe elevation in blood pressure.

**Management of ST-segment elevation myocardial infarction (STEMI)**

These notes give an overview of the initial and long-term management of myocardial infarction with ST segment elevation (STEMI). For advice on the management of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina, see above. The aims of management of STEMI are to provide supportive care and pain relief, to promote reperfusion and to reduce mortality. Oxygen, nitrates, and dexamethasone hydrochloride or morphine can provide initial support and pain relief; aspirin and percutaneous coronary intervention or thrombolitics promote reperfusion; anticoagulants help to reduce re-occlusion and systemic embolisation; long-term use of aspirin, beta-blockers, ACE inhibitors, and statins help to reduce mortality further.

Local guidelines for the management of myocardial infarction should be followed where they exist.

**Initial management**

**Oxygen** should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hypoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

The pain (and anxiety) of myocardial infarction is managed with slow intravenous injection of dexamethasone hydrochloride or morphine; an antiemetic such as hydrochloride or morphine; an antiemetic such as hydrochloride, or a benzodiazepine such as midazolam, can be used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 207 is not effective, intravenous glyceryl trinitrate or isosorbide dinitrate p. 208 is given.

Early administration of an **ACE inhibitor**, and angiotensin-II receptor antagonists if an ACE inhibitor cannot be used, are also of benefit to patients who have no contra-indications; in hypertensive and normotensive patients treatment with an ACE inhibitor, or an angiotensin-II receptor antagonist, can be started within 24 hours of the myocardial infarction and continued for at least 5–6 weeks (see below for long-term treatment). All patients should be closely monitored for hyperglycaemia; those with diabetes or raised blood-glucose concentration should receive insulin p. 652.

**Long-term management**

Long-term management following STEMI involves the use of several drugs which should ideally be started before the patient is discharged from hospital.

Aspirin p. 114 should be given to all patients, unless contra-indicated. The addition of clopidogrel p. 115 has been shown to reduce morbidity and mortality. Prasugrel p. 203 or ticagrelor p. 204 are alternatives to clopidogrel in certain patients. For those intolerant of clopidogrel, and who are at low risk of bleeding, the combination of warfarin sodium p. 131 and aspirin should be considered. In those intolerant of both aspirin and clopidogrel, warfarin sodium alone can be used. Warfarin sodium should be continued for those who are already being treated for another indication, such as atrial fibrillation, with the addition of aspirin if there is a low risk of bleeding. The combination of aspirin with clopidogrel or warfarin sodium increases the risk of bleeding. Low-dose rivaroxaban p. 120, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following STEMI—see Prevention of cardiovascular events. For details of antiplatelet drug duration following coronary stenting—see also Antiplatelet drugs and coronary stents in Antiplatelet drugs p. 113.

**Beta-blockers** should be given to all patients in whom they are not contra-indicated. Acebutolol p. 143, metoprolol tartrate p. 145, propranolol hydrochloride p. 142 and timolol maleate p. 142 are suitable; for patients with left ventricular dysfunction, carvedilol p. 139, bisoprolol fumarate p. 144, or long-acting metoprolol tartrate may be appropriate.

Diltiazem hydrochloride p. 148 [unlicensed] or verapamil hydrochloride p. 155 can be considered if a beta-blocker cannot be used; however, they are contra-indicated in those with left ventricular dysfunction. Other calcium–channel blockers have no place in routine long-term management after a myocardial infarction.

An **ACE inhibitor** should be considered for all patients, especially those with evidence of left ventricular damage. Patients undergoing percutaneous coronary intervention should also receive either heparin (unfractionated) or a low molecular weight heparin (e.g. enoxaparin sodium p. 124); bivalirudin is an alternative to the combination of a glycoprotein IIb/IIIa inhibitor plus a heparin (see also NICE guidance). In patients who cannot be offered percutaneous coronary intervention within 90 minutes of diagnosis, a thrombolytic drug should be administered along with either heparin (unfractionated) (for maximum 2 days), a low molecular weight heparin (e.g. enoxaparin sodium), or fondaparinux sodium. See use of antiplatelet drugs in patients undergoing coronary stenting in Antiplatelet drugs p. 113.

Patients who do not receive reperfusion therapy (with percutaneous coronary intervention or a thrombolytic) should be treated with either fondaparinux sodium, enoxaparin sodium, or heparin (unfractionated). Prescribers should consult product literature and local protocols (where they exist) for details of anticoagulant dose and duration. Nitrates are used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 207 is not effective, intravenous glyceryl trinitrate or isosorbide dinitrate p. 208 is given.

ACE inhibitors, and angiotensin-II receptor antagonists if an ACE inhibitor cannot be used, are also of benefit to patients who have no contra-indications; in hypertensive and normotensive patients treatment with an ACE inhibitor, or an angiotensin-II receptor antagonist, can be started within 24 hours of the myocardial infarction and continued for at least 5–6 weeks (see below for long-term treatment).
dysfunction. If an ACE inhibitor cannot be used, an angiotensin-II receptor antagonist may be used for patients with heart failure. A relatively high dose of either the ACE inhibitor or angiotensin-II receptor antagonist may be required to produce benefit.

Nitrites are used for patients with angina.

Eplerenone p. 180 is licensed for use following a myocardial infarction in those with left ventricular dysfunction and evidence of heart failure.

See also the role of statins in preventing recurrent cardiovascular events in Lipid-regulating drugs p. 183.

**Prevention of cardiovascular events**

Patients with stable angina, unstable angina, or NSTEMI should be given advice and treatments to reduce their cardiovascular risk. The importance of lifestyle changes, especially stopping smoking, should be emphasised. Aspirin should be given indefinitely. Antihypertensive treatment should be initiated if appropriate, and a statin should also be given.

In patients with stable angina, addition of an ACE inhibitor should be considered for patients with diabetes (and should be continued if indicated for a co-morbidity).

In patients with unstable angina or NSTEMI, clopidogrel is given, in combination with aspirin, for up to 12 months—most benefit occurs during the first 3 months. Prasugrel or ticagrelor are alternatives to clopidogrel in certain patients. An ACE inhibitor should also be given.

Low-dose rivaroxaban, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers.

### Other drugs used for Acute coronary syndromes

- Captopril, p. 159
- Dalteparin sodium, p. 123
- Lisinopril, p. 161
- Perindopril arginine, p. 162
- Perindopril erbumine, p. 163
- Ramipril, p. 164
- Trandolapril, p. 165
- Valsartan, p. 170

### ANTITHROMBOTIC DRUGS > ANTIPLATELET DRUGS

#### Prasugrel

- **INDICATIONS AND DOSE**
  - In combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention
    - **BY MOUTH**
    - Adult 18–74 years (body-weight up to 60 kg): Initially 60 mg for 1 dose, then 5 mg once daily usually for up to 12 months
    - Adult 18–74 years (body-weight 60 kg and above): Initially 60 mg for 1 dose, then 10 mg once daily usually for up to 12 months
    - Adult 75 years and over: Initially 60 mg for 1 dose, then 5 mg once daily usually for up to 12 months
  - Patients undergoing coronary angiography within 48 hours of admission for unstable angina or NSTEMI
    - **BY MOUTH**
    - Adult: Loading dose 60 mg, not to be administered until the time of percutaneous coronary intervention in order to minimise the risk of bleeding, maintenance dose of 10 mg or 5 mg daily should then be selected as appropriate based on age and weight
  - Alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention
    - **BY MOUTH**
    - Adult: 60 mg, as a single dose

- **CONTRA-INDICATIONS** Active bleeding - history of stroke or transient ischaemic attack
- **CAUTIONS** Body-weight less than 60 kg - discontinue at least 7 days before elective surgery if antiplatelet effect not desirable - elderly - patients at increased risk of bleeding (e.g. from recent trauma, surgery, gastro-intestinal bleeding, or active peptic ulcer disease)
- **INTERACTIONS** Appendix 1 (prasugrel). Caution with concomitant use of drugs that increase risk of bleeding.
- **SIDE-EFFECTS**
  - Common or very common: Anaemia - gastro-intestinal haemorrhage - haematoma - haematuria - haemorrhage - intracranial haemorrhage - rash
  - Uncommon: Angioedema - hypersensitivity reactions
  - Rare: Thrombocytopenia
  - Frequency not known: Thrombotic thrombocytopenic purpura
- **ALLERGY AND CROSS-SENSITIVITY** Caution in patients with history of hypersensitivity reactions to thienopyridines (e.g. clopidogrel).
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Use with caution in moderate impairment—increased risk of bleeding. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Use with caution—increased risk of bleeding.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (July 2014) NICE TA317
  - Prasugrel 10 mg in combination with aspirin is recommended as an option, within its marketing authorisation, for preventing atherothrombotic events in adults with acute coronary syndrome (unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI)) having primary or delayed percutaneous coronary intervention.
  - [www.nice.org.uk/TA317](http://www.nice.org.uk/TA317)

- **Scottish Medicines Consortium (SMC) Decisions**
  - The Scottish Medicines Consortium has advised (August 2009) that prasugrel (Efient®), in combination with aspirin, be accepted for restricted use within NHS Scotland for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention who are eligible to receive the 10 mg dose of prasugrel.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

#### Table

- **Efient** (Eli Lilly and Company Ltd)
  - Prasugrel (as Prasugrel hydrochloride) 5 mg | Efient 5mg tablets | 28 tablet [Pack] | £47.56 DT price = £47.56
  - Prasugrel (as Prasugrel hydrochloride) 10 mg | Efient 10mg tablets | 28 tablet [Pack] | £47.56 DT price = £47.56
204 Myocardial ischaemia

Ticagrelor

- **INDICATIONS AND DOSE**
  - In combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome
    - **BY MOUTH**
    - Adult: Initially 180 mg for 1 dose, then 90 mg twice daily usually for up to 12 months
  - **Alternative to clopidogrel in patients undergoing percutaneous coronary intervention**
    - **BY MOUTH**
    - Adult: 180 mg, as a single dose

- **CONTRA-INDICATIONS**
  - Active bleeding - history of intracranial haemorrhage
  - **CAUTIONS**
    - Asthma - bradycardia (unless pacemaker fitted)
    - chronic obstructive pulmonary disease - discontinue 7 days before elective surgery if antiplatelet effect not desirable - history of hyperuricaemia - patients at increased risk of bleeding (e.g. from recent trauma, surgery, gastrointestinal bleeding, or coagulation disorders) - second- or third-degree AV block (unless pacemaker fitted) - sick sinus syndrome (unless pacemaker fitted)
  - **INTERACTIONS**
    - Caution with concomitant use of drugs that increase risk of bleeding.
  - **SIDE-EFFECTS**
    - Common or very common
      - Bruising • dyspnoea • haemorrhage
    - Uncommon
      - Abdominal pain • diarrhoea • dizziness • dyspepsia • gastritis • headache • nausea • pruritus • rash • vomiting
    - Rare
      - Confusion • constipation • hyperuricaemia • paraesthesia • raised serum creatinine • vertigo
  - **PREGNANCY**
    - Manufacturer advises avoid — toxicity in animal studies.
  - **BREAST FEEDING**
    - Manufacturer advises avoid — present in milk in animal studies.
  - **HEPATIC IMPAIRMENT**
    - Avoid in moderate or severe impairment — no information available.
  - **MONITORING REQUIREMENTS**
    - Monitor renal function 1 month after initiation.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - NICE technology appraisals (TAs)
      - Ticagrelor for the treatment of acute coronary syndromes (October 2011) NICE TA236

Ticagrelor, in combination with low-dose aspirin, is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes, that is, people:
- with ST-segment elevation myocardial infarction — defined as ST elevation or new left bundle branch block on electrocardiogram — that cardiologists intend to treat with primary percutaneous coronary intervention, or
- with non-ST-segment elevation myocardial infarction (NSTEMI), or
- admitted to hospital with unstable angina — defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined below. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist. Characteristics to be used in defining treatment with ticagrelor for unstable angina are:
  - age 60 years or older;
  - previous myocardial infarction or previous coronary artery bypass grafting;
  - coronary artery disease with stenosis of 50% or more in at least two vessels;
  - previous ischaemic stroke;
- previous transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation;
- diabetes mellitus;
- peripheral arterial disease, or
- chronic arterial disease, or
- chronic renal dysfunction (creatinine clearance less than 60 mL/minute/1.73 m²).

www.nice.org.uk/TA236

- **M EDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Brilique (AstraZeneca UK Ltd)
      - Ticagrelor 60 mg Brilique 60mg tablets | 56 tablet Pkt £54.60 DT price = £54.60
      - Ticagrelor 90 mg Brilique 90mg tablets | 56 tablet Pkt £54.60 DT price = £54.60

ANTITHROMBOTIC DRUGS > TISSUE PLASMINOGEN ACTIVATORS

Fibrinolytic drugs

**Overview**

The value of thrombolytic drugs for the treatment of myocardial infarction has been established. Streptokinase p. 206 and alteplase p. 205 have been shown to reduce mortality. Retepcase p. 205 and tenecteplase p. 206 are also licensed for acute myocardial infarction. Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment. Trials have shown that the benefit is greatest in those with ECG changes that indicate ST segment elevation (especially in those with anterior infarction) and in patients with bundle branch block. Patients should not be denied thrombolytic treatment on account of age alone because mortality in the elderly is high and the reduction in mortality is the same as in younger patients. Alteplase should be given within 6–12 hours of symptom onset, reteplase and streptokinase within 12 hours of symptom onset, but ideally all should be given within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given as early as possible and usually within 6 hours of symptom onset.

Alteplase, streptokinase and urokinase p. 129 can be used for other thromboembolic disorders such as deep-vein thrombosis and pulmonary embolism. Alteplase is also used for acute ischaemic stroke.

Urokinase is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.

Fibrinolytics

- **DRUG ACTION**
  - Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

- **CONTRA-INDICATIONS**
  - Active pulmonary disease with cavitation • acute pancreatitis • aneurysm • aortic dissection • bacterial endocarditis • bleeding diatheses • coagulation defects •coma • heavy vaginal bleeding • history of cerebrovascular disease (especially recent events or with any residual disability) • oesophageal varices • pericarditis • recent haemorrhage • recent surgery (including dental extraction) • recent symptoms of possible peptic ulceration • recent trauma • severe hypertension

- **CAUTIONS**
  - Conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation) • elderly • external chest compression • hypertension • risk of bleeding (including that from venepuncture or invasive procedures)
Alteplase
(rt-PA; Tissue-type plasminogen activator)

**INDICATIONS AND DOSE**

**Acute myocardial infarction, accelerated regimen**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult (body-weight up to 65 kg): Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 0.75 mg/kg, to be given over 30 minutes, then (by intravenous infusion) 0.5 mg/kg, to be given over 60 minutes, maximum total dose of 100 mg administered over 90 minutes
  - Adult (body-weight 65 kg and above): Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 30 minutes, then (by intravenous infusion) 35 mg, to be given over 60 minutes, maximum total dose of 100 mg administered over 90 minutes

**Acute myocardial infarction**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 10 mg, to be initiated within 6–12 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 60 minutes, then (by intravenous infusion) 10 mg for 4 infusions, each 10 mg infusion dose to be given over 30 minutes, total dose of 100 mg over 3 hours; maximum 1.5 mg/kg in patients less than 65 kg

**Pulmonary embolism**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 10 mg, to be given over 1–2 minutes, followed by (by intravenous infusion) 90 mg, to be given over 2 hours, maximum 1.5 mg/kg in patients less than 65 kg

**Acute ischaemic stroke (under specialist neurology physician only)**

- **BY INTRAVENOUS INJECTION**
  - Adult 18–79 years: Initially 900 micrograms/kg (max. per dose 90 mg), treatment must begin within 4.5 hours of symptom onset, to be given over 60 minutes, the initial 10% of dose is to be administered by intravenous injection and the remainder by intravenous infusion

**ACTILYSE CATHFLO®**

Thrombolytic treatment of occluded central venous access devices (including those used for haemodialysis)

- **BY INTRAVENOUS INJECTION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS**

- When used for acute ischaemic stroke Convulsion accompanying stroke; history of stroke in patients with diabetes; hyperglycaemia; hypoglycaemia; severe stroke; stroke in last 3 months

**INTERACTIONS**

- Contra-indicated if concomitant treatment with oral anticoagulants.

**SIDE-EFFECTS**

- Risk of cerebral bleeding increased in acute stroke

**ALLERGY AND CROSS-SENSITIVITY**

- Contra-indicated if history of hypersensitivity to gentamicin (residue from manufacturing process).

**MONITORING REQUIREMENTS**

- When used for acute ischaemic stroke Monitor for intracranial haemorrhage, and monitor blood pressure (antihypertensive recommended if systolic above 180 mmHg or diastolic above 105 mmHg).

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Actilyse®), give intermittently or continuously in Sodium chloride 0.9%; dissolve in water for injections to a concentration of 1 mg/mL or 2 mg/mL and infuse intravenously; alternatively dilute the solution further in the infusion fluid to a concentration of not less than 200 micrograms/mL; not to be infused in glucose solution.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Alteplase for the treatment of acute ischaemic stroke (September 2012) NICE TA264

Alteplase is recommended for the treatment of acute ischaemic stroke in adults in accordance with its licensed indication if:

- treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and
- intracranial haemorrhage has been excluded by appropriate imaging techniques.

www.nice.org.uk/TA264

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Powder and solvent for solution for injection**

- **Actilyse** (Boehringer Ingelheim Ltd)
  - Alteplase 10 mg Actilyse 10mg powder and solvent for solution for injection vials | 1 vial (PST) £144.00
  - Alteplase 20 mg Actilyse 20mg powder and solvent for solution for injection vials | 1 vial (PST) £216.00
- **Actilyse Cathflo** (Boehringer Ingelheim Ltd)
  - Alteplase 2 mg Actilyse Cathflo 2mg powder and solvent for solution for injection vials | 5 vial (PST) £225.00 (Hospital only)

**Powder and solvent for solution for infusion**

- **Actilyse** (Boehringer Ingelheim Ltd)
  - Alteplase 50 mg Actilyse 50mg powder and solvent for solution for infusion vials | 1 vial (PST) £360.00

Retepase

**INDICATIONS AND DOSE**

**Acute myocardial infarction**

- **BY INTRAVENOUS INJECTION**
  - Adult: 10 units, initiated within 12 hours of onset of symptoms, dose to be given over not more than 2 minutes, followed by 10 units after 30 minutes

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**HEPATIC IMPAIRMENT**

Avoid in severe hepatic impairment as there is an increased risk of bleeding.

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**SIDE-EFFECTS**

- Allergic reactions · anaphylaxis · angina (when used in myocardial infarction) · back pain · bleeding · bleeding (usually limited to the site of injection, but can occur from other sites) · cerebral oedema (caused by reperfusion) · convulsions · fever · flushing · hypotension · intracerebral haemorrhage · nausea · pulmonary oedema (caused by reperfusion) · rash · recurrent ischaemia (when used in myocardial infarction) · reperfusion arrhythmias (when used in myocardial infarction) · uveitis · vomiting

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**SIDE-EFFECTS, FURTHER INFORMATION**

- Bleeding: Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antibrinolytic drugs (e.g. tranexamic acid). Rarely further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli).

- Hypotension: Hypotension can usually be controlled by elevating the patient’s legs, or by reducing the rate of infusion or stopping it temporarily.

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**PREGNANCY**

Thrombolytic drugs can possibly lead to thrombus or to cholesterol crystal emboli). Rarely further embolism may occur from other sites). Acute ischaemic stroke (under specialist neurology physician only).
**BREAST FEEDING** Manufacturer advises avoid breastfeeding for 24 hours after dose (express and discard milk during this time).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

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**Streptokinase**

**INDICATIONS AND DOSE**

**Acute myocardial infarction**

- BY INTRAVENOUS INFUSION
  - Adult: 1,500,000 units, to be initiated within 12 hours of symptom onset, dose to be given over 60 minutes

**Deep-vein thrombosis | Pulmonary embolism | Acute arterial thromboembolism | Central retinal venous or arterial thrombosis**

- BY INTRAVENOUS INFUSION
  - Adult: 250,000 units, dose to be given over 30 minutes, then 100,000 units every 1 hour for up to 12–72 hours, duration is adjusted according to condition with monitoring of clotting parameters (consult product literature)

**SIDE-EFFECTS**

- Rare Guillain-Barré syndrome

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if previous allergic reaction to either streptokinase or anistreplase (no longer available). Prolonged persistence of antibodies to streptokinase and anistreplase (no longer available). Prolonged persistence of antibodies to streptokinase and anistreplase (no longer available). There can be variation in the licensing of different medicines containing the same drug.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- Streptokinase 1,500,000 unit powder for solution for infusion vials | 1 vial | £85.44
- Streptokinase 250,000 unit powder for solution for infusion vials | 1 vial | £15.91
- Streptokinase 750,000 unit powder for solution for infusion vials | 1 vial | £41.72

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**Tenecteplase**

**INDICATIONS AND DOSE**

**Acute myocardial infarction**

- BY INTRAVENOUS INJECTION
  - Adult: 30–50 mg (max. pass dose 50 mg), dose to be given over 10 seconds and Initiated within 6 hours of symptom onset, dose varies according to body weight—consult product literature

**BREAST FEEDING** Manufacturer advises avoid breastfeeding for 24 hours after dose (express and discard milk during this time).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- Metalyse (Boehringer Ingelheim Ltd)
  - Tenecteplase 8,000 unit powder and solvent for solution for injection vials | 1 vial | £50.25
  - Tenecteplase 10,000 unit powder and solvent for solution for injection vials | 1 vial | £50.25

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**NITRATES**

**Nitrates**

**Overview**

Nitrates have a useful role in angina. Although they are potent coronary vasodilators, their principal benefit follows from a reduction in venous return which reduces left ventricular work. Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially when angina is severe or when patients are unusually sensitive to the effects of nitrates.

Sublingual glyceryl trinitrate p. 207 is one of the most effective drugs for providing rapid symptomatic relief of angina, but its effect lasts only for 20 to 30 minutes; the 300-microgram tablet is often appropriate when glyceryl trinitrate is first used. The aerosol spray provides an alternative method of rapid relief of symptoms for those who find difficulty in dissolving sublingual preparations. Duration of action may be prolonged by modified-release preparations (but tolerance may develop).

Isosorbide dinitrate p. 208 is active sublingually and is a more stable preparation for those who only require nitrates infrequently. It is also effective by mouth for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action of up to 12 hours is claimed for modified-release preparations. The activity of isosorbide dinitrate may depend on the production of active metabolites, the most important of which is isosorbide mononitrate p. 209. Isosorbide mononitrate itself is also licensed for angina prophylaxis; modified-release formulations (for once daily administration) are available.

Glyceryl trinitrate or isosorbide dinitrate may be tried by intravenous injection when the sublingual form is ineffective in patients with chest pain due to myocardial infarction or severe ischaemia. Intravenous injections are also useful in the treatment of congestive heart failure.

**Nitrates**

**CONTRA-INDICATIONS** Aortic stenosis | cardiac tamponade | constrictive pericarditis | hypertrophic cardiomyopathy | hypertensive conditions | hypovolaemia | marked anaemia | mitral stenosis | raised intracranial pressure due to cerebral haemorrhage | raised intracranial pressure due to head trauma | toxic pulmonary oedema

**CAUTIONS** Heart failure due to obstruction | hypothermia | hypothyroidism | hypoxaemia | malnutrition | metal-containing transdermal systems should be removed before magnetic resonance imaging procedures, cardioversion, or diathermy | recent history of myocardial infarction | susceptibility to angle-closure glaucoma | tolerance | ventilation and perfusion abnormalities

**Tolerance** Many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 12 hours each day usually maintains effectiveness in such patients. If tolerance is suspected during the use of transdermal patches they should be left off for 8–12 hours (usually...
Glyceryl trinitrate

INDICATIONS AND DOSE
Prophylaxis and treatment of angina
- By sublingual administration using sublingual tablets
  - Adult: 0.3–1 mg, dose may be repeated as required
Control of hypertension and myocardial ischaemia during and after cardiac surgery | Induction of controlled hypotension during surgery | Congestive heart failure | Unstable angina
- By intravenous infusion
  - Adult: 10–200 micrograms/minute (max. per dose 400 micrograms/minute), adjusted according to response, consult product literature for recommended starting doses specific to indication
Treatment or prophylaxis of angina
- By sublingual administration using aerosol spray
  - Adult: 1–2 sprays, dose be administered under tongue and then close mouth

SIDE-EFFECTS
- With rectal use Burning · diarrhoea · itching · rectal bleeding
- With intravenous use For intravenous infusion (Nitrocine®, Nitronal®), give continuously in Glucose 5% or Sodium Chloride 0.9%. For Nitrocine®, suggested infusion concentration 100 micrograms/mL; incompatible with polyvinyl chloride infusion containers such as Viaflex® or ACTIVIA®

BREAST FEEDING
No information available among manufacturers advise use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT
Caution in severe impairment.

RENAL IMPAIRMENT
Manufacturers advise use with caution in severe impairment.

MONITORING REQUIREMENTS
Monitor blood pressure and heart rate during intravenous infusion.

TREATMENT CESSATION
Avoid abrupt withdrawal.

Anal fissure
- By rectum using ointment
  - Adult: Apply 2.5 centimetres every 12 hours until pain stops. Max. duration of use 8 weeks, apply to anal canal, 2.5 cm of ointment contains 1.5 mg of glyceryl trinitrate

DEPONIT®
Prophylaxis of angina
- By transdermal application
  - Adult: One ‘5’ or one ‘10’ patch to be applied to lateral chest wall, upper arm, thigh, abdomen, or shoulder; increase to two ‘10’ patches every 24 hours if necessary, to be replaced every 24 hours, sitting replacement patch on different area

MINITRAN®
Prophylaxis of angina
- By transdermal application
  - Adult: One ‘5’ patch to be applied to chest or upper arm; replace every 24 hours, sitting replacement patch on different area, dose to be adjusted according to response

Maintenance of venous patency (‘5’ patch only)
- By transdermal application
  - Adult: (consult product literature)

NITRO-DUR®
Prophylaxis of angina
- By transdermal application
  - Adult: One ‘0.2mg/h’ patch to be applied to chest or outer upper arm and replaced every 24 hours, sitting replacement patch on different area, dose adjusted according to response; maximum 15 mg per day

PERCUTOL®
Prophylaxis of angina (to determine dose)
- To the skin
  - Adult: Usual dose 1–2 inches every 3–4 hours as required, to be measured on to Applirule® and applied (usually to chest, arm, or thigh) without rubbing in and secured with surgical tape, approx. 800 micrograms/hour absorbed from 1 inch of ointment.

Transdermal-Nitro®
Prophylaxis of angina
- By transdermal application
  - Adult: One ‘5’ or one ‘10’ patch to be applied to lateral chest wall and replaced every 24 hours, sitting replacement patch on different area, max. two ‘10’ patches daily

Prophylaxis of phlebitis and extravasation (‘5’ patch only)
- By transdermal application
  - Adult: (consult product literature)

DIRECTIONS FOR ADMINISTRATION
- With intravenous use For intravenous infusion (Nitrocine®, Nitronal®), give continuously in Glucose 5% or Sodium Chloride 0.9%. For Nitrocine®, suggested infusion concentration 100 micrograms/mL; incompatible with polyvinyl chloride infusion containers such as Viaflex® or ACTIVIA®
Nitrocine®; use glass or polyethylene containers or give via a syringe pump.

- With intravenous use Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used. Glyceryl trinitrate 1 mg/ml to be diluted before use or given undiluted with syringe pump. Glyceryl trinitrate 5 mg/ml to be diluted before use.

**PRESCRIBING AND DISPENSING INFORMATION**

- With sublingual use Glyceryl trinitrate tablets should be supplied in glass containers of not more than 100 tablets, closed with a foil-lined cap, and containing no cotton wool wadding; they should be discarded after 8 weeks in use.

**PATIENT AND CARER ADVICE** Rectal ointment should be discarded 8 weeks after first opening.

**PERCUTOL®** Patients or carers should be given advice on how to administer glyceryl trinitrate ointment.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (January 2008) that glyceryl trinitrate 0.4% ointment (Rectogesic®) is not recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

### Sublingual tablet

- **Glyceryl trinitrate (Non-proprietary)**
  - Glyceryl trinitrate 300 microgram sublingual tablets | 100 tablet
  - Glyceryl trinitrate 500 microgram sublingual tablets | 100 tablet
  - Glyceryl trinitrate 600 microgram sublingual tablets | 100 tablet

### Sublingual spray

- **Glyceryl trinitrate (Non-proprietary)**
  - Glyceryl trinitrate 400 microgram per 1 dose
  - Glyceryl trinitrate 400 micrograms/dose pump sublingual spray | 180 dose
  - Glyceryl trinitrate 500 microgram sublingual spray | 100 dose
  - Glyceryl trinitrate 600 microgram sublingual spray | 100 dose

### Transdermal patch

- **Nitronal** (Merck Serono Ltd)
  - Glyceryl trinitrate 1 mg per 1 ml Nitronal 5mg/5ml solution for infusion ampoules | 10 ampoule
  - Nitronal 50mg/50ml solution for infusion vials | 1 vial

### Transdermal ointment

- **Deponit** (UCB Pharma Ltd)
  - Glyceryl trinitrate 5 mg per 24 hour Deponit 5 transdermal patches | 28 patch
  - Glyceryl trinitrate 10 mg per 24 hour Deponit 10 transdermal patches | 28 patch

- **Minitrans** (Meda Pharmaceuticals Ltd)
  - Glyceryl trinitrate 5 mg per 24 hour Minitran 5 transdermal patches | 30 patch

- **Transderm-Nitro** (Novartis Pharmaceuticals UK Ltd)
  - Glyceryl trinitrate 5 mg per 24 hour Transderm-Nitro 5 transdermal patches | 28 patch

### Ointment

- **Excipients**: May contain Wool fat and related substances including lanolin

- **Percutol** (Aspire Pharma Ltd)
  - Glyceryl trinitrate 20 mg per 1 gram Percutol 2% ointment | 60 gram

### Rectal ointment

- **Excipients**: May contain Propylene glycol, wool fat and related substances including lanolin

- **Rectogesic** (Kyowa Kirin Ltd)
  - Glyceryl trinitrate 4 mg per 1 gram Rectogesic 0.4% rectal ointment | 30 gram

### Isosorbine dinitrate

**INDICATIONS AND DOSE**

Prophylaxis and treatment of angina

- **By mouth using immediate-release medicines**
  - Adult: 30–120 mg daily in divided doses

- **By INTRAVENOUS INFUSION**
  - Adult: 2–10 mg/hour, increased if necessary up to 20 mg/hour

**Left ventricular failure**

- **By mouth using immediate-release medicines**
  - Adult: 40–160 mg daily in divided doses, increased if necessary up to 240 mg daily in divided doses

- **By INTRAVENOUS INFUSION**
  - Adult: Initially 2–10 mg/hour, increased if necessary up to 20 mg/hour

**Prophylaxis of angina**

- **By mouth using modified-release medicines**
  - Adult: 40 mg daily in 1–2 divided doses, increased if necessary to 60–80 mg daily in 2–3 divided doses

**PREGNANCY** May cross placenta—manufacturers advise avoid unless potential benefit outweighs risk.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Isoket 0.05%, Isoket 0.1%) give continuously in Glucose 5% or Sodium chloride 0.9%. Adsorbed to some extent by polyvinyl chloride infusion containers; preferably use glass or polyethylene containers or give via a syringe pump; Isoket 0.05% can alternatively be administered undiluted using a syringe pump with a glass or rigid plastic syringe. Glass or polyethylene infusion apparatus is preferable; loss of potency if PVC used.
MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

- **Isosorbide dinitrate (Non-proprietary)**
  - Isosorbide dinitrate 10 mg Isosorbide dinitrate 10mg tablets | 56 tablet | £13.41 DT price = £13.41
  - Isosorbide dinitrate 20 mg Isosorbide dinitrate 20mg tablets | 56 tablet | £14.38 DT price = £14.38

Modified-release tablet

- **Isosorbide dinitrate (Non-proprietary)**
  - Isosorbide dinitrate 20 mg Isosorbide dinitrate 20mg modified-release tablets | 56 tablet | no price available DT price = £2.58
  - Isosorbide dinitrate 40 mg Isosorbide dinitrate 40mg modified-release tablets | 56 tablet | no price available DT price = £6.36

- **Isoket Retard (UCB Pharma Ltd)**
  - Isoket Retard 20 mg Isoket Retard 20 tablets | 56 tablet | £2.58 DT price = £2.58
  - Isoket Retard 40 mg Isoket Retard 40 tablets | 56 tablet | £6.36 DT price = £6.36

Solution for injection

- **Isosorbide dinitrate (Non-proprietary)**
  - Isosorbide dinitrate 1 mg per 1 ml Isosorbide dinitrate 1mg/1ml concentrate for solution for injection ampoules | 10 ampoule | £21.80
  - Isoket (UCB Pharma Ltd)
  - Isosorbide dinitrate 1 mg per 1 ml Isoket 0.1% solution for injection 10ml ampoules | 10 ampoule | £26.93 (Hospital only)

Solution for infusion

- **Isosorbide dinitrate (Non-proprietary)**
  - Isosorbide dinitrate 1 mg per 1 ml Isosorbide dinitrate 50mg/50ml concentrate for solution for infusion vials | 10 vial | £66.50
  - Isosorbide dinitrate 25mg/50ml solution for infusion vials | 10 vial | £50.40

Isosorbide mononitrate

- **INDICATIONS AND DOSE**

**Prophylaxis of angina | Adjunct in congestive heart failure**

- **By mouth using immediate-release medicines**
  - Adult: Initially 20 mg 2–3 times a day, alternatively initially 40 mg twice daily, increased if necessary up to 120 mg daily in divided doses

**Prophylaxis of angina (for patients who have not previously had a nitrate) | Adjunct in congestive heart failure (for patients who have not previously had a nitrate)**

- **By mouth using immediate-release medicines**
  - Adult: Initially 10 mg twice daily, increased if necessary up to 120 mg daily in divided doses

CHEMYDUR® 60XL

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 0.5 tablet daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet daily, increased if necessary to 2 tablets daily, dose to be taken in the morning

ELANTAN® LA

**Prophylaxis of angina**

- **By mouth**
  - Adult: 25–50 mg once daily, then increased if necessary to 50–100 mg once daily, dose to be taken in the morning, the lowest effective dose should be used

IMDUR®

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 0.5 tablet once daily, to minimise the occurrence of headache, then 1 tablet once daily, then increased if necessary to 2 tablets once daily, dose to be taken in the morning

ISIB® 60XL

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 0.5 tablet once daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

ISONER®

**Prophylaxis of angina**

- **By mouth**
  - Adult: 25–50 mg once daily, then increased if necessary to 50–100 mg once daily, dose to be taken in the morning

ISOMA®

**Prophylaxis of angina**

- **By mouth**
  - Adult: 25–60 mg once daily, if headaches occur with 60 mg tablet, half a 60 mg tablet may be given for 2–4 days, then increased if necessary to 50–120 mg once daily, dose to be taken in the morning

MOSA® XL

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 0.5 tablet once daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

MOSA® SR

**Prophylaxis of angina**

- **By mouth**
  - Adult: 40–60 mg daily, increased if necessary to 120 mg daily, dose to be taken in the morning

MOSA® XL

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 0.5 tablet once daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

MONOSORB® XL60

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 0.5 tablet daily for the first 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

ZEMON®

**Prophylaxis of angina**

- **By mouth**
  - Adult: Initially 30 mg once daily for 2–4 days, to minimise the occurrence of headache, then 40–60 mg once daily, increased if necessary to 80–120 mg once daily, dose to be taken in the morning
**SYMPATHOMIMETICS > INOTROPIC**

### Dobutamine

- **DRUG ACTION** Dobutamine is a cardiac stimulant which acts on beta, receptors in cardiac muscle, and increases contractility with little effect on rate.

- **INDICATIONS AND DOSE**
  - **Inotropic support in infarction, cardiac surgery, cardiomyopathies, septic shock, cardiogenic shock, and during positive end expiratory pressure ventilation**
  - **BY INTRAVENOUS INFUSION**
    - **Adult:** Usual dose 2.5–10 micrograms/kg/minute, adjusted according to response, alternatively 0.5–40 micrograms/kg/minute

- **Cardiac stress testing**
  - **BY INTRAVENOUS INFUSION**
  - **Adult:** (consult product literature)

- **CONTRA-INDICATIONS** Phaeochromocytoma

- **CAUTIONS**
  - Acute heart failure - acute myocardial infarction
  - Arrhythmias - correct hypercapnia before starting and during treatment
  - Cardiac surgery
  - Cardiomyopathies
  - Septic shock
  - Cardiogenic shock
  - Myocardial infarction
  - Hypervolaemia
  - Pulmonary oedema
  - Angle-closure glaucoma
  - Myocardial infarction
  - Cardiac biopsy
  - Cardiac sarcoma
  - Cardiac neoplasm

- **SIDE-EFFECTS**
  - Rare Psychosis
  - Very rare Angina
  - Heartburn
  - Myocardial infarction
  - Cardiac collapse
  - Cardiac arrest
  - Coronary artery spasm
  - Hypokalaemia
  - Myocardial infarction
  - Petechial bleeding
  - Frequency not known Anxiety - arrhythmias - bronchospasms - cerebral haemorrhage - chest pain - dyspnoea - eosinophilia - fever - headache - hypertension (marked increase in systolic blood pressure indicates overdose) - hypotension - increased urinary urgency - myoclonic spasm - nausea - palpitation - paraesthesia - phlebitis - puritis of scalp - pulmonary oedema - rash - reduced platelet aggregation (on prolonged use) - tachycardia - tremor - vomiting

- **PREGNANCY** No evidence of harm in animal studies — manufacturers advise use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturers advise avoid — no information available.

- **MONITORING REQUIREMENTS** Monitor serum-potassium concentration.

- **DIRECTIONS FOR ADMINISTRATION** Dobutamine injection should be diluted before use or given undiluted with syringe pump. Dobutamine concentrate for intravenous infusion should be diluted before use.

  - For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to a concentration of 0.5–1 mg/mL and give via an infusion pump; give higher concentration (max. 5 mg/mL) through central venous catheter; incompatible with bicarbonate and other strong alkaline solutions.
DRUG ACTION

Adrenaline/epinephrine
Acts on both alpha and beta receptors and increases both heart rate and contractility (beta, effects); it can cause peripheral vasodilatation (a beta2 effect) or vasoconstriction (an alpha effect).

INDICATIONS AND DOSE

Cardiopulmonary resuscitation

BY INTRAVENOUS INJECTION

Adult: 1 mg every 3–5 minutes as required, a 1 in 10000 (100 micrograms/mL) solution is recommended

BY INTRAMUSCULAR INJECTION

Child 1 month–5 years: 150 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, suitable syringe to be used for measuring small volume; injected preferably into the anterolateral aspect of the middle third of the thigh

Child 6–11 years: 300 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, to be injected preferably into the anterolateral aspect of the middle third of the thigh

Child 12–17 years: 500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, 300 micrograms (0.3 mL) to be administered if child small or prepubertal

Adult: 500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function

Acute anaphylaxis when there is doubt as to the adequacy of the circulation (specialist use only) | Angioedema (if laryngeal oedema is present) (specialist use only)

BY SLOW INTRAVENOUS INJECTION

Adult: 50 micrograms, using 0.5 mL of the dilute 1 in 10 000 adrenaline injection, dose to be repeated according to response, if multiple doses required, adrenaline should be given as a slow intravenous infusion stopping when a response has been obtained

Control of bradycardia in patients with arrhythmias after myocardial infarction, if there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine

BY INTRAVENOUS INFUSION

Adult: 2–10 micrograms/minute, adjusted according to response

EMERADE® 150 MICROGRAMS

Acute anaphylaxis (for self-administration)

BY INTRAMUSCULAR INJECTION

Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required

Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

EMERADE® 300 MICROGRAMS

Acute anaphylaxis (for self-administration)

BY INTRAMUSCULAR INJECTION

Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

Acute hypotension

BY CONTINUOUS INTRAVENOUS INFUSION

Neonate: Initially 100 nanograms/kg/minute, adjusted according to response, higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension.

Child: Initially 100 nanograms/kg/minute, adjusted according to response, higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension

Emergency treatment of acute anaphylaxis (under expert supervision) | Angioedema (if laryngeal oedema is present) (under expert supervision)

BY INTRAMUSCULAR INJECTION

Child 1 month–5 years: 150 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, suitable syringe to be used for measuring small volume; injected preferably into the anterolateral aspect of the middle third of the thigh

Child 6–11 years: 300 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, to be injected preferably into the anterolateral aspect of the middle third of the thigh

Child 12–17 years: 500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, 300 micrograms (0.3 mL) to be administered if child small or prepubertal

Adult: 500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function

Control of bradycardia in patients with arrhythmias after myocardial infarction, if there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine

BY INTRAVENOUS INFUSION

Adult: 2–10 micrograms/minute, adjusted according to response

EMERADE® 150 MICROGRAMS

Acute anaphylaxis (for self-administration)

BY INTRAMUSCULAR INJECTION

Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required

Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

EMERADE® 300 MICROGRAMS

Acute anaphylaxis (for self-administration)

BY INTRAMUSCULAR INJECTION

Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

7.1a Cardiac arrest

Cardiopulmonary resuscitation

Overview

The algorithm for cardiopulmonary resuscitation (Life support algorithm (image) inside back cover) reflects the most recent recommendations of the Resuscitation Council (UK). These guidelines are available at www.resus.org.uk.

Cardiac arrest can be associated with ventricular fibrillation, pulseless ventricular tachycardia, asystole, and pulseless electrical activity (electromechanical dissociation). Adrenaline/epinephrine below 1 in 10000 (100 micrograms/mL) is recommended by intravenous injection repeated every 3–5 minutes if necessary. Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest compressions; drugs administered peripherally must be followed by a flush of at least 20 mL. Sodium Chloride 0.9% injection to aid entry into the central circulation. Intravenous injection of amiodarone hydrochloride p. 99 should be considered after adrenaline/epinephrine to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. An additional dose of amiodarone hydrochloride can be given if necessary, followed by an intravenous infusion of amiodarone hydrochloride. Lidocaine hydrochloride p. 97, is an alternative if amiodarone hydrochloride is not available. Atropine sulfate p. 1179 is no longer recommended in the treatment of asystole or pulseless electrical activity.

During cardiopulmonary arrest if intravenous access cannot be obtained, the intraosseous route can be used instead. Drug administration via the endotracheal route is no longer recommended.

For the management of acute anaphylaxis, see allergic emergencies under Antihistamines, allergen immunotherapy and allergic emergencies p. 259.

SYMPATHOMIMETICS > VASOCONSTRICTOR

Adrenaline/epinephrine

BY INTRAVENOUS INJECTION

Child 6 months–1 year: 1 microgram/kg/minute

Child 1 year–8 years: 2 micrograms/kg/minute

Child 8 years–12 years: 3 micrograms/kg/minute

Child 12 years–17 years: 5 micrograms/kg/minute

Child >17 years: 10 micrograms/kg/minute

BY INTRAMUSCULAR INJECTION

Neonate: 1 microgram/kg

Newborn: 2 micrograms/kg

Child: 1 microgram/kg

BY CONTINUOUS INTRAVENOUS INFUSION

Adult: 200 micrograms/kg/minute

Dobutamine (as Dobutamine hydrochloride) 12.5 mg per 1 ml Dobutamine 250mg/50ml solution for infusion vials | 1 vial £7.50

Dobutamine (as Dobutamine hydrochloride) 25 mg per 1 ml Dobutamine 250mg/50ml concentrate for solution for infusion ampoules | 5 ampoules £26.00–£26.25

EMERADE® 150 MICROGRAMS

Acute anaphylaxis (for self-administration)

BY INTRAMUSCULAR INJECTION

Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required

Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

EMERADE® 300 MICROGRAMS

Acute anaphylaxis (for self-administration)

BY INTRAMUSCULAR INJECTION

Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

continued →
Cardiovascular system

Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

**EMERADE® 500 MICROGRAMS**

**Acute anaphylaxis (for self-administration for patients at risk of severe anaphylaxis)**
- By intramuscular injection
- Child 12–17 years: 500 micrograms, then 500 micrograms after 5–15 minutes as required
- Adult: 500 micrograms, then 500 micrograms after 5–15 minutes as required

**EPINEP® AUTO-INJECTOR 0.3MG**

**Acute anaphylaxis (for self-administration)**
- By intramuscular injection
- Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required
- Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

**EPINEP® JR AUTO-INJECTOR 0.15MG**

**Acute anaphylaxis (for self-administration)**
- By intramuscular injection
- Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
- Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required

**JEXT® 150 MICROGRAMS**

**Acute anaphylaxis (for self-administration)**
- By intramuscular injection
- Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
- Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required

**JEXT® 300 MICROGRAMS**

**Acute anaphylaxis (for self-administration)**
- By intramuscular injection
- Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

**UNLICENSED USE**
- With intramuscular use for acute anaphylaxis in children Auto-injectors delivering 150-microgram dose of adrenaline may not be licensed for use in children with body-weight under 15 kg.
- With intravenous use for acute hypotension in children Adrenaline 1 in 1000 (1 mg/mL) solution is not licensed for intravenous administration.

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**
Intravenous route should be used with extreme care by specialists only.

**CAUTIONS**
- Arteriosclerosis (in adults) • arrhythmias • cerebrovascular disease • cor pulmonale • diabetes mellitus • elderly • hypercalcaemia • hyperreflexia • hypertension • hyperthyroidism • hypokalaemia • ischaemic heart disease • obstructive cardiomyopathy • occlusive vascular disease • organic brain damage • phaeochromocytoma • prostate disorders • psychoneurosis • severe angina • susceptibility to angle-closure glaucoma

**CAUTIONS, FURTHER INFORMATION**
- Cautions listed are only for non-life-threatening situations.
- INTERACTIONS → Appendix 1 (sympathomimetics) Severe anaphylaxis in patients taking beta-blockers may not respond to adrenaline—consider bronchodilator therapy. Furthermore, adrenaline can cause severe hypertension and bradycardia in those taking non-cardioselective beta-blockers.
- SIDE-EFFECTS
  - Angina • angle-closure glaucoma • anorexia • anxiety • arrhythmias • cold extremities • confusion • difficulty in micturition • dizziness • dry mouth • dyspnoea • headache • hyperglycaemia • hypersalivation • hypertension (risk of cerebral haemorrhage) • hypokalaemia • insomnia • metabolic acidosis • mydriasis • myocardial infarction • nausea • pallor • palpitation • psychosis • pulmonary oedema (on excessive dosage or extreme sensitivity) • restlessness • sweating • tachycardia • tissue necrosis at injection site • tissue necrosis of bowel • tissue necrosis of extremities • tissue necrosis of kidneys • tissue necrosis of liver • tremor • urinary retention • vomiting • weakness
- PREGNANCY
  - May reduce placental perfusion and cause tachycardia, cardiac irregularities, and extrasystoles in fetus. Can delay second stage of labour. Manufacturers advise use only if benefit outweighs risk.
- BREAST FEEDING
  - Present in milk but unlikely to be harmful as poor oral bioavailability.
- RENAL IMPAIRMENT
  - Manufacturers advise use with caution in severe impairment.
- MONITORING REQUIREMENTS
  - Monitor blood pressure and ECG.
- DIRECTIONS FOR ADMINISTRATION
  - Acute hypotension
    - With intravenous use in children For continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9% and give through a central venous catheter. Incompatible with bicarbonate and alkaline solutions. Neonatal intensive care, dilute 3 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 100 nanograms/kg/minute; infuse through a central venous catheter. Incompatible with bicarbonate and alkaline solutions. These infusions are usually made up with adrenaline 1 in 1000 (1 mg/mL) solution.
    - Cardiopulmonary resuscitation
      - With intravenous use in adults Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest compressions; drugs administered peripherally must be followed by a flush of at least 20 mL Sodium Chloride 0.9% injection to aid entry into the central circulation.
- PRESCRIBING AND DISPENSING INFORMATION
  - It is important, in acute anaphylaxis where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.
    - Great vigilance is needed to ensure that the correct strength of adrenaline injection is used; anaphylactic shock kits need to make a very clear distinction between the 1 in 10 000 strength and the 1 in 1000 strength.
    - Patients with severe allergy should be instructed in the self-administration of adrenaline by intramuscular injection.
    - Packs for self-administration need to be clearly labelled with instructions on how to administer adrenaline (intramuscularly, preferably at the midpoint of the outer thigh, through light clothing if necessary) so that in the case of rapid collapse someone else is able to give it. It is important to ensure individuals at risk and their carers understand that:
      - two injection devices should be carried at all times to treat symptoms until medical assistance is available; if, after the first injection, the individual does not start to
feel better, the second injection should be given 5 to 15 minutes after the first;
• an ambulance should be called after every administration, even if symptoms improve;
• the individual should lie down with their legs raised (unless they have breathing difficulties, in which case they should sit up) and should not be left alone.
Adrenaline for administration by intramuscular injection is available in ‘auto-injectors’ (e.g. Emerade®, EpiPen®, or Jext®), pre-assembled syringes fitted with a needle suitable for very rapid administration (if necessary by a bystander or a healthcare provider if it is the only preparation available); injection technique is device specific.
To ensure patients receive the auto-injector device that they have been trained to use, prescribers should specify the brand to be dispensed.

**Patient and Carer Advice**
Individuals at considerable risk of anaphylaxis need to carry (or have available) adrenaline at all times and the patient, or their carers, need to be instructed in advance when and how to inject it.

JEXT® 300 MICROGRAMS 1.1 mL of the solution remains in the auto-injector device after use.

JEXT® 150 MICROGRAMS 1.25 mL of the solution remains in the auto-injector device after use.

EPIPEN® JR AUTO-INJECTOR 0.15MG 1.7 mL of the solution remains in the auto-injector device after use.

EMERADE® 300 MICROGRAMS 0.2 mL of the solution remains in the auto-injector device after use.

EPIPEN® AUTO-INJECTOR 0.3MG 1.7 mL of the solution remains in the auto-injector device after use.

EMERADE® 150 MICROGRAMS No solution remains in the auto-injector device after use.

Medicines for Children leaflet: Adrenaline auto-injector for anaphylaxis www.medicinesforchildren.org.uk/adrenaline-for-anaphylaxis

**Exceptions to Legal Category**
POM restriction does not apply to the intramuscular administration of up to 1 mg of adrenaline injection 1 in 1000 (1 mg/mL) for the emergency treatment of anaphylaxis.

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for Injection**
**Excipients:** May contain Sulfites

- **Adrenaline (epinephrine) (Non-Proprietary)**
  - Adrenaline 100 microgram per 1 mL
    - Adrenaline (base) 100micrograms/1mL (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (Pom) £60.09
    - Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pom) £6.67 | 1 pre-filled disposable injection (Pom) £18.00 (Hospital only) | 10 pre-filled disposable injection (Pom) £180.00 (Hospital only)
  - Adrenaline 1 mg per 1 mL
    - Adrenaline (base) 10mg/10ml (1 in 1,000) solution for injection ampoules | 10 ampoule (Pom) £75.65
    - Adrenaline (base) for anaphylaxis 1mg/1ml (1 in 1,000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pom) £10.40
  - Adrenaline (base) 1mg/1ml (1 in 1,000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pom) £10.40 | 30.00
  - Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL
    - Adrenaline (base) 5mg/5ml (1 in 1,000) solution for injection ampoules | 10 ampoule (Pom) £75.66
    - Adrenaline (base) 50micrograms/0.5ml (1 in 1,000) solution for injection ampoules | 10 ampoule (Pom) £58.40 | £58.41 DT price = £58.41
    - Adrenaline (base) 1mg/1ml (1 in 1,000) solution for injection ampoules | 10 ampoule (Pom) £6.03 DT price = £6.01
  - Adrenaline (as Adrenaline acid tartrate) 100 microgram per 1 mL
    - Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection ampoules | 1 ampoule (Pom) £43.53 | 10 ampoule (Pom) £63.65
  - Emerade (Bausch & Lomb Uk Ltd)
    - Adrenaline 1 mg per 1 mL
      - Emerade 300micrograms/0.3ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (Pom) £26.94 DT price = £26.45
      - Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL
        - Emerade 150micrograms/0.15ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (Pom) £26.94
        - Emerade 500micrograms/0.5ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (Pom) £28.74
  - EpiPen (Meda Pharmaceuticals Ltd)
    - Adrenaline 500 microgram per 1 mL
      - EpiPen Jr. 150micrograms/0.3ml (1 in 2,000) solution for injection auto-injectors | 1 pre-filled disposable injection (Pom) £26.45 | 2 pre-filled disposable injection (Pom) £52.90
    - Jext (ALK-Abello Ltd)
      - Adrenaline 1 mg per 1 mL
        - EpiPen 300micrograms/0.3ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (Pom) £23.99 DT price = £26.45
      - Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL
        - Jext 150micrograms/0.15ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (Pom) £23.99

**8 Oedema**

**Diuretics**

**Overview**

Thiazides are used to relieve oedema due to chronic heart failure and, in lower doses, to reduce blood pressure.

Loop diuretics are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure.

Combination diuretic therapy may be effective in patients with oedema resistant to treatment with one diuretic. Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.

Thiazides and Related Diuretics

Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and must have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

In the management of hypertension a low dose of a thiazide produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control. Chlorthalidone p. 219 and indapamide p. 158 are the preferred diuretics in the management of hypertension. Thiazides also have a role in chronic heart failure.

Bendroflumethiazide p. 157 can be used for mild or moderate heart failure; it is licensed for the treatment of hypertension but is no longer considered the first-line diuretic for this indication, although patients with stable and controlled blood pressure currently taking bendroflumethiazide can continue treatment.

Chlortalidone, a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days to control oedema. It is also useful if acute retention is liable to be precipitated by a more rapid diuresis or if patients dislike the altered pattern of micturition caused by other diuretics. Chlortalidone can also be used under

Cardiovascular System
close supervision for the treatment of ascites due to cirrhosis in stable patients.

Xipamide p. 220 and indapamide are chemically related to chlortalidone. Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.

Metolazone p. 220 is particularly effective when combined with a loop diuretic (even in renal failure); profound diuresis can occur and the patient should therefore be monitored carefully.

The thiazide diuretics benzthiazide, clopamide, cyclophenazide p. 220, hydrochlorothiazide, and hydroflumethiazide do not offer any significant advantage over other thiazides and related diuretics.

**Loop diuretics**

Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g. bendroflumethiazide or metolazone).

If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension, or in patients with impaired renal function or heart failure.

Loop diuretics can exacerbate diabetes (but hyperglycaemia is less likely than with thiazides) and gout. If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially.

Furosemide p. 215 and bumetanide p. 215 are similar in activity: both act within 1 hour of oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following intravenous administration furosemide has a peak effect within 30 minutes. The diuresis associated with these drugs is dose related.

Torasemide p. 217 has properties similar to those of furosemide and bumetanide, and is indicated for oedema and for hypertension.

**Potassium-sparing diuretics and aldosterone antagonists**

Amiloride hydrochloride p. 218 and triamterene p. 219 on their own are weak diuretics. They cause retention of potassium and are therefore given with thiazide or loop diuretics as a more effective alternative to potassium supplements. See compound preparations with thiazides or loop diuretics.

Potassium supplements must **not** be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

**Aldosterone antagonists**

Spironolactone p. 180 potentiates thiazide or loop diuretics by antagonising aldosterone; it is a potassium-sparing diuretic. Spironolactone is of value in the treatment of oedema and ascites caused by cirrhosis of the liver; furosemide can be used as an adjunct. Low doses of spironolactone are beneficial in moderate to severe heart failure and when used in resistant hypertension [unlicensed indication].

Spironolactone is also used in primary hyperaldosteronism (Conn’s syndrome). It is given before surgery or if surgery is not appropriate, in the lowest effective dose for maintenance.

Eplerenone p. 180 is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction; it is also licensed as an adjunct in chronic mild heart failure with left ventricular systolic dysfunction.

Potassium supplements must **not** be given with aldosterone antagonists

**Potassium-sparing diuretics with other diuretics**

Although it is preferable to prescribe thiazides and potassium-sparing diuretics separately, the use of fixed combinations may be justified if compliance is a problem. Potassium-sparing diuretics are not usually necessary in the routine treatment of hypertension, unless hypokalaemia develops.

**Other diuretics**

Manitol p. 217 is an osmotic diuretic that can be used to treat cerebral oedema and raised intra-ocular pressure.

Mercurial diuretics are effective but are now almost never used because of their nephrotoxicity.

The carbonic anhydrase inhibitor acetazolamide p. 1037 is a weak diuretic and is little used for its diuretic effect. It is used for prophylaxis against mountain sickness [unlicensed indication] but is not a substitute for acclimatisation.

Acetazolamide and eye drops of dorzolamide p. 1039 and brinzolamide p. 1038 inhibit the formation of aqueous humour and are used in glaucoma.

**Diuretics with potassium**

Many patients on diuretics do not need potassium supplements. For many of those who do, the amount of potassium in combined preparations may not be enough, and for this reason their use is to be discouraged.

Diuretics with potassium and potassium-sparing diuretics should **not** usually be given together. Diuretics and potassium supplements should be prescribed separately for children.

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**Other drugs used for Oedema**

Diamorphine hydrochloride, p. 423

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**DIURETICS › LOOP DIURETICS**

**Loop diuretics**

- **DRUG ACTION** Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henlé in the renal tubule and are powerful diuretics.

- **CONTRA-INDICATIONS** Anuria - comatose and precomatose states associated with liver cirrhosis - renal failure due to nephrotoxic or hepatotoxic drugs - severe hypokalaemia - severe hyponatraemia

- **CAUTIONS** Can exacerbate diabetes (but hyperglycaemia less likely than with thiazides) - can exacerbate gout - hypotension should be corrected before initiation of treatment - hypovolaemia should be corrected before initiation of treatment - urinary retention can occur in prostatic hyperplasia

**CAUTIONS, FURTHER INFORMATION**

- Elderly: Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

- **Potassium loss** Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus
greater with thiazides than with an equipotent dose of a loop diuretic.

Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics avoids the need to take potassium supplements.

In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis.

- Urinary retention If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially; an adequate urinary output should be established before initiating treatment.

**INTERACTIONS**  ➔ Appendix 1 (diuretics).

**SIDE-EFFECTS**

- Very rare Hyperuricaemia

- Frequency not known Acute urinary retention - blood disorders - bone-marrow depression - deafness (usually with high doses and rapid intravenous administration, and in renal impairment) - electrolyte disturbances - hepatic encephalopathy - hyperglycaemia (less common than with thiazides) - hypersensitivity reactions - hypocalcaemia - hypochloroaemia - hypokalaemia - hypomagnesaemia - hypoponatraemia - leucopenia - metabolic alkalosis - mild gastrointestinal disturbances - pancreatitis - photosensitivity - postural hypotension - pruritus - rash - temporary increase in serum-cholesterol and triglyceride concentration - thrombocytopenia - tinnitus (usually with high doses and rapid intravenous administration, and in renal impairment) - visual disturbances

- HEPATIC IMPAIRMENT Hypokalaemia induced by loop diuretics may precipitate hepatic encephalopathy and coma—potassium-sparing diuretics can be used to prevent this. Diuretics can increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias.

- RENAL IMPAIRMENT High doses of loop diuretics may occasionally be needed in renal impairment. High doses or rapid intravenous administration can cause tinnitus and deafness.


**Bumetanide**

**INDICATIONS AND DOSE**

Oedema

- **BY MOUTH**
  - Adult: 1 mg, dose to be taken in the morning, then 1 mg after 6–8 hours if required
  - Elderly: 500 micrograms daily, this lower dose may be sufficient in elderly patients

Oedema, severe cases

- **BY MOUTH**
  - Adult: Initially 5 mg daily, increased in steps of 5 mg every 12–24 hours, adjusted according to response

**SIDE-EFFECTS**

- Breast pain · gynaecomastia · musculoskeletal pain (associated with high doses in renal failure)

Pregnancy

Bumetanide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.

**BREAST FEEDING**

No information available. May inhibit lactation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- **Bumetanide (Non-proprietary)**
  - Bumetanide 1 mg tablets | 28 tablet **PoM** £7.35 DT price = £1.43
  - Bumetanide 5 mg tablets | 28 tablet **PoM** £7.00 DT price = £6.98

**Oral solution**

- **Bumetanide (Non-proprietary)**
  - Bumetanide 200 microgram per 1 ml | Bumetanide 1mg/5ml oral solution sugar free sugar-free | 150 ml **PoM** £168.00 DT price = £168.00

Combinations available: Amiloride with bumetanide, p. 218

**Co-amilofruse**

**INDICATIONS AND DOSE**

Oedema

- **BY MOUTH**
  - Adult: 2.5/20–10/80 mg daily, dose to be taken in the morning

**DOSE EQUIVALENCE AND CONVERSION**

- A mixture of amiloride hydrochloride and furosemide (frusemide) in the mass proportions of 1 part amiloride hydrochloride to 8 parts furosemide (frusemide).

**CONTRA-INDICATIONS**

Addison’s disease · anuria · comatose or precomatose states associated with liver cirrhosis · dehydration · hyperkalaemia · hypovolaemia · renal failure · severe hypokalaemia · severe hypoproteinaemia

**CAUTIONS**

Correct hypovolaemia before using in oliguria · diabetes mellitus · elderly · gout · hepatorenal syndrome · hypoproteinaemia · hypotension · impaired micturition · prostatic enlargement

**INTERACTIONS**  ➔ Appendix 1 (diuretics).

**SIDE-EFFECTS**

Agranulocytosis · anaphylaxis · aplastic anaemia · blood disorders · bone marrow depression (withdraw treatment) · confusion · deafness (usually in renal impairment or in hypoproteinaemia) · dry mouth · eosinophilia · exfoliative dermatitis · gastro-intestinal disturbances · gout · haemolytic anaemia · hepatic encephalopathy · hyperglycaemia · hypersensitivity reactions · hyperuricaemia · hypocalcaemia · hypokalaemia (due to furosemide—may be followed by hyperkalaemia due to amiloride) · hypomagnesaemia · hypophatraemia · hypotension · intrahepatic cholestasis · leucopenia · metabolic alkalosis or acidosis · pancreatitis · paraesthesia · photosensitivity · purpura · rashes · Stevens-Johnson syndrome · temporary increase in serum cholesterol and triglyceride concentrations · thrombocytopenia · tinnitus · toxic epidermal necrolysis

**PREGNANCY**

Not used to treat hypertension in pregnancy.

**BREAST FEEDING**

Manufacturers advise avoid—no information regarding amiloride component available. Amount of furosemide in milk too small to be harmful. Furosemide may inhibit lactation.

**HEPATIC IMPAIRMENT**

Increased risk of hypomagnesaemia in alcoholic cirrhosis.

**RENAL IMPAIRMENT**

Risk of hyperkalaemia in renal impairment but may need higher doses. Avoid if eGFR less than 30 mL/minute/1.73 m². Monitor plasma-potassium concentration.

**MONITORING REQUIREMENTS**

Monitor electrolytes.
**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Co-amilofruse (Non-proprietary)
  - Amiloride hydrochloride 2.5 mg, Furosemide 20 mg Co-amilofruse 2.5mg/20mg tablets 28 tablet £10.95 DT price = £1.40 56 tablet £66.66
- Amiloride hydrochloride 5 mg, Furosemide 40 mg Co-amilofruse 5mg/40mg tablets 28 tablet £13.95 DT price = £1.48 56 tablet £8.48
- Amiloride hydrochloride 10 mg, Furosemide 80 mg Co-amilofruse 10mg/80mg tablets 28 tablet £19.95 DT price = £1.52
- Frumil (Sanofi)
  - Amiloride hydrochloride 2.5 mg, Furosemide 20 mg Frumil LS 20mg/2.5mg tablets 28 tablet £4.32 DT price = £1.40 56 tablet £8.48
- Amiloride hydrochloride 5 mg, Furosemide 40 mg Frumil 40mg/5mg tablets 28 tablet £5.29 DT price = £1.48 56 tablet £10.35

**Furosemide**
(\textit{Frusemide})

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
- Adult: Initially 40 mg daily, dose to be taken in the morning, then maintenance 20–40 mg daily
- **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENTRINE INFUSION**
- Adult: Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

**Resistant oedema**
- **BY MOUTH**
- Adult: 80–120 mg daily
- **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENTRINE INFUSION**
- Adult: Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

**Resistant hypertension**
- **BY MOUTH**
- Adult: 40–80 mg daily
- **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENTRINE INFUSION**
- Adult: Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

**CAUTIONS**
Hepatorenal syndrome · hypoproteinaemia may reduce diuretic effect and increase risk of side-effects

**SIDE-EFFECTS**
Gout · intrahepatic cholestasis

**PREGNANCY**
Furosemide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.

**BREAST FEEDING**
Amount too small to be harmful. May inhibit lactation.

**DIRECTIONS FOR ADMINISTRATION**
Intravenous administration rate should not usually exceed 4 mg/minute however single doses of up to 80 mg may be administered more rapidly; a lower rate of infusion may be necessary in renal impairment. For intravenous infusion

(Lasix\textsuperscript{\textregistered}), give continuously in Sodium chloride 0.9%; infusion pH must be above 5.5; glucose solutions are unsuitable.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Furosemide (Non-proprietary)
  - Furosemide 20 mg Furosemide 20mg tablets 28 tablet £1.02 DT price = £0.97 50 tablet £5.31
  - Furosemide 40 mg Furosemide 40mg tablets 28 tablet £1.03 DT price = £0.97 1000 tablet £28.21
  - Furosemide 500 mg Furosemide 500mg tablets 28 tablet £70.00 DT price = £37.82
  - Diureal (Ennogen Pharma Ltd)
  - Furosemide 500 mg Diureal 500mg tablets 28 tablet no price available DT price = £37.82

**Oral solution**
EXCIPIENTS: May contain Alcohol
- Furosemide (Non-proprietary)
  - Furosemide 4 mg per 1 ml Furosemide 20mg/5ml oral solution sugar free sugar-free | 150 ml £14.49 DT price = £14.49
  - Furosemide 8 mg per 1 ml Furosemide 40mg/5ml oral solution sugar-free sugar-free | 150 ml £18.99 DT price = £18.99
  - Furosemide 10 mg per 1 ml Furosemide 50mg/5ml oral solution sugar-free sugar-free | 150 ml £20.21 DT price = £20.21
  - Frusol (Rosemont Pharmaceuticals Ltd)
  - Furosemide 4 mg per 1 ml Frusol 20mg/5ml oral solution sugar-free | 150 ml £12.07 DT price = £12.07
  - Furosemide 8 mg per 1 ml Frusol 40mg/5ml oral solution sugar-free | 150 ml £15.58 DT price = £15.58
  - Furosemide 10 mg per 1 ml Frusol 50mg/5ml oral solution sugar-free | 150 ml £16.84 DT price = £16.84

**Solution for injection**
- Furosemide (Non-proprietary)
  - Furosemide 10 mg per 1 ml Furosemide 250mg/25ml solution for injection ampoules | 10 ampoule £4.50–£7.60
  - Furosemide 50mg/5ml solution for injection ampoules | 10 ampoule £5.50
  - Lasix (Sanofi)
  - Furosemide 10 mg per 1 ml Lasix 20mg/2ml solution for injection ampoules | 5 ampoule £3.74

**Combinations available:** \textit{Spiromolactone with furosemide,} p. 218

**Furosemide with potassium chloride**
The properties listed below are those particular to the combination only. For the properties of the components please consider, furosemide above, potassium chloride p. 929.

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
- Adult: (consult product literature)

**DIRECTIONS FOR ADMINISTRATION**
Furosemide with modified-release potassium chloride tablets should be swallowed whole with plenty of fluid during meals while sitting or standing.

**PATIENT AND CARER ADVICE**
Patients or carers should be given advice on how to administer furosemide with potassium chloride tablets.

**LESS SUITABLE FOR PRESCRIBING**
Furosemide with potassium chloride tablets are less suitable for prescribing.
Furosemide with triamterene

The properties listed below are those particular to the combination only. For the properties of the components please consider, furosemide p. 216, triamterene p. 219.

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
  - Adult: 0.5–2 tablets daily, dose to be taken in the morning

**CONTRA-INDICATIONS** Anuria, comatose or precomatose states associated with liver cirrhosis, dehydration, hyperkalaemia, hypovolaemia, renal failure, severe hypokalaemia, severe hyponatraemia

**CAUTIONS** Diabetes mellitus, elderly, gout, hepatorenal syndrome, hypotension, impaired micturition, may cause blue fluorescence of urine, prostatic enlargement

**INTERACTIONS** → Appendix 1 (diuretics).

**SIDE-EFFECTS**
- **Rare** Agranulocytosis, anaphylaxis, aplastic anaemia, blood disorders, bone marrow depression (withdraw treatment), deafness (usually in renal impairment or in hypoproteinaemia), eosinophilia, exfoliative dermatitis, haemolytic anaemia, hypersensitivity reactions, intrahepatic cholestasis, leucopenia, pancreatitis, paraesthesia, photosensitivity, purpura, rash, thrombocytopenia, tinnitus (usually in renal impairment or in hypoproteinaemia)

- **Frequency not known** Dry mouth, electrolyte disturbances, gastro-intestinal disturbances, gout, hyperglycaemia (less common than with thiazides), hyperkalaemia, hyperuricaemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hypoxatraemia, hypotension, metabolic alkalosis, temporary increase in plasma cholesterol and triglyceride concentration, triamterene found in kidney stones

**BREAST FEEDING** Triamterene present in milk—manufacturer advises avoid. Furosemide may inhibit lactation.

**HEPATIC IMPAIRMENT** Increased risk of hypomagnesaemia in alcoholic cirrhosis. Hypokalaemia may precipitate coma.

**RENAL IMPAIRMENT** May need high doses. Avoid in severe impairment. Monitor plasma-potassium concentration in renal impairment (high risk of hyperkalaemia).

**MONITORING REQUIREMENTS** Monitor electrolytes.

**PATIENT AND CARER ADVICE** Urine may look slightly blue in some lights.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Frusene (Orion Pharma (UK) Ltd) | Furosemide 40 mg, Triamterene 50 mg | 56 tablet | POM | £4.34 DT price = £4.34 |

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
  - Adult: 5 mg once daily, to be taken preferably in the morning, then increased if necessary to 20 mg once daily; maximum 40 mg per day

**Hypertension**
- **BY MOUTH**
  - Adult: 2.5 mg daily, then increased if necessary to 5 mg once daily

**SIDE-EFFECTS**
- **Rare** Limb paraesthesia
- **Frequency not known** Dry mouth

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Torasemide (Non-proprietary)**
  - Torasemide 5 mg Torasemide 5mg tablets | 28 tablet | POM | £14.50 DT price = £5.53
  - Torasemide 10 mg Torasemide 10mg tablets | 28 tablet | POM | £18.75 DT price = £8.14
  - Torem (Meda Pharmaceuticals Ltd)
  - Torasemide 2.5 mg Torem 2.5mg tablets | 28 tablet | POM | £3.78 DT price = £3.78
  - Torasemide 5 mg Torem 5mg tablets | 28 tablet | POM | £5.53 DT price = £5.53
  - Torasemide 10 mg Torem 10mg tablets | 28 tablet | POM | £8.14 DT price = £8.14

**DIURETICS > OSMOTIC DIURETICS**

**Mannitol**

**INDICATIONS AND DOSE**

**Cerebral oedema**
- **BY INTRAVENOUS INFUSION**
  - Adult: 0.25–2 g/kg, repeated if necessary, to be administered over 30-60 minutes, dose may be repeated 1–2 times after 4–8 hours

**Raised intra-ocular pressure**
- **BY INTRAVENOUS INFUSION**
  - Adult: 0.25–2 g/kg, repeated if necessary, to be administered over 30–60 minutes, dose may be repeated 1–2 times after 4–8 hours

**CONTRA-INDICATIONS** Anuria, intracranial bleeding (except during craniotomy), severe cardiac failure, severe dehydration, severe pulmonary oedema

**CAUTIONS** Extravasation causes inflammation and thrombophlebitis

**INTERACTIONS** → Appendix 1 (mannitol).

**SIDE-EFFECTS**
- **Uncommon** Electrolyte imbalance, fluid imbalance, hypotension, thrombophlebitis

- **Rare** Anaphylaxis, arrhythmia, blurred vision, chest pain, chills, convulsions, cramp, dehydration, dizziness, dry mouth, fever, focal osmotic nephrosis, headache, hypersensitivity reactions, hypotension, nausea, oedema, pulmonary oedema, raised intracranial pressure, rhinitis, skin necrosis, thirst, urinary retention, urticaria, vomiting

- **Very rare** Acute renal failure, congestive heart failure
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Infusion**
- **Mannitol (Non-proprietary)**

  - **Mannitol 100 mg per 1 ml** Mannitol 50g/500ml (10%) infusion Viaflo bags | 1 bag (£0.00) no price available | 20 bag (£0.00) no price available
  - **Mannitol 50g/500ml (10%) infusion Viaflo bags | 1 bag (£0.00) no price available | 20 bag (£0.00) no price available
  - **Polyfurus K mannitol 10% infusion 500ml bottles | 1 bottle (£4.46) | 12 bottle (£0.00) no price available
  - **Mannitol 150 mg per 1 ml** Mannitol 75g/500ml (15%) infusion Viaflo bags | 1 bag (£0.00) no price available | 20 bag (£0.00) no price available
  - **Mannitol 200 mg per 1 ml** Mannitol 100g/500ml (20%) infusion Viaflo bags | 1 bag (£0.00) no price available | 20 bag (£0.00) no price available
  - **Polyfurus M mannitol 20% infusion 500ml bottles | 1 bottle (£5.86) | 12 bottle (£0.00) no price available
  - **Mannitol 50g/250ml (20%) infusion Viaflo bags | 1 bag (£0.00) no price available | 30 bag (£0.00) no price available
  - **Mannitol 100g/500ml (20%) infusion Viaflo bags | 1 bag (£0.00) no price available | 20 bag (£0.00) no price available

**DIURETICS > POTASSIUM-SPARING DIURETICS > ALDOSTERONE ANTAGONISTS**

**Spironolactone with furosemide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, spironolactone p. 180, furosemide p. 216.

**INDICATIONS AND DOSE**

Resistant oedema
- **BY MOUTH**
- Adult: 20/50–80/200 mg daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **Lasilactone** (Sanofib)
  - **Furosemide 20 mg, Spironolactone 50 mg** Lasilactone 20mg/50mg capsules | 28 capsule (£0.07) 1.97

**DIURETICS > POTASSIUM-SPARING DIURETICS > OTHER**

**Amiloride hydrochloride**

**INDICATIONS AND DOSE**

**Oedema (monotherapy)**
- **BY MOUTH**
- Adult: Initially 10 mg daily, alternatively initially 5 mg twice daily, adjusted according to response; maximum 20 mg per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Amiloride hydrochloride (Non-proprietary)**
  - Amiloride hydrochloride 5 mg Amiloride 5mg tablets | 28 tablet (£0.00) 1.78

**Oral solution**

**EXCIPIENTS:** May contain Propylene glycol
- **Amiloride hydrochloride (Non-proprietary)**
  - Amiloride hydrochloride 1 mg per 1 ml Amiloride 5mg/5ml oral solution sugar free sugar-free | 150 ml (£0.00) no price available DT price = £37.35
  - **Amilamont** (Rosemont Pharmaceuticals Ltd)
  - **Amiloride hydrochloride 1mg per 1ml** Amiloride 5mg/5ml oral solution sugar free sugar-free | 150 ml (£0.00) 1.35 DT price = £37.35

**Amiloride with bumetanide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, amiloride hydrochloride above, bumetanide p. 215.

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
- Adult: 1–2 tablets daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Amiloride with bumetanide (Non-proprietary)**
  - Bumetanide 1 mg, Amiloride hydrochloride 5 mg Amiloride 5mg / Bumetanide 1mg tablets | 28 tablet (£0.00) 29.60 DT price = £29.60

**Potassium conservation when used as an adjunct to thiazide or loop diuretics for hypertension or congestive heart failure**
- **BY MOUTH**
- Adult: Initially 5–10 mg daily

**Potassium conservation when used as an adjunct to thiazide or loop diuretics for hepatic cirrhosis with ascites**
- **BY MOUTH**
- Adult: Initially 5 mg daily

**CONTRA-INDICATIONS**

Addison’s disease - anuria - hyperkalaemia

**CAUTIONS**

Diabetes mellitus - elderly

**INTERACTIONS**

- Appendix 1 (diuretics).

**SIDE-EFFECTS**


**PREGNANCY**

Not to be used to treat gestational hypertension.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**RENAI IMPAIRMENT**

Manufacturers advise avoid in severe impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

**MONITORING REQUIREMENTS**

Monitor electrolytes.
**Triamterene**

- **INDICATIONS AND DOSE**
  - **Oedema** | Potassium conservation with thiazide and loop diuretics
  - **BY MOUTH**
  - Adult: Initially 150–250 mg daily for 1 week, lower initial dose when given with other diuretics, then reduced to 150–250 mg daily on alternate days, to be taken in divided doses after breakfast and lunch

- **CONTRA-INDICATIONS** Addison's disease • anuria • hyperkalaemia
- **CAUTIONS** Diabetes mellitus • elderly • gout • may cause blue fluorescence of urine
- **INTERACTIONS** ➔ Appendix 1 (triamterene).
- **SIDE-EFFECTS**
  - *Common or very common* Diarrhoea • hyperkalaemia • nausea • vomiting
  - *Uncommon* Dry mouth • headache • hyperuricaemia • rash
  - *Rare* Megaloblastic anaemia • pancytopenia • photosensitivity • serum-sickness
  - *Very rare* Renal failure (reversible on discontinuation) • triamterene found in kidney stones
  - *Frequency not known* Jaundice • malaise • slight decrease in blood pressure
- **PREGNANCY** Not used to treat gestational hypertension. Avoid unless essential.
- **BREAST FEEDING** Present in milk — manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** Use with caution. Avoid in progressive impairment.
- **RENAL IMPAIRMENT** Avoid in progressive impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).
- **MONITORING REQUIREMENTS** Monitor electrolytes.
- **PATIENT AND CARER ADVICE** Urine may look slightly blue in some lights.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule** CAUTIONARY AND ADVISORY LABELS 14, 21
    - **Triamterene (Non-proprietary)**
      - Triamterene 50 mg | 30 capsule POM £41.90 DT price = £41.90
      - Combinations available: Co-triamterzide, below • Furosemide with triamterene, p. 217

**Triamterene with chlortalidone**

The properties listed below are those particular to the combination only. For the properties of the components please consider, triamterene above, chlortalidone below.

- **INDICATIONS AND DOSE**
  - **Hypertension** | Oedema
    - **BY MOUTH**
    - Adult: 50/50–100/100 mg once daily, dose to be taken in the morning
  - **DOSE EQUIVALENCE AND CONVERSION**
    - Dose expressed as x/y mg of triamterene/chlortalidone.

**Chlortalidone**

(Chlorthalidone)

- **INDICATIONS AND DOSE**
  - **Ascites due to cirrhosis in stable patients (under close supervision)** | Oedema due to nephrotic syndrome
    - **BY MOUTH**
    - Adult: Up to 50 mg daily
  - **Hypertension**
    - **BY MOUTH**
    - Adult: 25 mg daily, dose to be taken in the morning, then increased if necessary to 50 mg daily
  - **Mild to moderate chronic heart failure**
    - **BY MOUTH**
    - Adult: 25–50 mg daily, dose to be taken in the morning, then increased if necessary to 100–200 mg daily, reduce to lowest effective dose for maintenance
  - **Nephrogenic diabetes insipidus** | Partial pituitary diabetes insipidus
    - **BY MOUTH**
    - Adult: Initially 100 mg twice daily, then reduced to 50 mg daily

- **SIDE-EFFECTS**
  - *Rare* Allergic interstitial nephritis • jaundice
- **BREAST FEEDING** The amount present in milk is too small to be harmful. Large doses may suppress lactation.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
  - **Tablet**
    - **Chlortalidone (Non-proprietary)**
      - Chlortalidone 25 mg | 100 tablet POM no price available
      - Chlortalidone 50 mg | 30 tablet POM £90.55 DT price = £88.00
      - Combinations available: Triamterene with chlortalidone, above

**Co-triamterzide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, triamterene above, hydrochlorothiazide p. 158.

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
    - Adult: 50/25 mg daily, increased if necessary up to 200/100 mg daily, dose to be taken after breakfast
  - **Oedema**
    - **BY MOUTH**
    - Adult: 50/25 mg twice daily, to be taken after breakfast and after midday meal, increased if necessary to 150/75 mg daily, to be taken as 100/50 mg after breakfast and 50/25 mg after midday meal; continued ➔
220  Vascular disease

Cyclopenthiazide

INDICATIONS AND DOSE
Heart failure
- By mouth
  - Adult: 250–500 micrograms daily, take in the morning, then increased if necessary to 1 mg daily, reduce to lowest effective dose for maintenance

Hypertension
- By mouth
  - Adult: Initially 250 micrograms daily, take in the morning, then increased if necessary to 500 micrograms daily

Oedema
- By mouth
  - Adult: Up to 500 micrograms daily for a short period

SIDE-EFFECTS
- Rare Depression

BREAST FEEDING
- The amount present in milk is too small to be harmful. Large doses may suppress lactation.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - CAUTIONARY AND ADVISORY LABELS 14, 21
      - Dyazide (AMCs)
    - Hydrochlorothiazide 25 mg, Triamterene 50 mg Dyazide 50mg/25mg tablets | 30 tablet £0.95 DT price = £0.95

Metolazone

INDICATIONS AND DOSE
Oedema
- By mouth
  - Adult: 5–10 mg daily, dose to be taken in the morning; increased if necessary to 20 mg daily, dose increased in resistant oedema; maximum 80 mg per day

Hypertension
- By mouth
  - Adult: Initially 5 mg daily, dose to be taken in the morning; maintenance 5 mg once daily on alternate days

CAUTIONS
- Acute porphyrias p. 930

SIDE-EFFECTS
- Chest pain - chills

BREAST FEEDING
- The amount present in milk is too small to be harmful. Large doses may suppress lactation.

DIRECTIONS FOR ADMINISTRATION
- Tablets may be crushed and mixed with water immediately before use.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution
  - Tablet
    - Metolazone (Non-proprietary)
      - Metolazone 2.5 mg Zaroxolyn 2.5mg tablets | 100 tablet £0.50 no price available
      - Metolazone 5 mg Zaroxolyn 5mg tablets | 50 tablet £0.50 no price available

Xipamide

INDICATIONS AND DOSE
Oedema
- By mouth
  - Adult: Initially 40 mg daily, dose to be taken in the morning, increased if necessary to 80 mg daily, higher dose to be used in resistant cases; maintenance 20 mg daily, dose to be taken in the morning

Hypertension
- By mouth
  - Adult: 20 mg daily, dose to be taken in the morning

CAUTIONS
- Acute porphyrias p. 930

BREAST FEEDING
- No information available.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - Diurexan (Meda Pharmaceuticals Ltd)
      - Xipamide 20 mg Diurexan 20mg tablets | 140 tablet £19.46 DT price = £19.46

9  Vascular disease

Peripheral vascular disease

Classification and management
Peripheral vascular disease can be either occlusive (e.g. intermittent claudication) in which occlusion of the peripheral arteries is caused by atherosclerosis, or vasospastic (e.g. Raynaud’s syndrome). Peripheral arterial occlusive disease is associated with an increased risk of cardiovascular events; this risk is reduced by measures such as smoking cessation, effective control of blood pressure, regulating blood lipids, optimising glycaemic control in diabetes, taking aspirin p. 114 in a dose of 75 mg daily, and possibly weight reduction in obesity. Exercise training can improve symptoms of intermittent claudication; revascularisation procedures may be appropriate.

Naftidrofuryl oxalate p. 222 can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking naftidrofuryl oxalate should be assessed for improvement after 3–6 months.

Cilostazol p. 221 is licensed for use in intermittent claudication to improve walking distance in patients without peripheral tissue necrosis who do not have pain at rest; use is restricted to second-line treatment where lifestyle modifications and other appropriate interventions have failed to improve symptoms. Cilostazol should be initiated by those experienced in the management of intermittent claudication. Patients receiving cilostazol should be assessed for improvement after 3 months; consider discontinuation of treatment if there is no clinically relevant improvement in walking distance.
Inositol nicotinate below and pentoxifylline p. 222 are not established as being effective for the treatment of intermittent claudication.

Management of Raynaud’s syndrome includes avoidance of exposure to cold and stopping smoking. More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud’s syndrome. Nifedipine p. 153 is useful for reducing the frequency and severity of vasospastic attacks. Alternatively, naftidrofuryl oxalate may produce symptomatic improvement; inositol nicotinate (a nicotinic acid derivative) may also be considered. Pentoxifylline, prazosin p. 717, and moxisylyte p. 222 are not established as being effective for the treatment of Raynaud’s syndrome.

Vasodilator therapy is not established as being effective for chilblains.

ANTITHROMBOTIC DRUGS > ANTIPLATELET DRUGS

Cilostazol

- INDICATIONS AND DOSE
  - Intermittent claudication in patients without rest pain and no peripheral tissue necrosis
    - BY MOUTH
      - Adult: 100 mg twice daily, to be taken 30 minutes before food, cilostazol should be initiated by those experienced in the management of intermittent claudication, patients receiving cilostazol should be assessed for improvement after 3 months; consider discontinuation of treatment if there is no clinically relevant improvement in walking distance
  - DOSE ADJUSTMENTS DUE TO INTERACTIONS
    - Reduce dose to 50 mg twice daily with concomitant use of potent inhibitors of cytochrome P450 enzymes CYP3A4 (e.g. clarithromycin, itraconazole, ketoconazole, protease inhibitors) or CYP2C19, or with erythromycin or omeprazole.

- CONTRA-INDICATIONS
  - Active peptic ulcer · congestive heart failure · coronary intervention in previous 6 months · haemorrhagic stroke in previous 6 months · history of severe tachyarrhythmia · myocardial infarction in previous 6 months · poorly controlled hypertension · predisposition to bleeding · proliferative diabetic retinopathy · prolongation of QT interval · severe atrial flutter · unstable angina

- CAUTIONS
  - Atrial fibrillation · atrial or ventricular ectopy · diabetes mellitus (higher risk of intracranial bleeding) · mild to moderate atrial flutter · stable coronary disease · surgery

- INTERACTIONS
  - Appendix 1 (cilostazol).
  - Caution with concomitant use of drugs that increase risk of bleeding.
  - Contra-indicated with concomitant use of 2 or more antiplatelets or anticoagulants.

- SIDE-EFFECTS
  - Common or very common · Abdominal pain · angina · anorexia · arrhythmia · diarrhoea · dizziness · dyspepsia · ecchymosis · flatulence · headache · malaise · nausea · oedema · palpitation · pharyngitis · pruritus · rash · rhinitis · tachycardia · vomit
  - Uncommon · Abnormal dreams · anaemia · anxiety · congestive heart failure · cough · diabetes mellitus · dyspnoea · gastritis · haemorrhage · hyperglycaemia · insomnia · myalgia · myocardial infarction · pneumonia · postural hypotension
  - Rare · Bleeding disorders · increased urinary frequency · renal impairment · thrombocythaemia

- FREQUENCY NOT KNOWN
  - Agranulocytosis · aplastic anaemia · conjunctivitis · hepatitis · hot flushes · hypertension · leucopenia · pancytopenia · pyrexia · Stevens-Johnson syndrome · thrombocytopaenia · tinnitus · toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

- Blood Disorders
  - A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

- PREGNANCY
  - Avoid — toxicity in animal studies.

- BREAST FEEDING
  - Present in milk in animal studies—manufacturer advises avoid.

- HEPATIC IMPAIRMENT
  - Avoid in moderate or severe liver disease.

- RENAL IMPAIRMENT
  - Avoid if eGFR less than 25 mL/minute/1.73 m².

- PATIENT AND CARER ADVICE
  - Blood disorders. Patients should be advised to report any unexplained bleeding, bruising, sore throat, or fever.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
  - Cilostazol is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment should have the option to continue until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA223

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2005) that cilostazol is not recommended for the treatment of intermittent claudication within NHS Scotland.

MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Cilostazol (Non-proprietary)
  - Cilostazol 50 mg Cilostazol 50mg tablets | 56 tablet [POM] £40.05
  - Cilostazol 100 mg Cilostazol 100mg tablets | 56 tablet [POM] £31.70
  - Pletal (Otsuka Pharmaceuticals (U.K.) Ltd)
  - Cilostazol 50 mg Pletal 50mg tablets | 56 tablet [POM] £35.31
  - Cilostazol 100 mg Pletal 100mg tablets | 56 tablet [POM] £33.37

LIPID MODIFYING DRUGS > NICOTINIC ACID DERIVATIVES

Inositol nicotinate

- INDICATIONS AND DOSE
  - Peripheral vascular disease
    - BY MOUTH
      - Adult: 3 g daily in 2–3 divided doses; maximum 4 g per day

- CONTRA-INDICATIONS
  - Acute phase of a cerebrovascular accident · recent myocardial infarction

- CAUTIONS
  - Cerebrovascular insufficiency · unstable angina

- SIDE-EFFECTS
  - Dizziness · flushing · headache · hypotension · nausea · oedema · paraesthesia · rash · syncope · vomiting

- PREGNANCY
  - No information available—manufacturer advises avoid unless potential benefit outweighs risk.
● NATIONAL FUNDING/ACCESS DECISIONS
   NICE technology appraisals (TAs)
   ▶ Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
   Inositol nicotinate is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving treatment should have the option to continue until they and their clinician consider it appropriate to stop.
   www.nice.org.uk/TA223

● LESS SUITABLE FOR PRESCRIBING
   Less suitable for prescribing.

● MEDICINAL FORMS
   There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
   Tablet
   ▶ Hexopal (Genus Pharmaceuticals Ltd)
   Inositol nicotinate 500 mg Hexopal 500mg tablets | 100 tablet £26.15 DT price = £26.15
   Inositol nicotinate 750 mg Hexopal Forte 750mg tablets | 112 tablet £43.37 DT price = £43.37
   Capsule
   ▶ Inositol nicotinate (Non-proprietary)
   Inositol nicotinate 500 mg Solgar No-Flush Niacin 500mg capsules | 50 capsule no price available

VASCULAR DISEASES

VASODILATORS ➔ FLAVONOIDS

Oxerutins

● INDICATIONS AND DOSE
   Relief of symptoms of oedema associated with chronic venous insufficiency
   ▶ BY MOUTH
   ▶ Adult: 500 mg twice daily

● SIDE-EFFECTS
   Flushing · headache · mild gastro-intestinal disturbances · rash

● LESS SUITABLE FOR PRESCRIBING
   Oxerutins (rutosides) are not vasodilators and are not generally regarded as effective preparations as capillary sealants or for the treatment of cramps; they are less suitable for prescribing.

● MEDICINAL FORMS
   There can be variation in the licensing of different medicines containing the same drug.
   Capsule
   ▶ Paroven (Novartis Consumer Health UK Ltd)
   Oxerutins 250 mg Paroven 250mg capsules | 120 capsule £16.81 DT price = £16.81

Moxisylyte
(Thymoxamine)

● INDICATIONS AND DOSE
   Primary Raynaud’s syndrome (short-term treatment)
   ▶ BY MOUTH
   ▶ Adult: Initially 40 mg 4 times a day, increased if necessary to 80 mg 4 times a day, increase dose if poor initial response, discontinue after 2 weeks if no response

● CONTRA-INDICATIONS
   Active liver disease

● CAUTIONS
   Diabetes mellitus

● SIDE-EFFECTS
   Cholestatic jaundice · diarrhoea · dizziness · flushing · headache · hepatic reactions · hepatitis · nausea

● PREGNANCY
   Manufacturer advises avoid.

● LESSE SUITABLE FOR PRESCRIBING
   Less suitable for prescribing.

● MEDICINAL FORMS
   There can be variation in the licensing of different medicines containing the same drug.
   Tablet
   CAUTIONARY AND ADVISORY LABELS 21
   ▶ Moxisylyte (as Moxisylyte hydrochloride) 40 mg Opilon 40mg tablets | 112 tablet £90.22 DT price = £90.22

Naftidrofuryl oxalate

● INDICATIONS AND DOSE
   Peripheral vascular disease
   ▶ BY MOUTH
   ▶ Adult: 100–200 mg 3 times a day, patients taking naftidrofuryl should be assessed for improvement after 3–6 months

   Cerebral vascular disease
   ▶ BY MOUTH
   ▶ Adult: 100 mg 3 times a day, patients taking naftidrofuryl should be assessed for improvement after 3–6 months

● SIDE-EFFECTS
   Epigastric pain · hepatic failure · hepatitis · nausea · rash

● NATIONAL FUNDING/ACCESS DECISIONS
   NICE technology appraisals (TAs)
   ▶ Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
   Naftidrofuryl oxalate is an option for the treatment of intermittent claudication in patients with peripheral arterial disease in whom vasodilator therapy is considered appropriate.
   www.nice.org.uk/TA223

● MEDICINAL FORMS
   There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution
   Capsule
   CAUTIONARY AND ADVISORY LABELS 25, 27
   ▶ Naftidrofuryl oxalate (Non-proprietary)
   Naftidrofuryl oxalate 100 mg Naftidrofuryl 100mg capsules | 84 capsule £9.00 DT price = £4.38
   ▶ Praxilene (Merck Serono Ltd)
   Naftidrofuryl oxalate 100 mg Praxilene 100mg capsules | 84 capsule £8.10 DT price = £4.38

Pentoxifylline
(Oxpentifylline)

● INDICATIONS AND DOSE
   Peripheral vascular disease | Venous leg ulcer (adjunct)
   ▶ BY MOUTH
   ▶ Adult: 400 mg 2–3 times a day

● UNLICENSED USE
   Use of pentoxifylline as adjunct therapy for venous leg ulcers is an unlicensed indication.

● CONTRA-INDICATIONS
   Acute myocardial infarction · cerebral haemorrhage · extensive retinal haemorrhage · severe cardiac arrhythmias

● CAUTIONS
   Avoid in acute porphyrias

● INTERACTIONS
   ▶ Appendix 1 (pentoxifylline)

● SIDE-EFFECTS
   ▶ Rare: Angina · hypotension
Vein malformations

SCLEROSANTS

### Sodium tetrade cyl sulfate

**INDICATIONS AND DOSE**
Sclerotherapy of reticular veins and spider veins in legs and varicose veins
- **BY INTRAVENOUS INJECTION**
- Adult: Test dose recommended before each treatment (consult product literature)

**CONTRA-INDICATIONS**
- Acute infection
- Asthma
- Blood disorders
- Deep vein thrombosis
- High risk of thromboembolism
- Hyperthyroidism
- Inability to walk
- Neoplasm
- Oclusive arterial disease
- Phlebitis
- Pulmonary embolism
- Recent acute superficial thrombophlebitis
- Recent surgery
- Respiratory disease
- Significant valvular incompetence in deep veins
- Skin disease
- Symptomatic patent foramen ovale (if administered as foam)
- Uncontrolled diabetes mellitus
- Varicose veins caused by tumours (unless tumour removed)

**CAUTIONS**
- Arterial disease
- Asymptomatic patent foramen ovale (use smaller volumes and avoid Valsalva manoeuvre immediately after administration)
- Extravasation may cause necrosis of tissues
- History of migraine (use smaller volumes)
- Resuscitation facilities must be available
- Venous insufficiency with lymphoedema (pain and inflammation may worsen)

**SIDE-EFFECTS**
- **Common or very common**
  - Local burning
  - Local pain
  - Phlebitis
  - Skin discoloration
  - Superficial thrombophlebitis
  - Telangiectatic matting
- **Uncommon**
  - Deep vein thrombosis
  - Scrotum
- **Rare**
  - Chest pain
  - Cough
  - Headache
  - Migraine
  - Paroxysmal
  - Shortness of breath
  - Vasovagal reactions
- **Very rare**
  - Anaphylaxis
  - Circulatory collapse
  - Diarrhoea
  - Dry mouth
  - Fever
  - Hot flushes
  - Hypersensitivity reactions
  - Nausea
  - Necrosis of skin and tissues
  - Palpitation
  - Pulmonary embolism
  - Sloughing of skin and tissues
  - Stroke
  - Swollen tongue
  - Transient ischaemic attack
  - Vasculitis
  - Vomiting
  - Weakness
- **PREGNANCY**
  - Avoid unless benefits outweigh risks
- **BREAST FEEDING**
  - Use with caution

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Excipients:** May contain Benzyl alcohol
- **Fibro-Vein** (STD Pharmaceutical Products Ltd)
  - Sodium tetrade y sulfate 2 mg per 1 ml
    - Fibrovin 0.2% solution for injection 5 ml vials [10 vial [POM] £73.61
  - Sodium tetrade y sulfate 5 mg per 1 ml
    - Fibrovin 0.5% solution for injection 2 ml ampoules [5 ampoule [POM] £18.93
  - Sodium tetrade y sulfate 10 mg per 1 ml
    - Fibrovin 1% solution for injection 2 ml ampoules [5 ampoule [POM] £22.61
  - Sodium tetrade y sulfate 30 mg per 1 ml
    - Fibrovin 3% solution for injection 2 ml ampoules [5 ampoule [POM] £33.65

**Fibro-Vein**
- **Fibro-Vein 400 mg**

**Fibro-Vein 1000 mg**
- **Fibro-Vein 0% solution**
  - 5% solution | 5 ml [POM] £61.33
  - 10% solution | 5 ml [POM] £93.66

**Fibro-Vein 3000 mg**
- **Fibro-Vein 1% solution**
  - 2% solution | 10 ml [POM] £66.66

**Fibro-Vein 6000 mg**
- **Fibro-Vein 2% solution**
  - 3% solution | 10 ml [POM] £166.66

**NATIONAL FUNDING/ACCESS DECISIONS**

- NICE technology appraisals (TAs)
  - Citostazol, nafitidroyl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
  - Pentoxifylline is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment should have the option to continue until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA223

**LESS SUITABLE FOR PRESCRIBING**
Less suitable for prescribing.

**CONTRA-INDICATIONS**
- Arterial disease
- Uncontrolled diabetes mellitus
- Recent surgery
- Neoplasm
- Patent foramen ovale (if administered as foam)
- Deep vein thrombosis
- Scrotum
- Recent acute respiratory disease
- Skin discoloration
- Telangiectatic matting
- Local burning
- Local pain
- Phlebitis
- Skin discoloration
- Superficial thrombophlebitis
- Telangiectatic matting
- Deep vein thrombosis
- Sloughing of skin and tissues
- Stroke
- Swollen tongue
- Transient ischaemic attack
- Vasculitis
- Vomiting
- Weakness
- Avoid unless benefits outweigh risks
- Use with caution

**Cautionary and advisory labels**

- Oral solution
- May contain benzyl alcohol

| Sodium tetrade y sulfate 2 mg per 1 ml | Fibrovin 0.2% solution for injection 5 ml vials | 10 vial [POM] £73.61
| Sodium tetrade y sulfate 5 mg per 1 ml | Fibrovin 0.5% solution for injection 2 ml ampoules | 5 ampoule [POM] £18.93
| Sodium tetrade y sulfate 10 mg per 1 ml | Fibrovin 1% solution for injection 2 ml ampoules | 5 ampoule [POM] £22.61
| Sodium tetrade y sulfate 30 mg per 1 ml | Fibrovin 3% solution for injection 2 ml ampoules | 5 ampoule [POM] £33.65
| Fibrovin 3% solution for injection 5 ml vials | 10 vial [POM] £166.66

**Side-effects**
- **Common or very common**
  - Local burning
  - Local pain
  - Phlebitis
  - Skin discoloration
  - Superficial thrombophlebitis
  - Telangiectatic matting
- **Uncommon**
  - Deep vein thrombosis
  - Scrotum
- **Rare**
  - Chest pain
  - Cough
  - Headache
  - Migraine
  - Paroxysmal
  - Shortness of breath
  - Vasovagal reactions
- **Very rare**
  - Anaphylaxis
  - Circulatory collapse
  - Diarrhoea
  - Dry mouth
  - Fever
  - Hot flushes
  - Hypersensitivity reactions
  - Nausea
  - Necrosis of skin and tissues
  - Palpitation
  - Pulmonary embolism
  - Sloughing of skin and tissues
  - Stroke
  - Swollen tongue
  - Transient ischaemic attack
  - Vasculitis
  - Vomiting
  - Weakness
- **Pregnancy**
  - Avoid unless benefits outweigh risks
- **Breast Feeding**
  - Use with caution

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Excipients:** May contain benzyl alcohol
- **Fibro-Vein** (STD Pharmaceutical Products Ltd)
  - Sodium tetrade y sulfate 2 mg per 1 ml
    - Fibrovin 0.2% solution for injection 5 ml vials | 10 vial [POM] £73.61
  - Sodium tetrade y sulfate 5 mg per 1 ml
    - Fibrovin 0.5% solution for injection 2 ml ampoules | 5 ampoule [POM] £18.93
  - Sodium tetrade y sulfate 10 mg per 1 ml
    - Fibrovin 1% solution for injection 2 ml ampoules | 5 ampoule [POM] £22.61
  - Sodium tetrade y sulfate 30 mg per 1 ml
    - Fibrovin 3% solution for injection 2 ml ampoules | 5 ampoule [POM] £33.65
  - Fibrovin 3% solution for injection 5 ml vials | 10 vial [POM] £166.66

**National funding/access decisions**

- **NICE technology appraisals (TAs)**
  - Citostazol, nafitidroyl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
  - Pentoxifylline is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment should have the option to continue until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA223

**Less suitable for prescribing**
Less suitable for prescribing.
Chapter 3
Respiratory system

Respiratory system, drug delivery

Inhalation
This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side-effects are reduced.

Inhaler devices
These include pressurised metered-dose inhalers, breath-actuated inhalers, and dry powder inhalers. Many patients can be taught to use a pressurised metered-dose inhaler effectively but some patients, particularly the elderly and children, find them difficult to use. Spacer devices can help such patients because they remove the need to coordinate actuation with inhalation. Dry powder inhalers may be useful in adults and children over 5 years who are unwilling or unable to use a pressurised metered-dose inhaler. Alternatively, breath-actuated inhalers are suitable for adults and older children provided they can use the device effectively.

Pressurised metered-dose inhalers are an effective and convenient method of drug administration in mild to moderate asthma.

On changing from a pressurised metered-dose inhaler to a dry powder inhaler, patients may notice a lack of sensation in the mouth and throat previously associated with each actuation. Coughing may also occur.

The patient should be instructed carefully on the use of the inhaler and it is important to check that the inhaler continues to be used correctly because inadequate inhalation technique may be mistaken for a lack of response to the drug.

Spacer devices
Spacer devices remove the need for coordination between actuation of a pressurised metered-dose inhaler and inhalation. The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx and allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Spacer devices are particularly useful for patients with poor inhalation technique, for children, for patients requiring high doses of inhaled corticosteroids, for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids. The size of the spacer is important, the larger spacers with a one-way valve (Volumatic®) being most effective. It is important to prescribe a spacer device that is compatible with the metered-dose inhaler, see devices below. Spacer devices should not be regarded as interchangeable; patients should be advised not to switch between spacer devices.

Use and care of spacer devices
Patients should inhale from the spacer device as soon as possible after actuation because the drug aerosol is very short-lived; single-dose actuation is recommended. Tidal breathing is as effective as single breaths. The device should be cleaned once a month by washing in mild detergent and then allowed to dry in air without rinsing; the mouthpiece should be wiped clean of detergent before use. Some manufacturers recommend more frequent cleaning, but this should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

Nebulisers
Solutions for nebulisation are available for use in severe acute asthma. They are administered over 5–10 minutes from a nebuliser usually driven by oxygen in hospital.

Patients with a severe attack of asthma should preferably have oxygen during nebulisation since beta, agonists can increase arterial hypoxaemia.

A nebuliser converts a solution of a drug into an aerosol for inhalation. It is used to deliver higher doses of drug to the airways than is usual with standard inhalers. The main indications for use of a nebuliser are to deliver:

- a beta, agonist or ipratropium bromide p. 234 to a patient with an acute exacerbation of asthma or of chronic obstructive pulmonary disease;
- a beta, agonist, corticosteroid, or ipratropium bromide on a regular basis to a patient with severe asthma or reversible airways obstruction when the patient is unable to use other inhalational devices;
- an antibiotic (such as colistimethate sodium p. 512) or a mucolytic to a patient with cystic fibrosis;
- Budesonide p. 246 or adrenaline/epinephrine p. 211 to a child with severe croup;
- Pentamidine isetionate p. 555 for the prophylaxis and treatment of pneumocystis pneumonia.

The use of nebulisers in chronic persistent asthma and chronic obstructive pulmonary disease should be considered only:

- after a review of the diagnosis;
- after review of therapy (see also Chronic Obstructive Pulmonary Disease) and the patient’s ability to use handheld devices;
- after increased doses of inhaled therapy from hand-held inhalers (with a spacer if necessary) have been tried for 2 weeks;
- if the patient remains breathless, despite correctly using optimal therapy.

Before prescribing a nebuliser, a home trial should preferably be undertaken to monitor response for up to 2 weeks on standard treatment and up to 2 weeks on nebulised treatment. If prescribed, patients must:
have clear instructions from a doctor, specialist nurse, physiotherapist, or pharmacist on the use of the nebuliser (including maintenance and cleaning) and on peak-flow monitoring;

- be instructed not to treat acute attacks at home without also seeking help;

- have regular follow up by a doctor, specialist nurse or physiotherapist after about 1 month and annually thereafter.

The proportion of a nebuliser solution that reaches the lungs depends on the type of nebuliser and although it can be as high as 30%, it is more frequently close to 10% and sometimes below 10%. The remaining solution is left in the nebuliser as residual volume or is deposited in the mouthpiece and tubing. The extent to which the nebulised solution is deposited in the airways or alveoli depends on the droplet size, pattern of breath inhalation, and condition of the lung. Droplets with a mass median diameter of 1–5 microns are deposited in the airways and are therefore appropriate for asthma, whereas a particle size of 1–2 microns is needed for alveolar deposition of pentamidine isethionate to combat pneumocystis infection. The type of nebuliser is therefore chosen according to the deposition required and according to the viscosity of the solution.

**Jet nebulisers**

Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum gas flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

For patients at risk of hypercapnia, such as those with chronic obstructive pulmonary disease, oxygen can be dangerous and the nebuliser should be driven by air. If oxygen is required, it should be given simultaneously by nasal cannula.

**Tubing**

The Department of Health has reminded users of the need to use the correct grade of tubing when connecting a nebuliser to a medical gas supply or compressor.

**Ultrasonic nebulisers**

Ultrasonic nebulisers produce an aerosol by ultrasonic vibration of the drug solution and therefore do not require a gas flow; they are not suitable for the nebulisation of some drugs, such as dornase alfa p. 274 and nebulised suspensions.

**Nebuliser diluent**

Nebulisation may be carried out using an undiluted nebuliser solution or it may require dilution beforehand. The usual diluent is sterile sodium chloride 0.9% (physiological saline).

In England and Wales nebulisers and compressors are not available on the NHS (but they are free of VAT); some nebulisers (but not compressors) are available on form GP10A in Scotland (for details consult Scottish Drug Tariff).

**Oral**

The oral route is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta₂ agonists, corticosteroids, theophylline p. 256, and leukotriene receptor antagonists.

**Parenteral**

Drugs such as beta₂ agonists, corticosteroids, and aminophylline p. 255 can be given by injection in acute severe asthma when administration by nebulisation is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

**Peak flow meters**

When used in addition to symptom-based monitoring, peak flow monitoring has not been proven to improve asthma control in either adults or children, however measurement of peak flow may be of benefit in adult patients who are ‘poor perceivers’ and hence slow to detect deterioration in their asthma, and for those with more severe asthma.

When peak flow meters are used, patients must be given clear guidelines as to the action they should take if their peak flow falls below a certain level. Patients can be encouraged to adjust some of their own treatment (within specified limits) according to changes in peak flow rate.

Peak flow charts should be issued to patients where appropriate, and are available to purchase from:

- 3M Security Print and Systems Limited. Gorse Street, Chadderton, Oldham, OL9 9QH. Tel: 0845 610 1112
- GP practices can obtain supplies through their Area Team stores.
- NHS Hospitals can order supplies from www.nhsforms.co.uk/ or by emailing nhsforms@mmm.com.

In Scotland, peak flow charts can be obtained by emailing stockorders.dppas@apsgroup.co.uk.

**NICE technology appraisals (TAs)**

**Inhaler devices for children under 5 years with chronic asthma (August 2000) NICE TA10**

A child’s needs and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;
- if this is not effective, and depending on the child’s condition, nebulised therapy may be considered and, in children over 3 years, a dry powder inhaler may also be considered.

www.nice.org.uk/TA10

**Inhaler devices for children 5–15 years with chronic asthma (March 2002) NICE TA28**

A child’s needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- for other inhaled drugs, particularly bronchodilators, a wider range of devices should be considered;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored.

www.nice.org.uk/TA38

## 1 Airways disease, obstructive

### Asthma

**Description of condition**

Asthma is a common chronic inflammatory condition of the airways characterised by bronchoconstriction. The most frequent symptoms are cough, wheezing, chest tightness, and shortness of breath. The bronchoconstriction is usually reversible (either spontaneously or with the aid of...
medication) leading to intermittent symptoms, but in some patients with chronic asthma the inflammation may result in irreversible airway obstruction. Occasionally, asthma symptoms can get gradually or suddenly worse provoking an acute asthma attack that, if severe, may require hospitalisation.

Aims of treatment
In clinical practice, patients may choose to balance the aims of asthma management against the potential side-effects or inconvenience of taking medication necessary to achieve perfect control. Complete control of asthma is defined as no daytime symptoms, no night-time awakening due to asthma, no asthma attacks, no need for rescue medication, no limitations on activity including exercise, and normal lung function (in practical terms FEV₁ and/or peak flow > 80% predicted or best).

Lifestyle changes
Weight loss in overweight patients may lead to an improvement in asthma symptoms. Parents with asthma should be advised about the danger to themselves and to their children with asthma, of smoking, and be offered appropriate support to stop smoking. Breathing exercise programmes (including physiotherapist-taught methods) can be offered as an adjuvant to drug treatment in order to improve quality of life and reduce symptoms.

Management of chronic asthma
A stepwise approach aims to stop symptoms quickly and to improve peak flow. Start at the step most appropriate to initial severity of asthma. The aim is to achieve early control and to maintain it by stepping up treatment as necessary and stepping down treatment when control is good. Before initiating a new drug consider whether diagnosis is correct, check compliance and inhaler technique, and eliminate trigger factors for acute attacks.

Adult and child over 5 years
Step 1—Mild intermittent asthma
- Start inhaled short-acting beta₂ agonist (such as salbutamol p. 239 or terbutaline sulfate p. 241) as required.

Patients using more than one short-acting bronchodilator inhaler a month should have their asthma urgently assessed and action taken to improve poorly controlled asthma.

Inhaled ipratropium bromide p. 234, (or, if over 12 years, short-acting beta₂, agonist tablets and syrup, or theophylline p. 256) also act as short-acting bronchodilators but inhaled short-acting beta₂ agonists are preferred.

Move to step 2 if the patient presents with any one of the following features; is using an inhaled beta₂ agonist three times a week or more, being symptomatic three times a week or more, experiencing night-time symptoms at least once a week, or has had an asthma attack in the last 2 years.

Step 2—Regular preventer therapy
- Consider adding regular inhaled standard-dose corticosteroid (alternatives to inhaled corticosteroid are leukotriene receptor antagonists, theophylline, inhaled sodium cromoglicate p. 253, or inhaled nedocromil sodium p. 253, but are less effective).

Start the inhaled corticosteroid at a dose appropriate to severity of disease and adjust to the lowest effective dose at which control of asthma is maintained. Inhaled corticosteroids (except ciclosporine p. 247) should be initially taken twice daily, however, the same total daily dose can be considered once a day if good control is established.

Note, inhaled standard-dose corticosteroid
- Adult and child over 12 years: 200–800 micrograms/day beclometasone dipropionate p. 244 or equivalent
- Child 5–12 years: 200–400 micrograms/day beclometasone dipropionate or equivalent

Step 3—Initial add-on therapy
- Consider adding a regular inhaled long-acting beta₂ agonist (LABA) such as formoterol fumarate p. 237 or salmeterol p. 239 (or, in adults only, indacaterol p. 238 or olodaterol p. 238) to be used in conjunction with an inhaled corticosteroid (see also CHM advice for formoterol fumarate and salmeterol).

If the patient is gaining some benefit from addition of a LABA but control is inadequate then continue the LABA and increase dose of inhaled corticosteroid to top end of inhaled standard-dose corticosteroid range. If there is no response to the LABA, discontinue and increase dose of inhaled corticosteroid. If control is still inadequate, start a trial of either a leukotriene receptor antagonist (montelukast p. 251, or zafirlukast p. 252 if over 12 years) or modified-release theophylline.

Step 4—Persistent poor control
Consider the following options:
- Increase dose of inhaled corticosteroid (a spacer should be used), or
- Add a leukotriene receptor antagonist, modified-release theophylline, or modified-release oral beta₂ agonist (caution in patients already taking a LABA).

Note, increased inhaled corticosteroid dose
- Adult and child over 12 years: up to 2000 micrograms/day beclometasone dipropionate or equivalent
- Child 5–12 years: up to 800 micrograms/day beclometasone dipropionate or equivalent.

Step 5—Continuous or frequent use of oral corticosteroids
- Add a regular oral corticosteroid (prednisolone p. 622, as single daily dose) at lowest dose to provide adequate control; continue high-dose inhaled corticosteroid (in exceptional cases, this may exceed licensed doses).

Child under 5 years
Step 1—Mild intermittent asthma
- Inhaled short-acting beta₂ agonist (such as salbutamol or terbutaline sulfate) as required.

Children identified to be using more than one short-acting bronchodilator inhaler a month should have their asthma urgently assessed and action taken to improve poorly controlled asthma.

Move to step 2 if the child presents with any one of the following features; is using an inhaled beta₂ agonist three times a week or more, being symptomatic three times a week or more, experiencing night-time symptoms at least once a week.

Step 2—Regular preventer therapy
- Consider adding regular standard-dose inhaled corticosteroid

If the child is unable to take an inhaled corticosteroid, a leukotriene receptor antagonist (such as montelukast) is an effective first-line preventer.
Start inhaled corticosteroid at a dose appropriate to severity of disease and adjust to the lowest effective dose at which control of asthma is maintained. Note, inhaled standard-dose corticosteroid beclometasone dipropionate or equivalent Beclometasone dipropionate and budesonide are approximately equivalent in clinical practice although there may be variations with different drug delivery devices. Fluticasone p. 248 provides equal activity to beclometasone dipropionate p. 244 and budesonide p. 246 at half the dosage.

Administration of high doses of inhaled corticosteroids in children may be associated with systemic side-effects, including growth failure, reduced bone mineral density and adrenal suppression. If asthma is not adequately controlled, move to step 3.

**Step 3—Initial add-on therapy**
- In children 2–5 years, add a leukotriene receptor antagonist if not added during step 2. If a leukotriene receptor antagonist was added at step 2, reconsider addition of standard-dose inhaled corticosteroid
- In children under 2 years, consider proceeding to step 4

**Step 4—Persistent poor control**
- Refer child to respiratory paediatrician

**Stepping down**

Once asthma is controlled, it is recommended to step down therapy and continue to regularly review the patient. When deciding which drug to step down first and at what rate, the severity of asthma, the side-effects of treatment, duration on current dose, the beneficial effect achieved, and the patient’s preference, should be considered.

Patient should be maintained at the lowest possible dose of inhaled corticosteroid. Reductions should be considered every three months, decreasing the dose by approximately 25–50% each time. Reduce the dose slowly as patients deteriorate at different rates.

**Management of acute asthma**

**Adults**
The nature of treatment required for the management of acute asthma depends on the level of severity, described as follows:

**Moderate acute asthma**
- Increasing symptoms
- Peak flow > 50–75% best or predicted
- No features of acute severe asthma

**Severe acute asthma**
Any one of the following:
- Peak flow 33–50% best or predicted
- Respiratory rate ≥ 25/min
- Heart rate ≥ 110/min
- Inability to complete sentences in one breath

**Life-threatening acute asthma**
Any one of the following, in a patient with severe asthma:
- Peak flow < 33% best or predicted
- Arterial oxygen saturation (SpO₂) < 92%
- Partial arterial pressure of oxygen (PaO₂) < 8 kPa
- Normal partial arterial pressure of carbon dioxide (PaCO₂) (4.6–6.0 kPa)
- Silent chest
- Cyanosis
- Poor respiratory effort
- Arrhythmia
- Exhaustion
- Altered conscious level
- Hypotension

**Near-fatal acute asthma**
- Raised PaCO₂, requiring mechanical ventilation with raised inflation pressures, or both

**Patients with moderate asthma should be treated at home or in primary care according to response to treatment, while patients with severe or life-threatening acute asthma should start treatment as soon as possible and be admitted to hospital immediately following initial assessment.**

Supplementary oxygen should be given to all hypoxaemic patients with acute severe asthma to maintain a SpO₂ level between 94–98%.

First-line treatment for acute asthma is a high-dose inhaled short-acting beta₂ agonist (salbutamol p. 239 or terbutaline sulfate p. 241) given as soon as possible. A pressurised metered dose inhaler with spacer device is preferred in patients with non-life-threatening acute asthma. Whereas, in patients with life-threatening acute asthma, a beta₂ agonist administered by an oxygen-driven nebuliser is recommended. If the response to an initial dose of short-acting beta₂ agonist is poor, consider continuous nebulisation with an appropriate nebuliser. Intravenous beta₂ agonists are reserved for those patients in whom inhaled therapy cannot be used reliably.

In all cases of acute asthma, patients should be prescribed an adequate dose of oral prednisolone p. 622 once daily for at least 5 days or until recovery. Parenteral hydrocortisone p. 620 or intramuscular methylprednisolone p. 621 are alternatives in patients who are unable to take oral prednisolone.

Nebulised ipratropium bromide p. 234 may be combined with a nebulised beta₂ agonist in patients with acute severe asthma. A single intravenous dose of magnesium sulfate may be considered in patients with severe acute asthma (peak flow < 50% best or predicted) who have not had a good initial response to inhaled bronchodilator therapy [unlicensed use]. In an acute asthma attack, intravenous aminophylline p. 255 is not likely to produce any additional bronchodilation compared to standard therapy with inhaled bronchodilators and corticosteroids. However, in some patients with near-fatal or life-threatening acute asthma with a poor initial response to beta₂ agonist therapy to provide greater bronchodilation.

There is some evidence that magnesium sulfate p. 924 has bronchodilator effects. A single intravenous dose of magnesium sulfate may be considered in patients with severe acute asthma (peak flow < 50% best or predicted) who have not had a good initial response to inhaled bronchodilator therapy [unlicensed use]. In an acute asthma attack, intravenous aminophylline p. 255 is not likely to produce any additional bronchodilation compared to standard therapy with inhaled bronchodilators and corticosteroids. However, in some patients with near-fatal or life-threatening acute asthma with a poor initial response to beta₂ agonist therapy, intravenous aminophylline may provide some benefit. Magnesium sulfate by intravenous infusion or aminophylline should only be used after consultation with, or on the recommendation of, senior medical staff.

**Child over 2 years**
The nature of treatment required for the management of acute asthma depends on the level of severity, described as follows:

**Moderate acute asthma**
- Able to talk in sentences
- Arterial oxygen saturation (SpO₂) ≥ 92%
- Peak flow ≥ 50% best or predicted
- Heart rate ≤ 140/minute in children aged 2–5 years; heart rate ≤ 125/minute in children over 5 years
- Respiratory rate ≤ 40/minute in children aged 2–5 years; respiratory rate ≤ 30/minute in children over 5 years

**Severe acute asthma**
- Can’t complete sentences in one breath or too breathless to talk or feed
- SpO₂ < 92%
- Peak flow 33–50% best or predicted
- Heart rate > 140/minute in children aged 2–5 years; heart rate > 125/minute in children aged over 5 years
- Respiratory rate > 40/minute in children aged 2–5 years; respiratory rate > 30/minute in children aged over 5 years
Life-threatening acute asthma

Any one of the following in a child with severe asthma:
- SpO₂ < 92%
- Peak flow < 33% best or predicted
- Silent chest
- Cyanosis
- Poor respiratory effort
- Hypotension
- Exhaustion
- Confusion

Following initial assessment, supplementary high flow oxygen should be given to all children with life-threatening acute asthma or SpO₂ < 94% to achieve normal saturations of 94–98%.

First-line treatment for acute asthma is an inhaled short-acting beta agonist (salbutamol or terbutaline sulfate) given as soon as possible, ideally via a metered dose inhaler and spacer device in mild to moderate acute asthma. Children with severe or life-threatening acute asthma should be transferred to hospital urgently.

In all cases of acute asthma, children should be prescribed an adequate once daily dose of oral prednisolone. Treatment for up to 3 days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. Intravenous hydrocortisone should be reserved for severely affected children who are unable to retain oral medication.

Nebulised ipratropium bromide can be combined with beta₂ agonist treatment for children with severe or life-threatening acute asthma or in those with a poor initial response to beta₂ agonist therapy to provide greater bronchodilation. Consider adding magnesium sulfate p. 924 to nebulised salbutamol p. 239 and ipratropium bromide p. 234 in the first hour in children with a short duration of acute severe asthma symptoms presenting with an oxygen saturation less than 92%.

Children with continuing severe asthma despite frequent nebulated beta₂ agonists and ipratropium bromide plus oral corticosteroids, and those with life-threatening features, need urgent review by a specialist with a view to transfer to a high dependency unit or paediatric intensive care unit (PICU) to receive second-line intravenous therapies.

In a severe asthma attack where the child has not responded to initial inhaled therapy, early addition of a single bolus dose of intravenous salbutamol may be an option. Continuous intravenous infusion of salbutamol, administered under specialist supervision with continuous ECG and electrolyte monitoring, should be considered in children with unreliable inhalation or severe refractory asthma. Aminophylline p. 255 may be considered in children with severe or life-threatening acute asthma unresponsive to maximal doses of bronchodilators and corticosteroids. Aminophylline is not recommended in children with mild to moderate acute asthma. Intravenous magnesium sulfate has been used for acute asthma [unlicensed use] although its place in management is not yet established.

**Child under 2 years**

Inhaled short-acting beta₂ agonists are the initial treatment of choice for acute asthma in children under 2 years. For mild to moderate acute asthma attacks, a metered-dose inhaler with a spacer and mask is the optimal drug delivery device. In a hospital setting, consider oral prednisolone daily for up to 3 days, early in the management of severe asthma attacks. For more severe symptoms, inhaled ipratropium bromide in combination with an inhaled beta₂ agonist is also an option.

Follow up in all cases

Episodes of acute asthma may be a failure of preventative therapy, review is required to prevent further episodes. A careful history should be taken to establish the reason for the asthma attack. Inhaler technique should be checked and regular treatment should be reviewed. Patients should be given a written asthma action plan aimed at preventing relapse, optimising treatment, and preventing delay in seeking assistance in future attacks. It is essential that the patient’s GP practice is informed within 24 hours of discharge from the emergency department or hospital following an asthma attack. Patients who have had a near-fatal asthma attack should be kept under specialist supervision indefinitely. A respiratory specialist should follow up all patients admitted with a severe asthma attack for at least one year after the admission.

**Exercise-induced asthma**

For most patients, exercise-induced asthma is an illustration of poorly controlled asthma and regular treatment including inhaled corticosteroids should therefore be reviewed. If exercise is a specific problem in patients already taking inhaled corticosteroids who are otherwise well controlled, consider adding either a leukotriene receptor antagonist, a long-acting beta₂ agonist, an oral beta₂ agonist, sodium cromoglicate p. 253 or nedocromil sodium p. 253, or theophylline p. 256. An inhaled short-acting beta₂ agonist used immediately before exercise is the drug of choice.

**Pregnancy and breast-feeding**

Women with asthma should be closely monitored during pregnancy. It is particularly important that asthma should be well controlled during pregnancy; when this is achieved asthma has no important effects on pregnancy, labour, or on the fetus. Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control. Drugs for asthma should preferably be administered by inhalation to minimise exposure of the fetus. Short-acting beta₂ agonists, long-acting beta₂ agonists, oral and inhaled corticosteroids, sodium cromoglicate, nedocromil sodium, and oral and intravenous theophyllines can be used as normal during pregnancy. There is limited information on use of leukotriene receptor antagonists during pregnancy, however they may be used if potential benefit outweighs risk. Drugs for asthma, including corticosteroid tablets, can be used as normal and in-line with manufacturers’ recommendations in breast-feeding.

Severe acute attacks of asthma can have an adverse effect on pregnancy and should be treated promptly in hospital with conventional therapy, including nebulisation of a beta₂ agonist and oral or parenteral administration of a corticosteroid; prednisolone p. 622 is the preferred corticosteroid for oral administration since very little of the drug reaches the fetus. Oxygen should be given immediately to maintain arterial oxygen saturation of 94–98% and prevent maternal and fetal hypoxia.

**Useful Resources**


**Bronchodilators**

Adrenoceptor agonists (sympathomimetics)

Selective beta₂ agonists produce bronchodilation. A short-acting beta₂ agonist is used for immediate relief of asthma symptoms while some long-acting beta₂ agonists are added
to an inhaled corticosteroid in patients requiring prophylactic treatment.

The selective beta₂ agonists (selective beta₂-adrenoceptor agonists, selective beta₂ stimulants) such as salbutamol p. 239 or terbutaline sulfate p. 241 are the safest and most effective short-acting beta₂ agonists for asthma. Less selective beta₂ agonists such as ephedrine hydrochloride p. 254 is less suitable and less safe for use as a bronchodilator than the selective beta₂ agonists, because it is more likely to cause arrhythmias and other side-effects; it should be avoided whenever possible.

Adrenaline/epinephrine p. 211 (which has both alpha- and beta-adrenoceptor agonist properties) is used in the emergency management of acute allergic and anaphylactic reactions, in angioedema, in cardiopulmonary resuscitation, and in the management of severe croup.

**Short-acting beta₂ agonists**
Mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting beta₂ agonist such as salbutamol or terbutaline sulfate. If beta₂ agonist inhalation is needed more often than twice a week, or if night-time symptoms occur at least once a week, or if the patient has suffered an exacerbation in the last 2 years, then prophylactic treatment should be considered using a stepped approach.

A short-acting beta₂ agonist inhaled immediately before exertion reduces exercise-induced asthma; however, frequent exercise-induced asthma probably reflects poor overall control and calls for reassessment of asthma treatment.

**Long-acting beta₂ agonists**
Formoterol fumarate p. 237 (eformoterol) and salmeterol p. 238 are longer-acting beta₂ agonists which are administered by inhalation. They should be used for asthma only in patients who regularly use an inhaled corticosteroid. They have a role in the long-term management of chronic asthma and can be useful in nocturnal asthma.

Salmeterol should not be used for the relief of an asthma attack; it has a slower onset of action than salbutamol or terbutaline sulfate. Formoterol fumarate is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm; its speed of onset of action is similar to that of salbutamol.

Combination inhalers that contain a long-acting beta₂ agonist and a corticosteroid ensure that long-acting beta₂ agonists are not used without concomitant corticosteroids, but reduce the flexibility to adjust the dose of each component.

Indacaterol p. 238 and olodaterol p. 238 are long-acting beta₂ agonists licensed for chronic obstructive pulmonary disease in adults; they are not indicated for the relief of acute bronchospasm.

Vilanterol is a long-acting beta₂ agonist available only in a combination inhaler with fluticasone furoate or with umeclidinium p. 235.

**Oral**
Oral preparations of beta₂ agonists may be used by patients who cannot manage the inhaled route. They are sometimes used for children and the elderly, but inhaled beta₂ agonists are more effective and have fewer side-effects. The long-acting oral preparations, including bambuterol hydrochloride p. 236, may be of value in nocturnal asthma but they have a limited role and inhaled long-acting beta₂ agonists are usually preferred.

**Parenteral**
Salbutamol or terbutaline sulfate can be given intravenously for severe or life-threatening acute asthma; patients should be carefully monitored and the dose adjusted according to response and heart rate. The regular use of beta₂ agonists by the subcutaneous route is not recommended since the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started. In adults, beta₂ agonists may also be given by intramuscular injection.

**Children**
Selective beta₂ agonists are useful even in children under the age of 18 months. They are most effective by the inhaled route; a pressurised metered-dose inhaler should be used with a spacer device in children under 5 years. A beta₂ agonist may also be given by mouth but administration by inhalation is preferred; a long-acting inhaled beta₂ agonist may be used where appropriate. In severe attacks nebulisation using a selective beta₂ agonist or ipratropium bromide p. 234 is advisable.

**Antimuscarinic bronchodilators**
Ipratropium bromide can provide short-term relief in chronic asthma, but short-acting beta₂ agonists act more quickly and are preferred. Ipratropium bromide by nebulisation can be added to other standard treatment in life-threatening asthma or if acute asthma fails to improve with standard therapy.

The aerosol inhalation of ipratropium bromide can be used for short-term relief in mild chronic obstructive pulmonary disease in patients who are not using a long-acting antimuscarinic drug. Its maximal effect occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilatation can usually be maintained with treatment 3 times a day.

Acclidinium bromide p. 233, glycopyrronium bromide p. 233, tiotropium p. 235, and umeclidinium are licensed for the maintenance treatment of adults with chronic obstructive pulmonary disease. They are not suitable for the relief of acute bronchospasm. Tiotropium (via Respinat® device) is also licensed as an adjunct to inhaled corticosteroids and long-acting beta₂ agonists for the maintenance treatment of patients with asthma who have suffered one or more severe exacerbations in the last year.

**Theophylline**
Theophylline p. 256 is a xanthine used as a bronchodilator in asthma and stable chronic obstructive pulmonary disease; it is not generally effective in exacerbations of chronic obstructive pulmonary disease. Theophylline may have an additive effect when used in conjunction with small doses of beta₂ agonists; the combination may increase the risk of side-effects, including hypokalaemia.

Theophylline is given by injection as aminophylline p. 255, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe acute asthma.

**Compound bronchodilator preparations**
In general, patients are best treated with single-ingredient preparations, such as a selective beta₂ agonist or ipratropium bromide, so that the dose of each drug can be adjusted. This flexibility is lost with compound bronchodilator preparations. However, a combination product may be appropriate for patients stabilised on individual components in the same proportion.

**Chronic obstructive pulmonary disease**

**Management**
Smoking cessation reduces the progressive decline in lung function in chronic obstructive pulmonary disease (COPD, chronic bronchitis, or emphysema). Infection can complicate chronic obstructive pulmonary disease and may be prevented by vaccination (pneumococcal polysaccharide
conjunctivitis, and respiratory disorders. For example, a high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate or severe airflow obstruction if the diagnosis is in doubt.

Symptoms of chronic obstructive pulmonary disease may be alleviated by an inhaled short-acting beta₂ agonist or a short-acting antimuscarinic bronchodilator used as required.

When the airways obstruction is more severe, regular inhaled therapy should be used. It is important to check compliance and inhaler technique before initiating a new drug.

If the Forced Expiratory Volume in 1 second (FEV₁) is less than 50% of predicted or more, either a long-acting antimuscarinic bronchodilator or a long-acting beta₂ agonist should be used. Short-acting antimuscarinic bronchodilators should be discontinued when a long-acting antimuscarinic bronchodilator is started. A long-acting beta₂ agonist with a corticosteroid in a combination inhaler can be used for patients who remain symptomatic despite regular treatment with a long-acting beta₂ agonist.

If FEV₁ is less than 50% of predicted, either a long-acting antimuscarinic bronchodilator or a long-acting beta₂ agonist with a corticosteroid in a combination inhaler should be used.

In any patient who remains breathless or continues to have exacerbations, triple therapy with a long-acting beta₂ agonist and a corticosteroid in a combination inhaler plus a long-acting antimuscarinic bronchodilator should be used.

If symptoms persist or if the patient is unable to use an inhaler, oral modified-release aminophylline p. 255 or theophylline p. 256 can be used.

Indacaterol p. 238 is a long-acting beta₂ agonist licensed for the maintenance treatment of chronic obstructive pulmonary disease.

In patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations, roflumilast p. 254 is licensed as an adjunct to existing bronchodilator treatment.

A mucolytic drug may be considered for a patient with a chronic productive cough.

Long-term oxygen therapy prolongs survival in patients with severe chronic obstructive pulmonary disease and hypoxaemia.

During an exacerbation of chronic obstructive pulmonary disease, bronchodilator therapy can be administered through a nebuliser if necessary and oxygen given if appropriate. Aminophylline can be given intravenously if response to nebulised bronchodilators is poor. A short course of oral corticosteroid, such as prednisolone for 7–14 days, should be given if increased breathlessness interferes with daily activities. Antibacterial treatment is required if sputum becomes more purulent than usual, or if there are other signs of infection.

Patients who have had an episode of hypercapnic respiratory failure should be given a 24% or 28% Venturi mask and an oxygen alert card endorsed with the oxygen saturations required during previous exacerbations. Patients and their carers should be instructed to show the card to emergency healthcare providers in the event of an exacerbation.

### Oxygen alert card based on British Thoracic Society guideline for emergency oxygen use in adult patients (October 2008)

**Oxygen alert card**

**Name:**

I am at risk of type II respiratory failure with a raised CO₂ level.

Please use my ___% Venturi mask to achieve an oxygen saturation of ___% to ___% during exacerbations.

Use compressed air to drive nebulisers (with nasal oxygen at 2 litres/minute). If compressed air not available, limit oxygen-driven nebulisers to 6 minutes.

Oxygen alert card is available at [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk).

### Croup

#### Management

Mild croup is largely self-limiting, but treatment with a single dose of a corticosteroid (e.g. dexamethasone p. 618) by mouth may be of benefit.

More severe croup (or mild croup that might cause complications) calls for hospital admission; a single dose of a corticosteroid (e.g. dexamethasone or prednisolone p. 622 by mouth) should be administered before transfer to hospital. In hospital, dexamethasone (by mouth or by injection) or budesonide p. 246 (by nebulisation) will often reduce symptoms; the dose may need to be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised adrenaline/epinephrine solution 1 in 1000 (1 mg/mL) p. 211 should be given with close clinical monitoring; the effects of nebulised adrenaline/epinephrine last 2–3 hours and the child needs to be monitored carefully for recurrence of the obstruction.

### Oxygen

#### Overview

Oxygen should be regarded as a drug. It is prescribed for hypoxaemic patients to increase alveolar oxygen tension and decrease the work of breathing. The concentration of oxygen required depends on the condition being treated; the administration of an inappropriate concentration of oxygen can have serious or even fatal consequences.

Oxygen is probably the most common drug used in medical emergencies. It should be prescribed initially to achieve a normal or near-normal oxygen saturation; in most acutely ill patients with a normal or low arterial carbon dioxide (PₐCO₂), oxygen saturation should be 94–98% oxygen saturation. However, in some clinical situations such as cardiac arrest and carbon monoxide poisoning it is more appropriate to aim for the highest possible oxygen saturation until the patient is stable. A lower target of 88–92% oxygen saturation is indicated for patients at risk of hypercapnic respiratory failure.

High concentration oxygen therapy is safe in uncomplicated cases of conditions such as pneumonia, pulmonary thromboembolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions low arterial oxygen (PₐO₂) is usually associated with low or
normal arterial carbon dioxide ($P_{aCO_2}$), and therefore there is little risk of hypoventilation and carbon dioxide retention. In acute severe asthma, the arterial carbon dioxide ($P_{aCO_2}$) is usually subnormal but as asthma deteriorates it may rise steeply (particularly in children). These patients usually require high concentrations of oxygen and if the arterial carbon dioxide ($P_{aCO_2}$) remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for patients at risk of hypercapnic respiratory failure, which is more likely in those with:
- chronic obstructive pulmonary disease;
- advanced cystic fibrosis;
- severe non-cystic fibrosis bronchiectasis;
- severe kyphoscoliosis or severe ankylosing spondylitis;
- severe lung scarring caused by tuberculosis;
- musculoskeletal disorders with respiratory weakness, especially if on home ventilation;
- an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target oxygen saturation of 88–92%. The aim is to provide the patient with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis. Patients may carry an oxygen alert card.

**Domiciliary oxygen**
Oxygen should only be prescribed for use in the home after careful evaluation in hospital by respiratory experts. Patients should be advised of the risks of continuing to smoke when receiving oxygen therapy, including the risk of fire. Smoking cessation therapy should be recommended before home oxygen prescription.

**Air travel**
Some patients with arterial hypoxaemia require supplementary oxygen for air travel. The patient’s requirement should be discussed with the airline before travel.
Long-term oxygen therapy

Long-term administration of oxygen (usually at least 15 hours daily) prolongs survival in some patients with chronic obstructive pulmonary disease.

Assessment for long-term oxygen therapy requires measurement of arterial blood gas tensions. Measurements should be taken on 2 occasions at least 3 weeks apart to demonstrate clinical stability, and not sooner than 4 weeks after an acute exacerbation of the disease. Long-term oxygen therapy should be considered for patients with:

- chronic obstructive pulmonary disease with \( P_{aO_2} < 7.3 \text{kPa} \) when breathing air during a period of clinical stability;
- chronic obstructive pulmonary disease with \( P_{aO_2} 7.3–8 \text{kPa} \) in the presence of secondary polycythemia, nocturnal hypoaxemia, peripheral oedema, or evidence of pulmonary hypertension;
- severe chronic asthma with \( P_{aO_2} < 7.3 \text{kPa} \) or persistent disabling breathlessness;
- interstitial lung disease with \( P_{aO_2} < 8 \text{kPa} \) and in patients with \( P_{aO_2} > 8 \text{kPa} \) with disabling dyspnoea;
- cystic fibrosis when \( P_{aO_2} < 7.3 \text{kPa} \) or if \( P_{aO_2} 7.3–8 \text{kPa} \) in the presence of secondary polycythemia, nocturnal hypoaxemia, pulmonary hypertension, or peripheral oedema;
- pulmonary hypertension, without parenchymal lung involvement when \( P_{aO_2} < 8 \text{kPa} \);
- neuromuscular or skeletal disorders, after specialist assessment;
- obstructive sleep apnoea despite continuous positive airways pressure therapy, after specialist assessment;
- pulmonary malignancy or other terminal disease with disabling dyspnoea;
- heart failure with daytime \( P_{aO_2} < 7.3 \text{kPa} \) when breathing air or with nocturnal hypoaxemia;
- paediatric respiratory disease, after specialist assessment.

Increased respiratory depression is seldom a problem in patients with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; patients and relatives should be warned to call for medical help if drowsiness or confusion occur.

Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness not relieved by other treatment in patients with severe chronic obstructive pulmonary disease, interstitial lung disease, heart failure, and in palliative care. It is important, however, that the patient does not rely on oxygen instead of obtaining medical help or taking more specific treatment. Short-burst oxygen therapy can be used to improve exercise capacity and recovery; it should only be continued if there is proven improvement in breathlessness or exercise tolerance.

Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for patients on long-term oxygen therapy who need to be away from home on a regular basis. Patients who are not on long-term oxygen therapy can be considered for ambulatory oxygen therapy if there is evidence of exercise-induced oxygen desaturation and of improvement in blood oxygen saturation and exercise capacity with oxygen. Ambulatory oxygen therapy is not recommended for patients with heart failure or those who smoke.

Oxygen therapy equipment

Under the NHS oxygen may be supplied as oxygen cylinders. Oxygen flow can be adjusted as the cylinders are equipped with an oxygen flow meter with 'medium' (2 litres/minute) and 'high' (4 litres/minute) settings. Oxygen delivered from a cylinder should be passed through a humidifier if used for long periods.

Oxygen concentrators are more economical for patients who require oxygen for long periods, and in England and Wales can be ordered on the NHS on a regional tendering basis. A concentrator is recommended for a patient who requires oxygen for more than 8 hours a day (or 21 cylinders per month). Exceptionally, if a higher concentration of oxygen is required the output of 2 oxygen concentrators can be combined using a 'Y' connection.

A nasal cannula is usually preferred for long-term oxygen therapy from an oxygen concentrator. It can, however, produce dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the patient to talk, eat, and drink, but the concentration of oxygen is not controlled; this may not be appropriate for acute respiratory failure. When oxygen is given through a nasal cannula at a rate of 1–2 litres/minute the inspiratory oxygen concentration is usually low, but it varies with ventilation and can be high if the patient is underventilating.

Arrangements for supplying oxygen

The following oxygen services may be ordered in England and Wales:

- emergency oxygen;
- short-burst (intermittent) oxygen therapy;
- long-term oxygen therapy;
- ambulatory oxygen.

The type of oxygen service (or combination of services) should be ordered on a Home Oxygen Order Form (HOOF); the amount of oxygen required (hours per day) and flow rate should be specified. The clinician will determine the appropriate equipment to be provided. Special needs or preferences should be specified on the HOOF.

The clinician should obtain the patient or carers consent, to pass on the patient’s details to the supplier, the fire brigade, and other relevant organisations. The supplier will contact the patient to make arrangements for delivery, installation, and maintenance of the equipment. The supplier will also train the patient or carer to use the equipment.

The clinician should send the HOOF to the supplier who will continue to provide the service until a revised HOOF is received, or until notified that the patient no longer requires the home oxygen service.

- East of England, North East: BOC Medical: Tel: 0800 136 603 Fax: 0800 169 9989
- South West: Air Liquide: Tel: 0808 202 2229 Fax: 0191 497 4340
- London, East Midlands, North West: Air Liquide: Tel: 0500 823 773 Fax: 0800 781 4610
- Yorkshire and Humberside, West Midlands, Wales: Air Products: Tel: 0800 373 580 Fax: 0800 214 709
- South East Coast, South Central: Dolby Vivisol: Tel: 08443 814 402 Fax: 0800 781 4610

In Scotland refer the patient for assessment by a respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency. Prescribers should complete a Scottish Home Oxygen Order Form (SHOOOF) and email it to Health Facilities Scotland. Health Facilities Scotland will then liaise with their contractor to arrange the delivery of oxygen. Further information can be obtained at: www.dolbyvivisol.com/our-services/healthcare-professionals/home-oxygen-services.aspx

In Northern Ireland oxygen concentrators and cylinders should be prescribed on form HS21; oxygen concentrators are supplied by a local contractor. Prescriptions for oxygen cylinders and accessories can be dispensed by pharmacists contracted to provide domiciliary oxygen services.
**Antimuscarinics (inhaled)**

09-Feb-2016

- **CAUTIONS** Bladder outflow obstruction, paradoxical bronchospasm, prostatic hyperplasia, susceptibility to angle-closure glaucoma
- **INTERACTIONS** See Appendix 1 (antimuscarinics). However, note that interactions do not generally apply to antimuscarinics used by inhalation.
- **SIDE-EFFECTS**
  - **Common or very common** Constipation, cough, diarrhoea, dry mouth, gastro-intestinal motility disorder, headache, sinusitis
  - **Uncommon** Angle-closure glaucoma, atrial fibrillation, blurred vision, dizziness, gastro-oesophageal reflux disease (in adults), mydriasis, nasopharyngitis, nausea, palpitation, paradoxical bronchospasm, pharyngitis, rash, tachycardia, throat irritation, urinary retention
  - **Rare** Dental caries

**Aclidinium bromide**

19-Feb-2016

- **INDICATIONS AND DOSE**
  - **Maintenance treatment of chronic obstructive pulmonary disease**
    - **BY INHALATION OF POWDER**
    - **Adult:** 375 micrograms twice daily
  - **DOSE EQUIVALENCE AND CONVERSION**
    - Each 375 microgram inhalation of aclidinium bromide delivers 322 micrograms of aclidinium.

- **CAUTIONS** Arrhythmia (when newly diagnosed within last 3 months) - heart failure (hospitalisation with moderate or severe heart failure within last 12 months) - myocardial infarction within last 6 months - unstable angina
- **SIDE-EFFECTS**
  - **Uncommon** Dysphonia - stomatitis
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risks.
- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risks.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on appropriate inhaler technique.

**Glycopyrronium bromide**

17-Oct-2016

- **INDICATIONS AND DOSE**
  - **Maintenance treatment of chronic obstructive pulmonary disease**
    - **BY INHALATION OF POWDER**
    - **Adult:** 50 micrograms once daily
  - **DOSE EQUIVALENCE AND CONVERSION**
    - For inhalation of powder, each 50 microgram capsule of glycopyrronium delivers 44 micrograms of glycopyrronium.

- **CAUTIONS** Arrhythmia (excluding chronic stable atrial fibrillation) - history of myocardial infarction - history of QT-interval prolongation - left ventricular failure - unstable ischaemic heart disease
- **SIDE-EFFECTS**
  - **Common or very common** Insomnia
  - **Uncommon** Epistaxis - hyperglycaemia - hypoæsthesia - malaise - rhinitis
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risks.
- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risks.
- **RENAL IMPAIRMENT** Use with caution if eGFR less than 30 mL/minute/1.73 m².
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer glycopyrronium for inhalation.

**Acidinium bromide with formoterol**

19-Feb-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, acidinium bromide above, formoterol fumarate p. 237.

- **INDICATIONS AND DOSE**
  - **Maintenance treatment of chronic obstructive pulmonary disease**
    - **BY INHALATION OF POWDER**
    - **Adult:** 1 inhalation twice daily

- **CAUTIONS** Convulsive disorders - phaeochromocytoma
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on appropriate inhaler technique.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

- **Inhalation powder**
  - **Aclidinium bromide with formoterol (non-proprietary) ▼**
    - Formoterol fumarate dihydrate 11.8 microgram per 1 dose, Acidinium bromide 396 microgram per 1 dose Acidinium bromide 396micrograms/dose / Formoterol 11.8micrograms/dose dry powder inhaler | 60 dose [POD] no price available DT price = £32.50
  - Duaklir (AstraZeneica UK Ltd) ▼
    - Formoterol fumarate dihydrate 11.8 microgram per 1 dose, Acidinium bromide 396 microgram per 1 dose Duaklir 340micrograms/dose / 12micrograms/dose Genuair | 60 dose [POD] £32.50 DT price = £32.50

- **Glycopyrronium bromide (Glycopyrrolate)**

- **Indications and dose**
  - **Maintenance treatment of chronic obstructive pulmonary disease**
    - **By inhalation of powder**
    - **Adult:** 50 micrograms once daily
  - **Dose equivalence and conversion**
    - For inhalation of powder, each 50 microgram capsule of glycopyrronium delivers 44 micrograms of glycopyrronium.

- **Medicinal forms**
  - **Inhalation powder**
    - **Glycopyrronium bromide (non-proprietary) ▼**
      - Glycopyrronium bromide 55 microgram Glycopyrronium bromide 55microgram inhalation powder capsules with device | 6 capsule [POD] no price available | 30 capsule [POD] no price available DT price = £27.50

**Antimuscarinics**

- **Bladder outflow obstruction** - **paradoxical bronchospasm** - **prostatic hyperplasia** - **susceptibility to angle-closure glaucoma**

**INTERACTIONS**

See Appendix 1 (antimuscarinics). However, note that interactions do not generally apply to antimuscarinics used by inhalation.

**SIDE-EFFECTS**

- **Common or very common**
  - Constipation
  - Cough
  - Diarrhoea
  - Dry mouth
  - Gastro-intestinal motility disorder
  - Headache
  - Sinusitis

- **Uncommon**
  - Angle-closure glaucoma
  - Atrial fibrillation
  - Blurred vision
  - Dizziness
  - Gastro-oesophageal reflux disease (in adults)
  - Mydriasis
  - Nasopharyngitis
  - Nausea
  - Palpitation
  - Paradoxical bronchospasm
  - Pharyngitis
  - Rash
  - Tachycardia
  - Throat irritation
  - Urinary retention

- **Rare**
  - Dental caries

**Patient and carer advice**

Patients or carers should be given advice on appropriate inhaler technique.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

- **Inhalation powder**
  - **Aclidinium bromide (non-proprietary) ▼**
    - Acidinium bromide 375 microgram per 1 dose Acidinium bromide 375micrograms/dose dry powder inhaler | 60 dose [POD] no price available DT price = £28.60
  - Ekliira (AstraZeneica UK Ltd) ▼
    - Acidinium bromide 375 microgram per 1 dose Ekliira 322micrograms/dose Genuair | 60 dose [POD] £28.60 DT price = £28.60

**Cautions**

- **Uncommon**
  - Epistaxis

**Pregnancy**

Manufacturer advises use only if potential benefit outweighs risks.

**Breast feeding**

Manufacturer advises use only if potential benefit outweighs risks.

**Patient and carer advice**

Patients or carers should be given advice on appropriate inhaler technique.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

- **Inhalation powder**
  - **Glycopyrronium bromide (non-proprietary) ▼**
    - Glycopyrronium bromide 55 microgram Glycopyrronium bromide 55microgram inhalation powder capsules with device | 6 capsule [POD] no price available | 30 capsule [POD] no price available DT price = £27.50
Respiratory system

Pharmacokinetics

The maximal effect of inhaled ipratropium occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.

Unlicensed use

The dose of ipratropium for severe or life-threatening acute asthma is unlicensed.

Cautions

Cystic fibrosis

Caution, further information

Glaucoma

Acute angle-closure glaucoma has been reported with nebulised ipratropium, particularly when given with nebulised salbutamol (and possibly other beta; agonists); care needed to protect the patient’s eyes from nebulised drug or from drug powder.

Side-effects

Uncommon Laryngospasm · pharyngeal oedema · stomatitis · vomiting

Rare Ocular accommodation disorder

Pregnancy

Manufacturer advises only use if potential benefit outweighs the risk.

Breast Feeding

No information available—manufacturer advises only use if potential benefit outweighs risk.

Directions for administration

If dilution of ipratropium bromide nebuliser solution is necessary use only sterile sodium chloride 0.9%.

Patient and carer advice

Patients or carers should be given advice on appropriate inhaler technique.

Medical forms

There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder

 Ultibro Breezhaler (Novartis Pharmaceuticals UK Ltd) ▼ Glycopyrronium bromide 54 microgram per 1 dose, Indacaterol (as Indacaterol maleate) 85 microgram per 1 dose Ultibro Breezhaler 65microgram/43microgram inhalation powder capsules with device | 10 capsule: £10.07 | 30 capsule: £32.50

Ipratropium Bromide

24-Feb-2016

Indications and dose

Reversible airways obstruction

► By inhalation of aerosol
  ▶ Child 1 month–5 years: 20 micrograms 3 times a day
  ▶ Child 6–11 years: 20–40 micrograms 3 times a day
  ▶ Child 12–17 years: 20–40 micrograms 3–4 times a day

Reversible airways obstruction, particularly in chronic obstructive pulmonary disease

► By inhalation of nebulised solution
  ▶ Adult: 20–40 micrograms 3–4 times a day

► By inhalation of nebulised solution
  ▶ Adult: 250–500 micrograms 3–4 times a day

Acute bronchospasm

► By inhalation of nebulised solution
  ▶ Child 1 month–5 years: 125–250 micrograms as required; maximum 1 mg per day
  ▶ Child 6–11 years: 250 micrograms as required; maximum 1 mg per day
  ▶ Child 12–17 years: 500 micrograms as required, doses higher than max. can be given under medical supervision; maximum 2 mg per day
  ▶ Adult: 500 micrograms as required, doses higher than max. can be given under medical supervision; maximum 2 mg per day

Severe or life-threatening acute asthma

► By inhalation of nebulised solution
  ▶ Child 1 month–11 years: 250 micrograms every 20–30 minutes for the first 2 hours, then 250 micrograms every 4–6 hours as required
  ▶ Child 12–17 years: 500 micrograms every 4–6 hours as required
  ▶ Adult: 500 micrograms every 4–6 hours as required

Pharmacokinetics

The maximal effect of inhaled ipratropium occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.

Unlicensed use

The dose of ipratropium for severe or life-threatening acute asthma is unlicensed.

Caution

Cystic fibrosis

Caution, further information

Glaucoma

Acute angle-closure glaucoma has been reported with nebulised ipratropium, particularly when given with nebulised salbutamol (and possibly other beta; agonists); care needed to protect the patient’s eyes from nebulised drug or from drug powder.

Side-effects

Uncommon Laryngospasm · pharyngeal oedema · stomatitis · vomiting

Rare Ocular accommodation disorder

Pregnancy

Manufacturer advises only use if potential benefit outweighs the risk.

Breast Feeding

No information available—manufacturer advises only use if potential benefit outweighs risk.

Directions for administration

If dilution of ipratropium bromide nebuliser solution is necessary use only sterile sodium chloride 0.9%.

Patient and carer advice

Patients or carers should be given advice on appropriate inhaler technique.

Medical forms

There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation

► Ipratropium bromide (Non-proprietary)
  ► Ipratropium bromide 20 microgram per 1 dose Ipratropium bromide 20micrograms/dose inhaler CFC free | 200 dose (POD) no price available DT price = £5.56
  ▶ Atrovent (Boehringer Ingelheim Ltd)
  ▶ Ipratropium bromide 20 microgram per 1 dose Atrovent 20micrograms/inhaler CFC free | 200 dose (POD) £5.56 DT price = £5.56

Nebuliser liquid

► Ipratropium bromide (Non-proprietary)
  ► Ipratropium bromide 250 microgram per 1 ml Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials | 20 unit dose (POD) £3.35 DT price = £2.75
  ▶ Atrovent (Boehringer Ingelheim Ltd)
  ▶ Ipratropium bromide 250 microgram per 1 ml Atrovent 250micrograms/inhaler CFC free | 200 dose (POD) £5.56 DT price = £2.75
  ▶ Respontin (GlaxoSmithKline UK Ltd)
  ▶ Ipratropium bromide 250 microgram per 1 ml Respontin 500micrograms/2ml Nebules | 20 unit dose (POD) £5.60 DT price = £2.75

Ipratropium with salbutamol

17-Feb-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, ipratropium bromide above, salbutamol p. 239.

Indications and dose

Bronchospasm in chronic obstructive pulmonary disease

► By inhalation of nebulised solution
  ▶ Adult: 0.5/2.5 mg 3–4 times a day
**Indications and Dose**

**Maintenance treatment of chronic obstructive pulmonary disease**
- **By Inhalation of Powder**
- **Adult:** 18 micrograms once daily

**SPIRIVA RESPIMAT®**

Maintenance treatment of chronic obstructive pulmonary disease | Adjunct to inhaled corticosteroids and long-acting beta, agonists for the maintenance treatment of patients with asthma who have suffered one or more severe exacerbations in the last year
- **By Inhalation of Aerosol**
- **Adult:** 2 puffs once daily

**Side-Effects**
- **Rare** Laryngitis
- **Frequency not known** Skin ulcer

**Patient and Carer Advice**
- Patient or carers should be given advice on appropriate inhaler technique.

**Medicinal Forms**
- **Nebuliser Liquid**
  - Ipratropium with salbutamol (Non-proprietary)
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml
  - Combivent (Boehringer Ingelheim Ltd)
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml
  - Ipramol (Teva UK Ltd)
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml
  - Salipraneb (Actavis UK Ltd)

**CAUTIONS**
- Arrhythmia (unstable, life-threatening or requiring intervention in the previous 12 months) · heart failure (hospitalisation for moderate to severe heart failure in the previous 12 months) · myocardial infarction in the previous 6 months

**PRESCRIBING AND DISPENSING INFORMATION**

**SPIRIVA RESPIMAT®**

Use Spiriva Respimat® only when patient unable to use Spiriva Handihaler® device.

**Patient and Carer Advice**
- Patients or carers should be given advice on appropriate inhaler technique and reminded that the powder inhalation capsules are not for oral administration.
Respiratory system

In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when given intravenously). High doses of beta₂ agonists can be dangerous in some children (in children) - hypertension, hyperthermia, hypokalaemia - susceptibility to QT-interval prolongation.

**MONITORING REQUIREMENTS**
- In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).
- In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when beta₂ agonist given intravenously).

**SIDE-EFFECTS**
- Angioedema - arrhythmias - behavioural disturbances - collapse - fine tremor (particularly in the hands) - hyperglycaemia - hypersensitivity reactions - hypokalaemia (with high doses) - hypotension - ketoacidosis - muscle cramps - myocardial ischaemia - nervous tension - peripheral vasodilation - sleep disturbances - urticaria.

**INTERACTIONS**
- β₂-adrenoceptor agonists, selective

**CONTRA-INDICATIONS** Severe pre-eclampsia

**CAUTIONS**
- Arrhythmias - cardiovascular disease - diabetes (risk of hyperglycaemia and ketoacidosis, especially with intravenous use) - high doses of beta₂ agonists can be dangerous in some children (in children) - hypertension - hyperthermia - hypokalaemia - susceptibility to QT-interval prolongation.

**MONITORING REQUIREMENTS**
- In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).
- In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when given intravenously).

**PATIENT AND CARER ADVICE**
- Patient or carers should be given advice on appropriate inhaler technique.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Hepatic Impairment**
- Manufacturer advises to use with caution in severe impairment - no information available.

**Patient and Carer Advice**
- Patient or carers should be given advice on appropriate inhaler technique.

**Umeclidinium with vilanterol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, umeclidinium p. 235.

**INDICATIONS AND DOSE**

Maintenance treatment of chronic obstructive pulmonary disease
- By Inhalation of Powder
  - Adult: 1 inhalation once daily

**CONTRA-INDICATIONS**
- Severe pre-eclampsia

**CAUTIONS**
- Arrhythmias - cardiovascular disease - diabetes (risk of hyperglycaemia and ketoacidosis) - hypertension - hyperthermia - hypokalaemia - susceptibility to QT-interval prolongation

**SIDE-EFFECTS**
- Angioedema - arrhythmias - behavioural disturbances - collapse - fine tremor (particularly in the hands) - hyperglycaemia - hypersensitivity reactions - hypokalaemia (with high doses) - hypotension - ketoacidosis - muscle cramps - myocardial ischaemia - nervous tension - peripheral vasodilation - sleep disturbances - urticaria

**INTERACTIONS**
- β₂-adrenoceptor agonists, selective

**MONITORING REQUIREMENTS**
- In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).
- In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when beta₂ agonist given intravenously).

**PATIENT AND CARER ADVICE**
- Patient or carers should be given advice on appropriate inhaler technique.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**INHALATION POWDER**
- **Umeclidinium with vilanterol (non-proprietary) ▼**
  - Vilanterol (as Vilanterol trifenafate) 22 microgram per 1 dose, Umeclidinium bromide 65 microgram per 1 dose Umeclidinium bromide 65 micrograms/dose / Vilanterol 22 micrograms/dose dry powder inhaler | 30 dose price = £27.50
  - **Anoro Ellipta** (GlaxoSmithKline UK Ltd) ▼
    - Vilanterol (as Vilanterol trifenafate) 22 microgram per 1 dose, Umeclidinium bromide 65 microgram per 1 dose Anoro Ellipta 55 micrograms/dose / 22 micrograms/dose dry powder inhaler | 30 dose price = £32.50

**BETA₂-ADRENOCEPTOR AGONISTS, SELECTIVE ▶ LONG-ACTING**

**Bambuterol hydrochloride**

**DRUG ACTION**
- Bambuterol is a pro-drug of terbutaline.

**INDICATIONS AND DOSE**
- Asthma (patients who have previously tolerated beta₂ agonists) - Other conditions associated with reversible airways obstruction (patients who have previously tolerated beta₂-agonists)
  - By Mouth
    - Adult: 20 mg once daily, dose to be taken at bedtime

**CONTRA-INDICATIONS**
- Severe pre-eclampsia

**CAUTIONS**
- Arrhythmias - cardiovascular disease - diabetes (risk of hyperglycaemia and ketoacidosis, especially with intravenous use) - high doses of beta₂ agonists can be dangerous in some children (in children) - hypertension - hyperthermia - hypokalaemia - susceptibility to QT-interval prolongation

**CAUTIONS, FURTHER INFORMATION**
- Hypokalaemia. Potentially serious hypokalaemia may result from beta₂ agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, diuretics, and by hypoxia.

**INTERACTIONS**
- → Appendix 1 (sympathomimetics, beta₂)
- Hypokalaemia may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics.

**SIDE-EFFECTS**
- Angioedema - arrhythmias - behavioural disturbances - collapse - fine tremor (particularly in the hands) - hyperglycaemia - hypersensitivity reactions - hypokalaemia (with high doses) - hypotension - ketoacidosis (especially when given intravenously) - muscle cramps - myocardial ischaemia - nervous tension - palpitation - paradoxical bronchospasm (occasionally severe) - peripheral vasodilation - rash - sleep disturbances - tachycardia - urticaria

**PREGNANCY**
- Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

**MONITORING REQUIREMENTS**
- In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).
- In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when beta₂ agonist given intravenously).

**PATIENT AND CARER ADVICE**
- When used by inhalation The dose, the frequency, and the maximum number of inhalations in 24 hours of the beta₂ agonist should be stated explicitly to the patient or their carer. The patient or their carer should be advised to seek medical advice when the prescribed dose of beta₂ agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the patient may require a prophylactic drug. Patients or their carers should be advised to follow manufacturers' instructions on the care and cleansing of inhaler devices.

**BETA₂-ADRENOCEPTOR AGONISTS, SELECTIVE ▶ LONG-ACTING**

**Bambuterol hydrochloride**

**DRUG ACTION**
- Bambuterol is a pro-drug of terbutaline.

**INDICATIONS AND DOSE**
- Asthma (patients who have previously tolerated beta₂-agonists) - Other conditions associated with reversible airways obstruction (patients who have previously tolerated beta₂-agonists)
  - By Mouth
    - Adult: 20 mg once daily, dose to be taken at bedtime

**CONTRA-INDICATIONS**
- Severe pre-eclampsia

**CAUTIONS**
- Arrhythmias - cardiovascular disease - diabetes (risk of hyperglycaemia and ketoacidosis, especially with intravenous use) - high doses of beta₂ agonists can be dangerous in some children (in children) - hypertension - hyperthermia - hypokalaemia - susceptibility to QT-interval prolongation

**CAUTIONS, FURTHER INFORMATION**
- Hypokalaemia. Potentially serious hypokalaemia may result from beta₂ agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, diuretics, and by hypoxia.

**INTERACTIONS**
- → Appendix 1 (sympathomimetics, beta₂)
- Hypokalaemia may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics.

**SIDE-EFFECTS**
- Angioedema - arrhythmias - behavioural disturbances - collapse - fine tremor (particularly in the hands) - hyperglycaemia - hypersensitivity reactions - hypokalaemia (with high doses) - hypotension - ketoacidosis (especially when given intravenously) - muscle cramps - myocardial ischaemia - nervous tension - palpitation - paradoxical bronchospasm (occasionally severe) - peripheral vasodilation - rash - sleep disturbances - tachycardia - urticaria

**PREGNANCY**
- Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

**MONITORING REQUIREMENTS**
- In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).
- In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when beta₂ agonist given intravenously).

**PATIENT AND CARER ADVICE**
- When used by inhalation The dose, the frequency, and the maximum number of inhalations in 24 hours of the beta₂ agonist should be stated explicitly to the patient or their carer. The patient or their carer should be advised to seek medical advice when the prescribed dose of beta₂ agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the patient may require a prophylactic drug. Patients or their carers should be advised to follow manufacturers' instructions on the care and cleansing of inhaler devices.

**BETA₂-ADRENOCEPTOR AGONISTS, SELECTIVE ▶ LONG-ACTING**

**Bambuterol hydrochloride**

**DRUG ACTION**
- Bambuterol is a pro-drug of terbutaline.

**INDICATIONS AND DOSE**
- Asthma (patients who have previously tolerated beta₂-agonists) - Other conditions associated with reversible airways obstruction (patients who have previously tolerated beta₂-agonists)
  - By Mouth
    - Adult: 20 mg once daily, dose to be taken at bedtime
Asthma (patients who have not previously tolerated beta,-agonists) Other conditions associated with reversible airways obstruction (patients who have not previously tolerated beta,-agonists)

- **BY INHALATION OF POWDER**
  - Adult: Initially 10 mg once daily for 1–2 weeks, then increased if necessary to 20 mg once daily, dose to be taken at bedtime
  - Child 6–12 years: 12 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Child 12–17 years: 12 micrograms twice daily, may be increased in more severe airway obstruction; increased to 24 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Adult: 12 micrograms twice daily, may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

- **BY INHALATION OF AEROSOL**
  - Child 6–12 years: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Adult: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

**Chronic obstructive pulmonary disease**

- **BY INHALATION OF POWDER**
  - Adult: 12 micrograms twice daily

**Formoterol fumarate**

(Eformoterol fumarate)

**INDICATIONS AND DOSE**

Reversible airways obstruction in patients requiring long-term regular bronchodilator therapy | Nocturnal asthma in patients requiring long-term regular bronchodilator therapy | Prophylaxis of exercise-induced bronchospasm in patients requiring long-term regular bronchodilator therapy | Chronic asthma in patients who regularly use an inhaled corticosteroid

- **BY INHALATION OF POWDER**
  - Child 6–11 years: 12 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Child 12–17 years: 12 micrograms twice daily, may be increased in more severe airway obstruction; increased to 24 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Adult: 12 micrograms twice daily, may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

- **BY INHALATION OF AEROSOL**
  - Child 6–12 years: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Adult: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

**Pharmacokinetics**

At recommended inhaled doses, the duration of action of formoterol is about 12 hours.

**Important Safety Information**

**CHM Advice**

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta₂-agonist (formoterol) should:

- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- not be initiated in patients with rapidly deteriorating asthma;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

**Side-effects**

- Very rare QT-interval prolongation
- Frequency not known Dizziness · nausea · pruritus · taste disturbances

**Pregnancy**

Inhaled drugs for asthma can be taken as normal during pregnancy.

**Breast feeding**

Inhaled drugs for asthma can be taken as normal during breast-feeding.

**Patient and Carer Advice**

Advising patients not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled formoterol fails to provide adequate relief, a doctor’s advice should be
obtained as soon as possible. Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta<sub>2</sub> agonist. Patient or carer should be given advice on how to administer formoterol fumarate inhalers.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **Atimos Modulite** (Chiesi Ltd)
  
  Formoterol fumarate dihydrate 12 microgram per 1 dose
  
  Formoterol Easyhaler 12microgram/dose dry powder inhaler | 60 capsule £28.06 DT price = £28.06

- **Foradil** (Novartis Pharmaceuticals UK Ltd)
  
  Formoterol fumarate dihydrate 12 microgram per 1 dose
  
  Foradil 12microgram inhalation powder capsules with device | 60 capsule £24.80 DT price = £24.80
  
  **Oxis Turbhaler** (AstraZeneca UK Ltd)
  
  Formoterol fumarate dihydrate 6 microgram per 1 dose
  
  Oxis 6 Turbhaler | 60 dose £24.80 DT price = £24.80

**Combination available:**

- **Acidinium bromide with formoterol**, p. 233
- **Beclometasone with formoterol**, p. 245
- **Budesonide with formoterol**, p. 247
- **Fluticasone with formoterol**, p. 248

**Indacaterol**

**INDICATIONS AND DOSE**

Maintenance treatment of chronic obstructive pulmonary disease

- **BY INHALATION OF POWDER**
- **Adult:** 150 micrograms once daily, then increased to 300 micrograms once daily

**CAUTIONS**

- Convulsive disorders

**SIDE-EFFECTS**

- Common or very common: Cough - dizziness - nasopharyngitis - oropharyngeal pain - peripheral oedema - rhinorrhea - sinusitis
- Uncommon: Atrial fibrillation - chest pain - paraesthesia - pruritus

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Use with caution in severe impairment—no information available.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer indacaterol inhalation powder.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**

- **Onbrez Brezhaler** (Novartis Pharmaceuticals UK Ltd)
  
  Indacaterol (as Indacaterol maleate) 150 microgram
  
  Onbrez Brezhaler 150microgram inhalation powder capsules with device | 30 capsule £22.19 DT price = £22.19
  
  Indacaterol (as Indacaterol maleate) 300 microgram
  
  Onbrez Brezhaler 300microgram inhalation powder capsules with device | 30 capsule £32.19 DT price = £32.19

**Combination available:**

- **Glycopyrronium with indacaterol**, p. 234

**Olodaterol**

**INDICATIONS AND DOSE**

Maintenance treatment of chronic obstructive pulmonary disease

- **BY INHALATION**
- **Adult:** 5 micrograms once daily

**DOSE EQUIVALENCE AND CONVERSION**

- 2 puffs is equivalent to 5 micrograms.

**CAUTIONS**

- Aneurysm - convulsive disorders

**SIDE-EFFECTS**

- Uncommon: Dizziness - nasopharyngitis
- Rare: Arthralgia - hypertension

**PREGNANCY**

Manufacturer advises avoid—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Use with caution in severe hepatic impairment—no information available.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer olodaterol solution for inhalation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **Striverdi Respimat** (Boehringer Ingelheim Ltd)
  
  Olodaterol (as Olodaterol hydrochloride) 2.5 microgram per 1 dose
  
  Striverdi Respimat 2.5micrograms/dose solution for inhalation cartridge with device | 60 dose £26.35 DT price = £26.35

**Combination available:**

- **Tiotropium with olodaterol**, p. 225

**Salmeterol**

**INDICATIONS AND DOSE**

Reversible airways obstruction in patients requiring long-term regular bronchodilator therapy / Nocturnal asthma in patients requiring long-term regular bronchodilator therapy / Prevention of exercise-induced bronchospasm in patients requiring long-term regular bronchodilator therapy / Chronic asthma only in patients who regularly use an inhaled corticosteroid (not for immediate relief of acute asthma)

- **BY INHALATION OF AEROSOL, OR BY INHALATION OF POWDER**
  
  Child 12–17 years: 50 micrograms twice daily, dose may be increased in more severe airflow obstruction; increased to 100 micrograms twice daily
  
  Adult: 50 micrograms twice daily, dose may be increased in more severe airflow obstruction; increased to 100 micrograms twice daily

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

- **BREATH FEEDING**
  
  Adult: 50 micrograms twice daily

**PHARMACOKINETICS**

At recommended inhaled doses, the duration of action of salmeterol is about 12 hours.

**UNLICENSED USE**

Neovent® not licensed for use in children under 12 years.

**IMPORTANT SAFETY INFORMATION**

**CHM ADVICE**

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta<sub>2</sub> agonist (salmeterol) should:
BETα₂-ADRENOCEPTOR AGONISTS, SELECTIVE > SHORT-ACTING

Salbutamol
(Albuterol)

**INDICATIONS AND DOSE**

**Asthma** / Other conditions associated with reversible airways obstruction

- **By mouth using immediate-release medicines**
  - Adult: 4 mg 3–4 times a day, maximum single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated), inhalation route preferred over oral route. Use elderly dose for sensitive patients.
  - Elderly: Initially 2 mg 3–4 times a day, maximum single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated), inhalation route preferred over oral route.

- **By subcutaneous injection, or by intramuscular injection**
  - Adult: 500 micrograms every 4 hours if required.
  - By slow intravenous injection.

- **By intravenous infusion**
  - Adult: 250 micrograms, repeated if necessary, injection to be diluted to a concentration of 50 micrograms/mL, reserve intravenous beta₂ agonists for those in whom inhaled therapy cannot be used reliably.

- **By inhalation of aerosol**
  - Adult: 100–200 micrograms, up to 4 times a day for persistent symptoms.
  - By inhalation of nebulised solution.

- **Adult**: 2.5–5 mg, repeated up to 4 times daily or more frequently in severe cases.

- **Prophylaxis of allergen- or exercise-induced bronchospasm**
  - By inhalation of aerosol.
  - Adult: 200 micrograms.

**Acute asthma**

- **By intravenous injection**
  - Child 1–23 months: 5 micrograms/kg for 1 dose, dose to be administered over 5 minutes, reserve intravenous beta₂ agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect.
  - Child 2–17 years: 15 micrograms/kg (max. per dose 250 micrograms) for 1 dose, dose to be administered over 5 minutes, reserve intravenous beta₂ agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect.

**Moderate, severe, or life-threatening acute asthma**

- **By inhalation of nebulised solution**
  - Child 1 month–4 years: 2.5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.
  - Child 5–11 years: 2.5–5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.
  - Child 12–17 years: 5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.
  - Adult: 5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.

**Side-effects**

- Arthralgia.
- Dizziness.
- Nausea.

**Pregnancy**

Inhaled drugs for asthma can be taken as normal during pregnancy.

**Breast-feeding**

Inhaled drugs for asthma can be taken as normal during breast-feeding.

**Patient and carer advice**

Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/salmeterol-inhaler-for-asthma-prevention

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **Salmeterol (Non-proprietary)**
  - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose Salmeterol 25 micrograms/dose inhaler CFC free | 120 dose [Pom] £29.26 DT price = £29.26
  - Neovent (Kent Pharmaceuticals Ltd)

- **Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose** Neovent 25 micrograms/dose inhaler CFC free | 120 dose [Pom] £29.26 DT price = £29.26

- **Serevent Evohaler (GlaxoSmithKline Ltd)**

- **Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose** Serevent 25 micrograms/dose inhaler CFC free | 120 dose [Pom] £29.26 DT price = £29.26

- **Vertine (Teva UK Ltd)**

- **Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose** Vertine 25 micrograms/dose inhaler CFC free | 120 dose [Pom] £23.40 DT price = £29.26

**Inhalation powder**

- **Serevent Accuhaler (GlaxoSmithKline Ltd)**

- **Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose** Serevent 50 micrograms/dose Accuhaler | 60 dose [Pom] £35.11 DT price = £35.11

**Combinations available:** Fluflutasone with salmeterol, p. 249

**Side-effects**

- Arthralgia.
- Dizziness.
- Nausea.

**Pregnancy**

Inhaled drugs for asthma can be taken as normal during pregnancy.

**Breast-feeding**

Inhaled drugs for asthma can be taken as normal during breast-feeding.

**Patient and carer advice**

Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/salmeterol-inhaler-for-asthma-prevention

**Medicinal forms**

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- **Vertine (Teva UK Ltd)**

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**Inhalation powder**

- **Serevent Accuhaler (GlaxoSmithKline Ltd)**

- **Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose** Serevent 50 micrograms/dose Accuhaler | 60 dose [Pom] £35.11 DT price = £35.11

**Combinations available:** Fluflutasone with salmeterol, p. 249

**INDICATIONS AND DOSE**

**Asthma** / Other conditions associated with reversible airways obstruction

- **By mouth using immediate-release medicines**
  - Adult: 4 mg 3–4 times a day, maximum single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated), inhalation route preferred over oral route. Use elderly dose for sensitive patients.
  - Elderly: Initially 2 mg 3–4 times a day, maximum single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated), inhalation route preferred over oral route.

- **By subcutaneous injection, or by intramuscular injection**
  - Adult: 500 micrograms every 4 hours if required.
  - By slow intravenous injection.

- **By intravenous infusion**
  - Adult: Initially 5 micrograms/minute, adjusted according to response and heart rate, usual dose 3–20 micrograms/minute, higher doses may be required, reserve intravenous beta₂ agonists for those in whom inhaled therapy cannot be used reliably.

- **By inhalation of aerosol**
  - Adult: 100–200 micrograms, up to 4 times a day for persistent symptoms.
  - By inhalation of nebulised solution.

- **Adult**: 2.5–5 mg, repeated up to 4 times daily or more frequently in severe cases.

**Prophylaxis of allergen- or exercise-induced bronchospasm**

- **By inhalation of aerosol**.
  - Adult: 200 micrograms.

**Acute asthma**

- **By intravenous injection**
  - Child 1–23 months: 5 micrograms/kg for 1 dose, dose to be administered over 5 minutes, reserve intravenous beta₂ agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect.
  - Child 2–17 years: 15 micrograms/kg (max. per dose 250 micrograms) for 1 dose, dose to be administered over 5 minutes, reserve intravenous beta₂ agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect.

**Moderate, severe, or life-threatening acute asthma**

- **By inhalation of nebulised solution**
  - Child 1 month–4 years: 2.5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.
  - Child 5–11 years: 2.5–5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.
  - Child 12–17 years: 5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.
  - Adult: 5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available.

**continued →**
Moderate and severe acute asthma
▶ BY INHALATION OF AEROSOL
- Child: 2–10 puffs, each puff is to be inhaled separately, repeat every 10–20 minutes or when required, give via large volume spacer (and a close-fitting face mask in children under 3 years), each puff is equivalent to 100 micrograms
- Adult: 2–10 puffs, each puff is to be inhaled separately, repeat every 10–20 minutes or when required, give via large volume spacer, each puff is equivalent to 100 micrograms

Exacerbation of reversible airways obstruction (including nocturnal asthma) Prophylaxis of allergen- or exercise-induced bronchospasm
▶ BY INHALATION OF AEROSOL
- Child: 100–200 micrograms, up to 4 times a day for persistent symptoms
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Child 1 month–1 year: 100 micrograms/kg 3–4 times a day (max. per dose 2 mg), inhalation route preferred over oral route
- Child 2–5 years: 1–2 mg 3–4 times a day, inhalation route preferred over oral route
- Child 6–11 years: 2 mg 3–4 times a day, inhalation route preferred over oral route
- Child 12–17 years: 2–4 mg 3–4 times a day, inhalation route preferred over oral route

Chronic asthma
▶ BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Child 3–11 years: 4 mg twice daily
- Child 12–17 years: 8 mg twice daily
- Adult: 8 mg twice daily

Uncomplicated premature labour (between 22 and 37 weeks of gestation) (specialist supervision in hospital)
▶ BY INTRAVENOUS INFUSION
- Adult: Initially 10 micrograms/minute, rate increased gradually according to response at 10-minute intervals until contractions diminish then increase rate slowly until contractions cease (maximum rate 45 micrograms/minute), maintain rate for 1 hour after contractions have stopped, then gradually reduce by 50% every 6 hours, maximum duration 48 hours

ASMASAL CLICKHALER®
Acute bronchospasm
▶ BY INHALATION OF POWDER
- Adult: 1–2 puffs, up to 4 times daily for persistent symptoms

Prophylaxis of allergen- or exercise-induced bronchospasm
▶ BY INHALATION OF POWDER
- Adult: 1–2 puffs
EASYHALER® SALBUTAMOL
Acute bronchospasm
▶ BY INHALATION OF POWDER
- Adult: Initially 100–200 micrograms, increased if necessary to 400 micrograms; maximum 800 micrograms per day

Prophylaxis of allergen- or exercise-induced bronchospasm
▶ BY INHALATION OF POWDER
- Adult: 200 micrograms
PULVINAL® SALBUTAMOL
Acute bronchospasm
▶ BY INHALATION OF POWDER
- Child 5–17 years: Initially 200 micrograms, up to 800 micrograms daily for persistent symptoms
- Adult: Initially 200 micrograms, up to 800 micrograms daily for persistent symptoms

Prophylaxis of allergen- or exercise-induced bronchospasm
▶ BY INHALATION OF POWDER
- Child 5–17 years: 200 micrograms
- Adult: 200 micrograms

SALBULIN NOVOLIZER®
Acute bronchospasm
▶ BY INHALATION OF POWDER
- Adult: Initially 100–200 micrograms, up to 800 micrograms daily for persistent symptoms

Prophylaxis of allergen- or exercise-induced bronchospasm
▶ BY INHALATION OF POWDER
- Adult: 200 micrograms
VENTOLIN ACCUHALER®
Acute bronchospasm
▶ BY INHALATION OF POWDER
- Adult: Initially 200 micrograms, up to 4 times daily for persistent symptoms

Prophylaxis of allergen- or exercise-induced bronchospasm
▶ BY INHALATION OF POWDER
- Adult: 200 micrograms

PHARMACOKINETICS
At recommended inhaled doses, the duration of action of salbutamol is about 3 to 5 hours.


- CONTRA-INDICATIONS
  - When used for uncomplicated premature labour under specialist supervision Abruptio placenta · antepartum haemorrhage · cord compression · eclampsia · history of cardiac disease · intra-uterine fetal death · intra-uterine infection · placenta praevia · pulmonary hypertension · severe pre-eclampsia · significant risk factors for myocardial ischaemia · threatened miscarriage

- CAUTIONS
  - With intravenous use Mild to moderate pre-eclampsia (when used for uncomplicated premature labour) · suspected cardiovascular disease (should be assessed by a cardiologist before initiating therapy for uncomplicated premature labour)

- SIDE-EFFECTS
  - GENERAL SIDE-EFFECTS
    Lactic acidosis (with high doses) · nausea
  - SPECIFIC SIDE-EFFECTS
    - When used for uncomplicated premature labour Bronchospasm · muscle tension · pulmonary oedema · vomiting

- BREAST FEEDING Inhaled drugs for asthma can be taken as normal during breast-feeding.

- MONITORING REQUIREMENTS
  - In uncomplicated premature labour it is important to monitor blood pressure, pulse rate (should not exceed 120 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), blood glucose and lactate concentrations, and the patient’s fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs).

- DIRECTIONS FOR ADMINISTRATION
  - With intravenous use in children Dilute to a concentration of 50 micrograms/mL with Glucose 5%, Sodium Chloride 0.9%, or Water for injections.
  - When used by inhalation For nebulisation, dilute nebuliser solution with a suitable volume of sterile

- DIRECTIONS For nebulisation
  - With solution for intravenous infusion
    - For uncomplicated premature labour
      - Adult: 50 micrograms/kg 1–2 mg 3–4 times a day
      - Increase by 50 micrograms/kg every 30 minutes until contractions diminish then increase rate slowly until contractions cease (maximum rate 45 micrograms/minute), maintain rate for 1 hour after contractions have stopped, then gradually reduce by 50% every 6 hours, maximum duration 48 hours

- DIRECTIONS For intravenous use
  - Intra-uterine infection Abruptio placenta · severe pre-eclampsia · intra-uterine fetal death

- DIRECTIONS For nasopharyngeal use
  - Therapy before planned extubation
    - Adult: \( \frac{3700}{3} \) micrograms
    - Child: \( \frac{3700}{3} \) micrograms
  - Therapy during extubation
    - Adult: \( \frac{3700}{3} \) micrograms
    - Child: \( \frac{3700}{3} \) micrograms
  - Therapy after extubation
    - Adult: \( \frac{3700}{3} \) micrograms
    - Child: \( \frac{3700}{3} \) micrograms

- DIRECTIONS For local use
  - Bronchospasm \( \frac{3700}{3} \) micrograms
  - Contra-indication Normal during breast-feeding.
Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; salbutamol and ipratropium bromide solutions are compatible and can be mixed for nebulisation.

- With intravenous use in adults For bronchodilation by continuous intravenous infusion, dilute to a concentration of 200 micrograms/mL with glucose 5% or sodium chloride 0.9%. For premature labour by continuous intravenous infusion, dilute with glucose 5% to a concentration of 200 micrograms/mL for use in a syringe pump or for other infusion methods (preferably via controlled infusion device), dilute to a concentration of 20 micrograms/mL; close attention to patient’s fluid and electrolyte status essential.

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Salbutamol inhaler for asthma and wheeze www.medicinesforchildren.org.uk/salbutamol-inhaler-for-asthma-and-wheeze

- When used by inhalation For inhalation by aerosol or dry powder, advise patients and carers not to exceed prescribed dose and to follow manufacturer’s directions; if a previously effective dose of inhaled salbutamol fails to provide at least 3 hours relief, a doctor’s advice should be obtained as soon as possible. For inhalation by nebuliser, the dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- *Salbutamol (Non-proprietary)*
  - Salbutamol (as Salbutamol sulfate) 2 mg: Salbutamol 2mg tablets 28 tablet (PoM) £113.09 DT price = £104.95
  - Salbutamol (as Salbutamol sulfate) 4 mg: Salbutamol 4mg tablets 28 tablet (PoM) £115.76 DT price = £107.43

**Oral solution**
- *Salbutamol (Non-proprietary)*
  - Salbutamol (as Salbutamol sulfate) 400 microgram per 1 ml: Salbutamol 2mg/5ml oral solution sugar free-sugar free 150 ml (PoM) no price available DT price = £0.72
  - Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 400 microgram per 1 ml: Salbutamol 2mg/5ml syrup sugar-free 150 ml (PoM) £0.72 DT price = £0.72

**Solution for injection**
- *Ventolin (GlaxoSmithKline UK Ltd)*
  - Salbutamol (as Salbutamol sulfate) 500 microgram per 1 ml: Salbutamol 500micrograms/1ml solution for injection ampoules 5 ampoule (PoM) £1.91

**Solution for infusion**
- *Ventolin (GlaxoSmithKline UK Ltd)*
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml: Ventolin 5mg/5ml solution for infusion ampoules 10 ampoule (PoM) £24.81

**Pressurised inhalation**
- *Salbutamol (Non-proprietary)*
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose: Salbutamol 100micrograms/dose inhaler CFC free 200 dose (PoM) £1.50 DT price = £1.50
  - AirSals (Sandoz Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose: Salbutamol 100micrograms/dose inhaler CFC free 200 dose (PoM) £1.50 DT price = £1.50
  - Airomir (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose: Airomir 100micrograms/dose inhaler 200 dose (PoM) £1.97 DT price = £1.97
  - Airomir Autohaler (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose: Airomir 100micrograms/dose Autohaler 200 dose (PoM) £6.02 DT price = £6.30

**Inhalation powder**
- *Easylhaler (salbutamol)* (Orion Pharma (UK) Ltd)
  - Salbutamol 100 microgram per 1 dose: Easylhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler 200 dose (PoM) £3.31 DT price = £3.31

**Nebuliser liquid**
- *Salbutamol (Non-proprietary)*
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml: Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials 20 unit dose (PoM) £1.91 DT price = £1.91
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml: Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials 20 unit dose (PoM) £3.82 DT price = £3.82
  - Salbutamol Steri-Neb (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml: Salbutamol 2.5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials 20 unit dose (PoM) £1.91 DT price = £1.91
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml: Salbutamol 5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials 20 unit dose (PoM) £3.82 DT price = £3.82
  - Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 5 mg per 1 ml: Ventolin 5mg/ml respirator solution 20 unit dose (PoM) £2.18 DT price = £2.18
  - Ventolin Nebules (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml: Ventolin 2.5mg Nebules 20 unit dose (PoM) £1.65 DT price = £1.91
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml: Ventolin 5mg Nebules 20 unit dose (PoM) £2.78 DT price = £3.82

**Combinations available:** *Ipratropium with salbutamol*, p. 234

**Terbutaline sulfate**

**INDICATIONS AND DOSE**
Asthma | Other conditions associated with reversible airways obstruction

- **BY MOUTH**
- Adult: Initially 2.5 mg 3 times a day for 1–2 weeks, then increased to up to 5 mg 3 times a day, use by inhalation preferred over by mouth
- **BY SUBCUTANEOUS INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
- Adult: 250–500 micrograms up to 4 times a day, reserve intravenous beta; agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect
- **BY CONTINUOUS INTRAVENOUS INFUSION**
- Adult: 90–300 micrograms/hour for 8–10 hours, to be administered as a solution containing 3–5 micrograms/mL, high doses require close monitoring, reserve intravenous
beta₂ agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

- **BY INHALATION OF POWDER**
- **Adult**: 500 micrograms up to 4 times a day, for persistent symptoms
- **BY INHALATION OF NEBULISED SOLUTION**
- **Adult**: 5–10 mg 2–4 times a day, additional doses may be necessary in severe acute asthma

### Acute asthma

- **BY SUBCUTANEOUS INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
  - **Child 1 month**
  - **Child 5–10 years**
  - **Child 11–17 years**
  - **Adult**

### Moderate, severe, or life-threatening acute asthma

- **BY INHALATION OF NEBULISED SOLUTION**
  - **Child 1 month–4 years**
  - **Child 5–11 years**
  - **Child 12–17 years**
  - **Adult**

### Exacerbation of reversible airways obstruction (including nocturnal asthma) / Prevention of exercise-induced bronchospasm

- **BY INHALATION OF POWDER**
  - **Child 5–17 years**
  - **Child 18 years and over**

### Uncomplicated premature labour (between 22 and 37 weeks of gestation) (specialist supervision in hospital)

- **BY INTRAVENOUS INFUSION**
  - **Adult**: Initially 5 micrograms/minute for 20 minutes, then increased in steps of 2.5 micrograms/minute every 20 minutes until contractions have ceased (more than 10 micrograms/minute should seldom be given—20 micrograms/minute should not be exceeded), continue for 1 hour, then reduced in steps of 2.5 micrograms/minute every 20 minutes to lowest dose that maintains suppression (maximum total duration 48 hours)

### PHARMACOKINETICS

At recommended inhaled doses, the duration of action of terbutaline is about 3 to 5 hours.

### UNLICENSED USE

- Injection not licensed for use in children under 2 years.

### CONTRA-INDICATIONS

- When used for uncomplicated premature labour: Abruptio placentae, antepartum haemorrhage, cord compression, eclampsia, history of cardiac disease, intra-uterine fetal death, intra-uterine infection, placenta praevia, pulmonary hypertension, severe pre-eclampsia, significant risk factors for myocardial ischaemia, threatened miscarriage

### CAUTIONS

- Mild to moderate pre-eclampsia (when used for uncomplicated premature labour) / suspected cardiovascular disease (should be assessed by a cardiologist before initiating therapy for uncomplicated premature labour)

### SIDE-EFFECTS

#### GENERAL SIDE-EFFECTS

- Nausea

#### SPECIFIC SIDE-EFFECTS

- When used for uncomplicated premature labour: Muscle tension / pulmonary oedema / vomiting

#### PREGNANCY

- Inhaled drugs for asthma can be taken as normal during pregnancy.

#### BREAST FEEDING

- Inhaled drugs for asthma can be taken as normal during breast-feeding.

### MONITORING REQUIREMENTS

- In uncomplicated premature labour it is important to monitor blood pressure, pulse rate (should not exceed 120 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), blood glucose and lactate concentrations, and the patient’s fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs).

### DIRECTIONS FOR ADMINISTRATION

- With intravenous use in children: For continuous intravenous infusion, dilute to a concentration of 5 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; if fluid-restricted, dilute to a concentration of 10 micrograms/mL.
- When used by inhalation: For nebulisation, dilute nebuliser solution with sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; terbutaline and ipratropium bromide solutions are compatible and may be mixed for nebulisation.
- With intravenous use in adults: For bronchodilation by continuous intravenous infusion, dilute 1.5–2.5 mg with 500 mL glucose 5% or sodium chloride 0.9% and give over 8–10 hours. For premature labour by continuous intravenous infusion, dilute in glucose 5% and give via controlled infusion device preferably a syringe pump; if syringe pump available dilute to a concentration of 100 micrograms/mL; if syringe pump not available dilute to a concentration of 10 micrograms/mL; close attention to patient’s fluid and electrolyte status essential.

### PATIENT AND CARER ADVICE

- When used by inhalation: For inhalation by dry powder, advise patients and carers not to exceed prescribed dose and to follow manufacturer’s directions; if a previously effective dose of inhaled terbutaline fails to provide at least 3 hours relief, a doctor’s advice should be obtained as soon as possible. For inhalation by nebuliser, the dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution.
Corticosteroids

Airways disease, use of corticosteroids

Asthma

Inhaled corticosteroids

An inhaled corticosteroid used for 3–4 weeks may help to distinguish asthma from chronic obstructive pulmonary disease; clear improvement over 3–4 weeks suggests asthma.

Corticosteroids are effective in asthma; they reduce airway inflammation (and hence reduce oedema and secretion of mucus into the airway).

An inhaled corticosteroid is used regularly for prophylaxis of asthma when patients require a beta₂ agonist more than twice a week, or if symptoms disturb sleep at least once a week, or if the patient has suffered an exacerbation in the last 2 years requiring a systemic corticosteroid. Regular use of inhaled corticosteroids reduces the risk of exacerbation of asthma.

Current and previous smoking reduces the effectiveness of inhaled corticosteroids and higher doses may be necessary.

Corticosteroid inhalers must be used regularly for maximum benefit; alleviation of symptoms usually occurs 3 to 7 days after initiation. Beclometasone dipropionate p. 244, budesonide p. 246, fluticasone p. 248, and mometasone furoate p. 250 appear to be equally effective. Preparations that combine a corticosteroid with a long-acting beta₂ agonist may be helpful for patients stabilised on the individual components in the same proportion.

In adults using an inhaled corticosteroid and a long-acting beta₂ agonist for the prophylaxis of asthma, but who are poorly controlled, Symbicort® or DuoResp Spirax® (both containing budesonide with formoterol p. 247) can be used as relievers (instead of a short-acting beta₂ agonist), in addition to their regular use for the prophylaxis of asthma. Symbicort® can also be used in this way in adults using an inhaled corticosteroid with a dose greater than beclometasone dipropionate 400 micrograms daily, but who are poorly controlled (standard doses of other inhaled corticosteroids can be used). When starting this treatment, the total regular daily dose of inhaled corticosteroid should not be reduced. Patients must be carefully instructed on the appropriate dose and management of exacerbations before initiating this therapy. Patients using budesonide with formoterol as a reliever once a day or more should have their treatment reviewed regularly. The use of Symbicort® for both reliever and maintenance therapy is also used by some specialists in children 12–18 years [unlicensed]. Fostair® can also be used in adults as a reliever (instead of a short-acting beta₂ agonist) in addition to its regular use for the prophylaxis of asthma. It may be particularly useful for patients with poorly controlled asthma requiring reliever therapy, or for those who have had previous exacerbations of asthma which needed additional intervention. Patients requiring frequent daily use of Fostair® as a reliever should have their maintenance treatment reviewed. This approach has not been investigated with combination inhalers containing other corticosteroids and long-acting beta₂ agonists.

High doses of inhaled corticosteroid can be prescribed for patients who respond only partially to standard doses with a long-acting beta₂ agonist or another long-acting bronchodilator. High doses should be continued only if there is clear benefit over the lower dose. The recommended maximum dose of an inhaled corticosteroid should not generally be exceeded. However, if a higher dose is required, then it should be initiated and supervised by a specialist. The use of high doses of inhaled corticosteroid can minimise the requirement for an oral corticosteroid.

Oral corticosteroids

Systemic corticosteroid therapy may be necessary during episodes of stress, such as severe infection, or if the asthma is worsening, when higher doses are needed and access of inhaled drug to small airways may be reduced; patients may need a reserve supply of corticosteroid tablets.

In chronic asthma, when the response to other drugs has been inadequate, longer term administration of an oral corticosteroid may be necessary; in such cases high doses of an inhaled corticosteroid should be continued to minimise oral corticosteroid requirements. Patients taking long-term oral corticosteroids for asthma can often be transferred to an inhaled corticosteroid but the transfer must be slow, with gradual reduction in the dose of the oral corticosteroid, and at a time when the asthma is well controlled.

An acute attack of asthma should be treated with a short course of an oral corticosteroid starting with a high dose. Patients whose asthma has deteriorated rapidly usually respond quickly to corticosteroids. The dose can usually be stopped abruptly; tapering is not needed provided that the patient receives an inhaled corticosteroid in an adequate dose (apart from those on maintenance oral corticosteroid treatment or where oral corticosteroids are required for 3 or more weeks). In patients who have needed several courses of oral corticosteroids and in whom the possibility of a period on maintenance corticosteroids is being considered, it may be useful to taper the corticosteroid dose gradually to identify a threshold dose for asthma control. This should only be done after other standard options for controlling asthma have been tried.

An oral corticosteroid should normally be taken as a single dose in the morning to reduce the disturbance to circadian cortisol secretion. Dosage should always be titrated to the lowest dose that controls symptoms. Regular peak-flow measurements help to optimise the dose.

Parenteral corticosteroids

Hydrocortisone injection p. 620 has a role in the emergency treatment of acute severe asthma.

Chronic obstructive pulmonary disease

Inhaled corticosteroids

In chronic obstructive pulmonary disease inhaled corticosteroid therapy may reduce exacerbations when given in combination with an inhaled long-acting beta₂ agonist. Oral corticosteroids

During an acute exacerbation of chronic obstructive pulmonary disease, prednisolone p. 622 should be given;
Respiratory system

In children

Inhaled corticosteroids for the treatment of chronic asthma in children

MONITORING REQUIREMENTS

Breast feeding

SIDE-EFFECTS

Paradoxical bronchospasm

Candidiasis

SIDE-EFFECTS, FURTHER INFORMATION

Pregnancy

Breast feeding

Monitoring requirements

NICE technology appraisals (TAs)

Inhaled corticosteroids for the treatment of chronic asthma in children under 12 years (November 2007) NICE TA131

In children

For children under 12 years with chronic asthma in whom treatment with an inhaled corticosteroid is considered appropriate, the least costly product that is suitable for an individual child (taking into consideration NICE TAs 38 and 10), within its marketing authorisation, is recommended. For children under 12 years with chronic asthma in whom treatment with an inhaled corticosteroid and a long-acting β2 agonist is considered appropriate, the following apply:

- the use of a combination inhaler within its marketing authorisation is recommended as an option;
- the decision to use a combination inhaler or two agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence;
- if a combination inhaler is chosen, then the least costly inhaler that is suitable for the individual child is recommended.

www.nice.org.uk/TA131

Inhaled corticosteroids for the treatment of chronic asthma in adults and children over 12 years (March 2008) NICE TA138

For adults and children over 12 years with chronic asthma in whom treatment with an inhaled corticosteroid is considered appropriate, the least costly product that is suitable for an individual (taking into consideration NICE TAs 38 and 10), within its marketing authorisation is recommended.

For adults and children over 12 years with chronic asthma in whom treatment with an inhaled corticosteroid and a long-acting β2 agonist is considered appropriate, the following apply:

- the use of a combination inhaler within its marketing authorisation is recommended as an option;
- the decision to use a combination inhaler or two agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need, and the likelihood of treatment adherence;
- if a combination inhaler is chosen, then the least costly inhaler that is suitable for the individual is recommended.

www.nice.org.uk/TA138

Beclometasone dipropionate

(Beclohasone dipropionate)

INDICATIONS AND DOSE

Prophylaxis of asthma

- By inhalation of powder
- Child 5–11 years: 100–200 micrograms twice daily, dose to be adjusted as necessary
- Child 12–17 years: 200–400 micrograms twice daily; increased if necessary up to 800 micrograms twice daily, dose to be adjusted as necessary
- Adult: 200–400 micrograms twice daily; increased if necessary up to 800 micrograms twice daily, dose to be adjusted as necessary

ASMAHEC CLICKHALER®

Prophylaxis of asthma

- By inhalation of powder
- Child 6–11 years: 100–200 micrograms twice daily, dose to be adjusted as necessary
- Child 12–17 years: 100–400 micrograms twice daily (max. per dose 1 mg twice daily), dose to be adjusted as necessary
- Adult: 100–400 micrograms twice daily (max. per dose 1 mg twice daily), dose to be adjusted as necessary

CLENIL MODULITE®

Prophylaxis of asthma

- By inhalation of aerosol
- Child 2–11 years: 100–200 micrograms twice daily
- Child 12–17 years: 200–400 micrograms twice daily, adjusted according to response; increased if necessary up to 1 mg twice daily
- Adult: 200–400 micrograms twice daily, adjusted according to response; increased if necessary up to 1 mg twice daily
Budesonide, or Clenil Modulite

▶ CAUTIONARY AND ADVISORY LABELS

Pressurised inhalation containing the same drug. There can be variation in the licensing of different medicines.

Dental practitioners should be issued with high doses of inhaled beclometasone dipropionate. Medicines for children leaflet: Beclometasone for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/beclometasone-inhaler-asthma-prevention-prophylaxis-0

▶ PROFESSIO SPECIFIC INFORMATION

Dental practitioners’ formulary

Beclometasone dipropionate 50 micrograms/metered inhalation may be prescribed.

▶ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation

Beclometasone dipropionate (Non-proprietary)

<table>
<thead>
<tr>
<th>Beclometasone dipropionate 50 microgram per 1 dose</th>
<th>Beclometasone 50micrograms/dose inhaler CFC free</th>
<th>200 dose (PStM) no price available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometasone dipropionate 100 microgram per 1 dose</td>
<td>Beclometasone 100micrograms/dose inhaler CFC free</td>
<td>200 dose (PStM) £54.20</td>
</tr>
</tbody>
</table>

▶ INDICATIONS AND DOSE

Asthma maintenance therapy

▶ BY INHALATION OF AEROSOL

Adult: 100/6–200/12 micrograms twice daily; maximum 400/24 micrograms per day

Asthma, maintenance and reliever therapy

▶ BY INHALATION OF AEROSOL

Adult: Maintenance 100/6 micrograms twice daily; 100/6 micrograms as required for relief of symptoms; maximum 800/48 micrograms per day

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted

▶ BY INHALATION OF AEROSOL

Adult: 200/12 micrograms twice daily

DOSE EQUIVALENCE AND CONVERSION

For inhalation of aerosol, when switching patients from other beclometasone dipropionate and formoterol fumarate inhalers, Fostair® 100/6 can be prescribed for patients already using beclometasone dipropionate 250 micrograms in another CFC-free inhaler; the dose of Fostair® should be adjusted according to response.

For inhalation of powder, when switching patients from other beclometasone dipropionate formulations with non-extrafine particle size distribution, the dose should be adjusted according to response. continued →
Budesonide

**INDICATIONS AND DOSE**

**Prophylaxis of mild to moderate asthma (in patients stabilised on twice daily dose)**
- **BY INHALATION OF POWDER**
  - Child 6–11 years: 200–400 micrograms once daily, to be given in the evening
  - Child 12–17 years: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening
  - Adult: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening

**Prophylaxis of asthma**
- **BY INHALATION OF POWDER**
  - Child 6–11 years: 100–400 micrograms twice daily, dose to be adjusted as necessary
  - Child 12–17 years: 100–800 micrograms twice daily, dose to be adjusted as necessary
  - Adult: 100–800 micrograms twice daily, dose to be adjusted as necessary
- **BY INHALATION OF NEBULISED SUSPENSION**
  - Child 6 months–11 years: 125–500 micrograms twice daily, adjusted according to response; maximum 2 mg per day
  - Child 12–17 years: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**
- **CAUTIONARY AND ADVISORY LABELS**: 8, 10
  - Fostair (Chiesi Ltd)
    - Formoterol fumarate dihydrate 6 microgram, Beclometasone dipropionate 200 microgram: Fostair 200 micrograms/dose / 6 micrograms/dose inhaler | 120 dose | £29.32
  - Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 100 microgram per 1 dose: Fostair 100 micrograms/dose / 6 micrograms/dose inhaler | 120 dose | £29.32

**Inhalation powder**
- **CAUTIONARY AND ADVISORY LABELS**: 8, 10
  - Fostair NEXThaler (Chiesi Ltd)
    - Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 100 microgram per 1 dose: Fostair NEXThaler 100 micrograms/dose / 6 micrograms/dose dry powder inhaler | 120 dose | £29.32

**POTENCY**

Dose adjustments may be required for some inhaler devices, see under individual preparations.

**UNLICENSED USE** Pulmicort® nebuliser solution not licensed for use in children under 3 months.

**DIRECTIONS FOR ADMINISTRATION** Budesonide nebuliser suspension is not suitable for use in ultrasonic nebulisers.

**PATIENT AND CARER ADVICE** With high doses, a steroid card should be supplied. Patients or carers should be given advice on how to administer budesonide dry powder inhaler and nebuliser suspension.


**BUDELIN NOVOLIZER** Patients or carers should be given advice on administration of Budelin Novolizer.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (JULY 2008)**

Fostair® contains extra-fine particles of beclometasone dipropionate and is more potent than traditional beclometasone dipropionate CFC-free inhalers. The dose of beclometasone dipropionate in Fostair® should be lower than non-extra-fine formulations of beclometasone dipropionate and will need to be adjusted to the individual needs of the patient.

**PATIENT AND CARER ADVICE** With high doses, a steroid card should be supplied. Patients or carers should be given advice on how to administer beclometasone with formoterol aerosol for inhalation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**
- **CAUTIONARY AND ADVISORY LABELS**: 8, 10
  - Fostair (Chiesi Ltd)
    - Formoterol fumarate dihydrate 6 microgram, Beclometasone dipropionate 200 microgram: Fostair 200 micrograms/dose / 6 micrograms/dose inhaler | 120 dose | £29.32
  - Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 100 microgram per 1 dose: Fostair 100 micrograms/dose / 6 micrograms/dose inhaler | 120 dose | £29.32

**Inhalation powder**
- **CAUTIONARY AND ADVISORY LABELS**: 8, 10
  - Fostair NEXThaler (Chiesi Ltd)
    - Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 100 microgram per 1 dose: Fostair NEXThaler 100 micrograms/dose / 6 micrograms/dose dry powder inhaler | 120 dose | £29.32

**UNLICENSED USE** Pulmicort® nebuliser solution not licensed for use in children under 3 months.

**DIRECTIONS FOR ADMINISTRATION** Budesonide nebuliser suspension is not suitable for use in ultrasonic nebulisers.

**PATIENT AND CARER ADVICE** With high doses, a steroid card should be supplied. Patients or carers should be given advice on how to administer budesonide dry powder inhaler and nebuliser suspension.


**BUDELIN NOVOLIZER** Patients or carers should be given advice on administration of Budelin Novolizer.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (JULY 2008)**

Fostair® contains extra-fine particles of beclometasone dipropionate and is more potent than traditional beclometasone dipropionate CFC-free inhalers. The dose of beclometasone dipropionate in Fostair® should be lower than non-extra-fine formulations of beclometasone dipropionate and will need to be adjusted to the individual needs of the patient.
Please consider, budesonide p.

The properties listed below are those particular to the combination only. For the properties of the components please consider, budesonide p. 246, formoterol fumarate p. 237.

**INDICATIONS AND DOSE**

**DUORESP SPIROMAX® 160MICROGRAMS/4.5MICROGRAMS**

**Asthma, maintenance therapy**
- **BY INHALATION OF POWDER**
- Adult: 1–2 inhalations twice daily, increased if necessary up to 4 inhalations twice daily

**Asthma, maintenance and reliever therapy**
- **BY INHALATION OF POWDER**
- Adult: 2 inhalations daily in 1–2 divided doses, increased if necessary to 2 inhalations twice daily. 1 inhalation (max. per dose 6 inhalations) as required, for relief of symptoms, a total daily dose of up to 12 inhalations can be used for a limited time but medical assessment is recommended if more than 8 inhalations daily are needed

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted**
- **BY INHALATION OF POWDER**
- Adult: 2 inhalations twice daily

**DUORESP SPIROMAX® 320MICROGRAMS/9MICROGRAMS**

**Asthma, maintenance therapy**
- **BY INHALATION OF POWDER**
- Adult: 1 inhalation twice daily

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted**
- **BY INHALATION OF POWDER**
- Adult: 1 inhalation twice daily

**SYMBICORT 100/6 TURBOHALER®**

**Asthma, maintenance therapy**
- **BY INHALATION OF POWDER**
  - Child 6-17 years: Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
  - Adult: Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**Asthma, maintenance and reliever therapy**
- **BY INHALATION OF POWDER**
  - Adult: Maintenance 2 puffs daily in 1–2 divided doses; 1 puff as required for relief of symptoms, increased if necessary up to 6 puffs as required, max. 8 puffs per day; up to 12 puffs daily can be used for a limited time but medical assessment should be considered

**SYMBOICRT 200/6 TURBOHALER®**

**Asthma, maintenance therapy**
- **BY INHALATION OF POWDER**
  - Child 12-17 years: Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
  - Adult: Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**Asthma, maintenance and reliever therapy**
- **BY INHALATION OF POWDER**
  - Adult: Maintenance 2 puffs daily in 1–2 divided doses, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted**
- **BY INHALATION OF POWDER**
  - Adult: 2 puffs twice daily

**SYMBOICRT 400/12 TURBOHALER®**

**Asthma, maintenance therapy**
- **BY INHALATION OF POWDER**
  - Child 12-17 years: Initially 1 puff twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
  - Adult: Initially 1 puff twice daily, increased if necessary up to 2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted**
- **BY INHALATION OF POWDER**
  - Adult: 1 puff twice daily

**PATIENT AND CARER ADVICE**

With high doses, a steroid card should be supplied. Patients counselling is advised for budesonide with formoterol dry powder inhalation (administration).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**

**CAUTIONARY AND ADVISORY LABELS 8, 10 (high doses)**
- **DuResp Spiromax** (Teva UK Ltd)
  - Formoterol fumarate dihydrate 6 microgram per 1 dose, Budesonide 200 microgram per 1 dose  DuResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler | 120 dose (Posm) £29.97 DT price = £38.00
  - Formoterol fumarate dihydrate 12 microgram per 1 dose, Budesonide 400 microgram per 1 dose  DuResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler | 60 dose (Posm) £29.97 DT price = £38.00
- **Symbicort Turbohaler** (AstraZeneca UK Ltd)
  - Formoterol fumarate dihydrate 6 microgram per 1 dose, Budesonide 100 microgram per 1 dose  Symbicort 100/6 Turbohaler | 120 dose (Posm) £33.00 DT price = £33.00
  - Formoterol fumarate dihydrate 6 microgram per 1 dose, Budesonide 200 microgram per 1 dose  Symbicort 200/6 Turbohaler | 120 dose (Posm) £38.00 DT price = £38.00
  - Formoterol fumarate dihydrate 12 microgram per 1 dose, Budesonide 400 microgram per 1 dose  Symbicort 400/12 Turbohaler | 60 dose (Posm) £38.00 DT price = £38.00

**Ciclesonide**

**INDICATIONS AND DOSE**

**Prophylaxis of asthma**
- **BY INHALATION OF AEROSOL**
  - Child 12-17 years: 160 micrograms once daily; reduced to 80 micrograms daily, if control maintained

continued →
Fluticasone

**INDICATIONS AND DOSE**

**Prophylaxis of asthma**

- **BY INHALATION OF POWDER**
  - Child 5–15 years: Initially 50–100 micrograms twice daily (max. per dose 200 micrograms twice daily), dose to be adjusted as necessary
  - Child 16–17 years: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist
  - Adult: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist

- **BY INHALATION OF AEROSOL**
  - Child 4–15 years: Initially 50–100 micrograms twice daily (max. per dose 200 micrograms twice daily), dose to be adjusted as necessary
  - Child 16–17 years: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist
  - Adult: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist

- **BY INHALATION OF NEBULISER SUSPENSION**
  - Child 4–15 years: 1 mg twice daily
  - Child 16–17 years: 0.5–2 mg twice daily
  - Adult: 0.5–2 mg twice daily

**SIDE-EFFECTS**

- Arthralgia
- Dyspepsia

**DIRECTIONS FOR ADMINISTRATION**

Fluticasone nebuliser liquid may be diluted with sterile sodium chloride 0.9%. It is not suitable for use in ultrasonic nebulisers.

**PATIENT AND CARER ADVICE**

With high doses, a steroid card should be supplied. Patients or carers should be given advice on how to administer fluticasone inhalation preparations.

Medicines for Children leaflet: Fluticasone inhaler for asthma prevention (prophylaxis) [www.medicinesforchildren.org.uk/fluticasone-inhaler-for-asthma-prevention](http://www.medicinesforchildren.org.uk/fluticasone-inhaler-for-asthma-prevention)

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Fluticasone with formoterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone above, formoterol fumarate p. 237.

**INDICATIONS AND DOSE**

**FLUTIFORM® 50**

**Prophylaxis of asthma**

- **BY INHALATION OF AEROSOL**
  - Child 12–17 years: 2 puffs twice daily
  - Adult: 2 puffs twice daily

**FLUTIFORM® 125**

**Prophylaxis of asthma**

- **BY INHALATION OF AEROSOL**
  - Child 12–17 years: 2 puffs twice daily
  - Adult: 2 puffs twice daily

**FLUTIFORM® 250**

**Prophylaxis of asthma**

- **BY INHALATION OF AEROSOL**
  - Adult: 2 puffs twice daily

**PATIENT AND CARER ADVICE**

With high doses, a steroid card should be provided. Patients or carers should be given advice on how to administer fluticasone with formoterol aerosol inhalation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

CAUTIONARY AND ADVISORY LABELS 8, 10

- **Flutiform** (Napp Pharmaceuticals Ltd)
  - Fluticasone propionate 50 microgram per 1 dose Flutiform 50 micrograms/dose inhaler | 120 dose POM £14.40 DT price = £14.40
Fluticasone with salmeterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 248, salmeterol p. 238.

INDICATIONS AND DOSE
SERETIDE 100 ACCUHALER®
Prophylaxis of asthma
▶ BY INHALATION OF POWDER
▶ Child 5–17 years: 1 inhalation twice daily, reduced to 1 inhalation daily, use reduced dose only if control maintained
▶ Adult: 1 inhalation twice daily, reduced to 1 inhalation daily, use reduced dose only if control maintained

SERETIDE 250 ACCUHALER®
Prophylaxis of asthma
▶ BY INHALATION OF POWDER
▶ Child 12–17 years: 1 inhalation twice daily
▶ Adult: 1 inhalation twice daily

SERETIDE 500 ACCUHALER®
Prophylaxis of asthma
▶ BY INHALATION OF POWDER
▶ Child 12–17 years: 1 inhalation twice daily
▶ Adult: 1 inhalation twice daily

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 60% of predicted
▶ BY INHALATION OF POWDER
▶ Adult: 1 inhalation twice daily

SERETIDE 50 EVOHALER®
Prophylaxis of asthma
▶ INITIALLY BY INHALATION OF AEROSOL
▶ Child 5–17 years: 2 puffs twice daily, (by inhalation) reduced to 2 puffs once daily, use reduced dose only if control maintained
▶ Adult: 2 puffs twice daily, (by inhalation) reduced to 2 puffs once daily, use reduced dose only if control maintained

SERETIDE 125 EVOHALER®
Prophylaxis of asthma
▶ BY INHALATION OF AEROSOL
▶ Child 12–17 years: 2 puffs twice daily
▶ Adult: 2 puffs twice daily

SERETIDE 250 EVOHALER®
Prophylaxis of asthma
▶ BY INHALATION OF AEROSOL
▶ Child 12–17 years: 2 puffs twice daily
▶ Adult: 2 puffs twice daily

PATIENT AND CARER ADVICE
With preparations containing greater than 100 micrograms fluticasone, a steroid card should be provided. Patients or carers should be given advice on how to administer fluticasone with salmeterol dry powder inhalation and aerosol inhalation.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
▶ In adults The Scottish Medicines Consortium has advised (December 2008) that Seretide 500 Accuhaler® is not recommended for use within NHS Scotland for chronic obstructive pulmonary disease in patients with a forced expiratory volume in 1 second (FEV1) less than 60% and greater than 50% of the predicted normal value, with significant symptoms despite regular bronchodilator therapy, and a history of repeated exacerbations.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation
CAUTIONARY AND ADVISORY LABELS 8, 10 (excluding Seretide 50 EVOHALER®)
 ▶ Seretide EVOHALER (GlaxoSmithKline UK Ltd)
 Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 50 microgram per 1 dose Seretide 50 EVOHALER | 120 dose (POD) £18.00 DT price = £18.00
 Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 50 microgram per 1 dose Seretide 50 EVOHALER | 60 dose (POD) £18.00 DT price = £18.00
 Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Seretide 250 EVOHALER | 120 dose (POD) £35.00 DT price = £35.00
 Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Seretide 250 EVOHALER | 60 dose (POD) £35.00 DT price = £35.00

Inhalation powder
CAUTIONARY AND ADVISORY LABELS 8, 10 (excluding Seretide 100 Accuhaler®)
 ▶ Seretide Accuhaler (GlaxoSmithKline UK Ltd)
 Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 100 microgram per 1 dose Seretide 100 Accuhaler | 120 dose (POD) £18.00 DT price = £18.00
 Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Seretide 250 Accuhaler | 120 dose (POD) £35.00 DT price = £35.00
 Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 500 microgram per 1 dose Seretide 500 Accuhaler | 60 dose (POD) £40.92 DT price = £40.92

Fluticasone with vilanterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 248.

INDICATIONS AND DOSE
RELVAR ELLIPTA® 184 MICROGRAMS/22 MICROGRAMS
Prophylaxis of asthma
▶ BY INHALATION OF POWDER
▶ Child 12–17 years: 1 inhalation once daily
▶ Adult: 1 inhalation once daily

DOSE EQUIVALENCE AND CONVERSION
1 inhalation (delivered dose) of fluticasone furoate
184 micrograms once daily is approximately equivalent to fluticasone propionate 500 micrograms twice daily.

RELVAR ELLIPTA® 92 MICROGRAMS/22 MICROGRAMS
Prophylaxis of asthma
▶ BY INHALATION OF POWDER
▶ Child 12–17 years: 1 inhalation once daily
▶ Adult: 1 inhalation once daily

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 70% of predicted
▶ BY INHALATION OF POWDER
▶ Adult: 1 inhalation once daily

DOSE EQUIVALENCE AND CONVERSION
1 inhalation (delivered dose) of fluticasone furoate
92 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily.

SIDE-EFFECTS
Abdominal pain • back pain

PREGNANCY
Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING
Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT
Max. dose fluticasone furoate 92 micrograms, vilanterol 22 micrograms.
**Relvar Ellipta®**
- 184 micrograms/22 micrograms
  - Avoid in moderate to severe impairment.

**Patient and Carer Advice**
- A steroid card should be provided.
  - Patients or carers should be given advice on how to administer fluticasone with vilanterol powder for inhalation.

**National Funding/Access Decisions**
- **Scottish Medicines Consortium (SMC) Decisions**
  - In adults, the Scottish Medicines Consortium (SMC) has advised (March 2014) that fluticasone furoate/vilanterol (Relvar Ellipta®) is accepted for restricted use within NHS Scotland in patients with severe chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) less than 50% of the predicted normal value.

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Inhalation Powder**
- **Cautionary and Advisory Labels**
  - Relvar Ellipta (GlaxoSmithKline UK Ltd) 
  - Vilanterol 22 microgram per 1 dose, fluticasone furoate 92 microgram per 1 dose Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler | 30 dose [Pack] £22.00 DT price = £22.00
  - Vilanterol 22 microgram per 1 dose, fluticasone furoate 184 microgram per 1 dose Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler | 30 dose [Pack] £29.50 DT price = £29.50

**Mometasone furoate**

**Indications and Dose**
- **Prophylaxis of asthma**
  - By inhalation of powder
  - Child 12-17 years: Initially 400 micrograms daily in 1–2 divided doses, single dose to be inhaled in the evening, reduced to 200 micrograms once daily, if control maintained
  - Adult: Initially 400 micrograms divided daily in 1–2 divided doses, single dose to be inhaled in the evening, reduced to 200 micrograms once daily, if control maintained

**Prophylaxis of Severe Asthma**
- By inhalation of powder
  - Child 12-17 years: Increased if necessary up to 400 micrograms twice daily
  - Adult: Increased if necessary up to 400 micrograms twice daily

**Side-Effects**
- Common or very common: Headache
- Uncommon: Dyspepsia - palpitation - weight gain

**Patient and Carer Advice**
- Patients or carers should be given advice on how to administer mometasone by inhaler. Medicines for Children leaflet: Mometasone furoate inhaler for asthma prevention (prophylaxis) [www.medicinesforchildren.org.uk/mometasone-furoate-inhaler-for-asthma-prevention-prophylaxis](http://www.medicinesforchildren.org.uk/mometasone-furoate-inhaler-for-asthma-prevention-prophylaxis)

**National Funding/Access Decisions**
- **Scottish Medicines Consortium (SMC) Decisions**
  - The Scottish Medicines Consortium has advised (November 2003) that Asmanex® is restricted for use following failure of first-line inhaled corticosteroids.

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Inhalation Powder**
- **Cautionary and Advisory Labels**
  - Asmanex Twikhaler (Merck Sharp & Dohme Ltd)
  - Mometasone furoate 200 microgram per 1 dose
    - Asmanex 200micrograms/dose Twikhaler | 30 dose [Pack] £15.70 DT price = £15.70 | 60 dose [Pack] £23.54 DT price = £23.54
    - Mometasone furoate 400 microgram per 1 dose
      - Asmanex 400micrograms/dose Twikhaler | 30 dose [Pack] £21.78 DT price = £21.78 | 60 dose [Pack] £36.05 DT price = £36.05

**Immunosuppressants > Monoclonal Antibodies**

**Omalizumab**

**Indications and Dose**
- **Prophylaxis of severe persistent allergic asthma**
  - By subcutaneous injection
  - Adult: Dose according to immunoglobulin E concentration and body-weight (consult product literature)

**Add-on therapy for chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment**
- By subcutaneous injection
  - Adult: 300 mg every 4 weeks

**Caution**
- Autoimmune disease - susceptibility to helminth infection—discontinue if infection does not respond to anthelminthic

**Side-Effects**
- Common or very common: Abdominal pain - arthralgia - headache - injection-site reactions - pyrexia - sinusitis - upper respiratory tract infection
- Rare: Angioedema - antibody formation - laryngoe德ma - parasitic infection
- Frequency not known: Alopecia - arterial thromboembolic events - Churg-Strauss syndrome - joint swelling - myalgia - serum sickness (including fever and lymphadenopathy) - thrombocytopenia

**Side-Effects, Further Information**
- Churg-Strauss syndrome: Churg-Strauss syndrome has occurred rarely in patients given omalizumab; the reaction is usually associated with the reduction of oral corticosteroid therapy. Churg-Strauss syndrome can present as eosinophilia, vasculitic rash, cardiac complications, worsening pulmonary symptoms, or peripheral neuropathy.
- Hypersensitivity reactions: Hypersensitivity reactions can also occur immediately following treatment with omalizumab or sometimes more than 24 hours after the first injection.

**Pregnancy**
- Manufacturer advises avoid unless essential—crosses the placenta.

**Breast Feeding**
- Manufacturer advises avoid—present in milk in animal studies.

**Hepatic Impairment**
- Manufacturer advises caution—no information available.

**Renal Impairment**
- Manufacturer advises caution—no information available.
NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Omalizumab for severe persistent allergic asthma (April 2013) NICE TA278
  Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in patients aged 6 years and over:
  - who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
  - only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme. Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

Patients currently receiving omalizumab whose disease does not meet the criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA278
- Omalizumab for previously treated chronic spontaneous urticaria (June 2015) NICE TA339
  Omalizumab is an option as add-on therapy for the treatment of severe chronic spontaneous urticaria in patients 12 years and over, only if:
  - the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more,
  - the patient’s condition has not responded to standard treatment with H1-antihistamines and leukotriene receptor antagonists,
  - omalizumab is stopped at or before the fourth dose if the condition has not responded,
  - omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded and is restarted only if the condition relapses,
  - omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy,
  - the manufacturer provides omalizumab with the discount agreed in the patient access scheme.

Patients currently receiving omalizumab whose disease does not meet the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA339

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (December 2014) that omalizumab (Xolair®) is accepted for restricted use within NHS Scotland for the treatment of chronic spontaneous urticaria in patients aged 12 years and over, who have had an inadequate response to combination therapy with H1-antihistamines, leukotriene receptor antagonists and H2-antihistamines, used according to current treatment guidelines.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Xolair (Novartis Pharmaceuticals UK Ltd)
  Omalizumab 150 mg per 1 ml Xolair 150mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £56.15
  Xolair 75mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £128.07

LEUKOTRIENE RECEPTOR ANTAGONISTS
Leukotriene receptor antagonists

The leukotriene receptor antagonists, montelukast below and zafirlukast p. 252, block the effects of cysteinyi leukotrienes in the airways. They are effective in asthma when used alone or with an inhaled corticosteroid.

Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid, but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis, but they are less effective in those with severe asthma who are also receiving high doses of other drugs.

Montelukast

INDICATIONS AND DOSE
Prophylaxis of asthma
- BY MOUTH
  - Child 6 months–5 years: 4 mg once daily, dose to be taken in the evening
  - Child 6–14 years: 5 mg once daily, dose to be taken in the evening
  - Child 15–17 years: 10 mg once daily, dose to be taken in the evening
  - Adult: 10 mg once daily, dose to be taken in the evening

Symptomatic relief of seasonal allergic rhinitis in patients with asthma.
- BY MOUTH
  - Child 15–17 years: 10 mg once daily, dose to be taken in the evening
  - Adult: 10 mg once daily, dose to be taken in the evening

INTERACTIONS
- Appendix 1 (leukotriene receptor antagonists).

SIDE-EFFECTS
- Common or very common Abdominal pain - headache - hyperkinesia (in young children) - thirst
- Rare Disturbance in attention - increased bleeding tendency - memory impairment - palpitation - tremor
- Very rare Churg-Strauss syndrome - disorientation - erythema multiforme - erythema nodosum - hallucinations - hepatic disorders - hepatic eosinophilic infiltration - suicidal behaviour - suicidal thoughts

SIDE-EFFECTS, FURTHER INFORMATION
Churg-Strauss syndrome has occurred very rarely in association with the use of montelukast; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

PREGNANCY
Manufacturer advises avoid unless essential. There is limited evidence for the safe use of montelukast during pregnancy; however, it can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant.
Respiratory system

Breastfeeding
Manufacturer advises avoid unless essential.

Directions for Administration
Granules may be swallowed or mixed with cold, soft food (not liquid) and taken immediately.

Prescribing and Dispensing Information
Flavours of chewable tablet formulations may include cherry.

Patient and Carer Advice
Patients or carers should be given advice on how to administer montelukast granules. Medicines for Children leaflet: Montelukast for asthma www.medicinesforchildren.org.uk/montelukast-for-asthma

National Funding/Access Decisions

SINGULAR® Granules
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2007) that Singulair® granules are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2–14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use and who are not capable of using inhaled corticosteroids; Singulair® granules should be initiated by a specialist in paediatric asthma.

SINGULAR® Chewable Tablets
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2007) that Singulair® chewable tablets are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2–14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use and who are not capable of using inhaled corticosteroids; Singulair® chewable tablets should be initiated by a specialist in paediatric asthma.

Medicinal Forms
There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Montelukast (Non-proprietary)
  Montelukast (as Montelukast sodium) 10 mg Montelukast 10mg tablets | 28 tablet | £26.97 DT price = £1.90
- Singulair (Merck Sharp & Dohme Ltd)
  Montelukast (as Montelukast sodium) 10 mg Singulair 10mg tablets | 28 tablet | £26.97 DT price = £1.90

Chewable tablet

CAUTIONARY AND ADVISORY LABELS 23, 24

EXCIPIENTS: May contain Aspartame

- Montelukast (Non-proprietary)
  Montelukast (as Montelukast sodium) 4 mg Montelukast 4mg chewable tablets sugar free sugar-free | 28 tablet | £25.69 DT price = £1.35
- Montelukast (as Montelukast sodium) 5 mg Montelukast 5mg chewable tablets sugar free sugar-free | 28 tablet | £25.69 DT price = £1.65
- Singulair (Merck Sharp & Dohme Ltd)
  Montelukast (as Montelukast sodium) 4 mg Singulair Paediatric 4mg chewable tablets sugar-free | 28 tablet | £25.69 DT price = £1.35
  Montelukast (as Montelukast sodium) 5 mg Singulair Paediatric 5mg chewable tablets sugar-free | 28 tablet | £25.69 DT price = £1.65

Granules

- Montelukast (Non-proprietary)
  Montelukast (as Montelukast sodium) 4 mg Montelukast 4mg granules sachets sugar free sugar free | 28 sachet | £4.16-
  £24.41 DT price = £4.16
- Singulair (Merck Sharp & Dohme Ltd)
  Montelukast (as Montelukast sodium) 4 mg Singulair Paediatric 4mg granules sachets sugar-free | 28 sachet | £25.69 DT price = £4.16

Zafirlukast

Indications and Dose
Prophylaxis of asthma

- BY MOUTH
  - Child 12-17 years: 20 mg twice daily
  - Adult: 20 mg twice daily

Caution
Elderly

Interactions → Appendix 1 (leukotriene receptor antagonists).

Side-effects

Common or very common Gastro-intestinal disturbances • headache • respiratory infections

Uncommon Insomnia • malaise

Rare Angioedema • arthralgia • bleeding disorders • hepatitis • hyperbilirubinaemia • hypersensitivity reactions • myalgia • skin reactions • thrombocytopenia

Very rare Agranulocytosis • Churg-Strauss syndrome

Side-effects, Further Information

Hepatic disorder Patients or their carers should be told how to recognise development of liver disorder and advised to seek medical attention if symptoms or signs such as persistent nausea, vomiting, malaise, or jaundice develop. Churg-Strauss syndrome has occurred very rarely in association with the use of zafirlukast; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

Pregnancy
Manufacturer advises use only if potential benefit outweighs risk. There is limited evidence for the safe use of zafirlukast during pregnancy; however, it can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant.

Breastfeeding
Present in milk—manufacturer advises avoid.

Hepatic Impairment
Manufacturer advises avoid.

Renal Impairment

In adults Manufacturer advises caution in moderate to severe impairment.

In children Manufacturer advises caution.

Patient and Carer Advice
Medicines for Children leaflet: Zafirlukast for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/zafirlukast-for-asthma-prevention

Medicinal Forms
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 23

- Accolate (AstraZeneca UK Ltd)
  Zafirlukast 20 mg Accolate 20mg tablets | 56 tablet | £17.75 DT price = £17.75

Cromoglicate and related therapy

Overview
The mode of action of sodium cromoglicate p. 253 and nedocromil sodium p. 253 is not completely understood. They may be of value in asthma with an allergic basis, but, in practice, it is difficult to predict who will benefit; they could probably be given for 4 to 6 weeks to assess response. Dose frequency is adjusted according to response but is usually...
3 to 4 times a day initially; this may subsequently be reduced.

In general, prophylaxis with sodium cromoglicate is less effective than prophylaxis with corticosteroid inhalations. There is evidence of efficacy of nedocromil sodium in children aged 5–12 years. Sodium cromoglicate and nedocromil sodium are of no value in the treatment of acute attacks of asthma.

Sodium cromoglicate can prevent exercise-induced asthma. However, exercise-induced asthma may reflect poor overall control and the patient should be reassessed.

Sodium cromoglicate and nedocromil sodium may also have a role in allergic conjunctivitis; sodium cromoglicate is used also in allergic rhinitis and allergy-related diarrhoea.

### Sodium cromoglicate

(Sodium cromoglycate)

#### INDICATIONS AND DOSE

**Prophylaxis of asthma**

- **By inhalation of aerosol**
  - Child 5–17 years: Initially 4 mg 4 times a day, when control achieved may be possible to reduce to twice daily
  - Adult: Initially 4 mg 4 times a day, when control achieved may be possible to reduce to twice daily

**Dose equivalence and conversion**

- 1 puff = 2 puffs = 4 mg.

#### UNLICENSED USE

Not licensed for use in children under 6 years.

#### SIDE-EFFECTS

- **Common or Very Common** Abdominal pain, dyspepsia, nausea, pharyngitis, vomiting
- **Rare** Taste disturbances
- **Frequency not known** Bronchospasm, cough, headache, paradoxical bronchospasm, throat irritation

#### SIDE-EFFECTS, FURTHER INFORMATION

- Paradoxical bronchospasm: If paradoxical bronchospasm occurs, a short-acting beta₂ agonist such as salbutamol or terbutaline should be used to control symptoms; treatment with nedocromil should be discontinued.

#### PREGNANCY

Inhaled drugs can be taken as normal during pregnancy.

#### BREAST FEEDING

Inhaled drugs can be taken as normal during breast-feeding.

#### TREATMENT CESSATION

Withdrawal should be done gradually over a period of one week—symptoms of asthma may recur.

#### PREScribing and Dispensing Information

Flavours of inhalers may include mint.

#### PATIENT AND CARER ADVICE

Regular use is necessary. Patient counselling is advised for Nedocromil aerosol for inhalation (administration).

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **Tilade** (Sanofi)

  **Nedocromil sodium 2 mg per 1 dose** Tilade 2mg/dose inhaler CFC free | 112 dose (SANFI) £39.94

#### CAUTIONS

- When used by inhalation: Discontinue if eosinophilic pneumonia occurs

#### SIDE-EFFECTS

- When used by inhalation: Bronchospasm, cough, eosinophilic pneumonia, headache, paradoxical bronchospasm, rhinitis, throat irritation
- With oral use: Joint pain, occasional nausea, rashes

#### SIDE-EFFECTS, FURTHER INFORMATION

- When used by inhalation: If paradoxical bronchospasm occurs, a short-acting beta₂ agonist such as salbutamol or terbutaline should be used to control symptoms; treatment with sodium cromoglicate should be discontinued.

#### PREGNANCY

Not known to be harmful. Inhaled drugs can be taken as normal during pregnancy.

#### BREAST FEEDING

Unlikely to be present in milk. Inhaled drugs can be taken as normal during breast-feeding.

#### TREATMENT CESSATION

- When used by inhalation: Withdrawal of sodium cromoglicate should be done gradually over a period of one week—symptoms of asthma may recur.

#### DIRECTIONS FOR ADMINISTRATION

- With oral use: Capsules may be swallowed whole or the contents dissolved in hot water and diluted with cold water before taking.

#### PATIENT AND CARER ADVICE

- With oral use: Patient counselling is advised for sodium cromoglicate capsules (administration).
- When used by inhalation: Patient counselling is advised for sodium cromoglicate pressurised inhalation (administration).
PHOSPHODIESTERASE TYPE-4 INHIBITORS

Roflumilast

**DRUG ACTION** Roflumilast is a phosphodiesterase type-4 inhibitor with anti-inflammatory properties.

**INDICATIONS AND DOSE**
Adjunct to bronchodilators for the maintenance treatment of patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations

- **BY MOUTH**
  - Adult: 500 micrograms once daily

**CONTRA-INDICATIONS** Cancer (except basal cell carcinoma)
- Concomitant treatment with immunosuppressives drugs (except short-term systemic corticosteroids)
- History of depression associated with suicidal ideation or behaviour
- Moderate to severe cardiac failure
- Severe acute infectious disease
- Severe immunological disease

**CAUTIONS**
- History of psychiatric illness (discontinue if new or worsening psychiatric symptoms occur)
- Caution with concomitant use of drugs likely to cause psychiatric events (discontinue if new or worsening psychiatric symptoms occur).

**SIDE-EFFECTS**
- Common or very common: Abdominal pain, decreased appetite, diarrhoea, headache, insomnia, nausea, weight loss
- Uncommon: Anxiety, back pain, dizziness, dyspepsia, gastritis, gastro-oesophageal reflux, malaise, muscle spasm, myalgia, palpitation, rash, tremor, vertigo, vomiting
- Rare: Constipation, depression, gynaecomastia, haematochezia, nervousness, raised creatine kinase, respiratory tract infections, suicidal behaviour, suicidal ideation, taste disturbances, urticaria
- CONCEPTION AND CONTRACEPTION: Women of child-bearing age should use effective contraception.
- PREGNANCY: Manufacturer advises avoid—toxicity in animal studies.
- BREAST FEEDING: Manufacturer advises avoid—present in milk in animal studies.
- HEPATIC IMPAIRMENT: Caution in mild impairment. Avoid in moderate to severe impairment.
- MONITORING REQUIREMENTS: Monitor body-weight.
- PATIENT AND CARER ADVICE: Patients should be given a patient card before starting treatment and advised to record body-weight at regular intervals.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Roflumilast for the management of severe chronic obstructive pulmonary disease (January 2012) NICE TA244
  Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe chronic obstructive pulmonary disease associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. Patients receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
  www.nice.org.uk/TA244

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- **Tablet**
  - Daxas (Takeda UK Ltd)
    - Roflumilast 500 microgram tablet Daxas 500microgram tablets 30 tablet £37.71 DT price = £37.71

**SYMPATHOMIMETICS**

Ephedrine hydrochloride

**INDICATIONS AND DOSE**
Reversal of hypotension from spinal or epidural anaesthesia
- **BY SLOW INTRAVENTOUS INJECTION**
  - Adult: 3–6 mg every 3–4 minutes (max. per dose 9 mg), adjusted according to response, injection solution to contain ephedrine hydrochloride 3 mg/ml; maximum 30 mg per course

Reversible airways obstruction
- **BY MOUTH**
  - Adult: 15–60 mg 3 times a day

**Neuropathic oedema**
- **BY MOUTH**
  - Adult: 30–60 mg 3 times a day

**UNLICENSED USE**
Not licensed for neuropathic oedema.

**CAUTIONS**
- **GENERAL CAUTIONS**
  - Diabetes mellitus, elderly, hypertension, hyperthyroidism, ischaemic heart disease, prostatic hypertrophy (risk of acute urinary retention)
  - SPECIFIC CAUTIONS
    - With intravenous use Susceptibility to angle-closure glaucoma

**INTERACTIONS**
- Appendix 1 (sympathomimetics).

**SIDE-EFFECTS**
- Common or very common
- With intravenous use Anginal pain, anorexia, changes in blood-glucose concentration, confusion, difficulty in micturition, dizziness, dysphonia, flushing, headache, hypersalivation, nau- seea, psychoses, sweating, urinary retention, vasoconstriction with hypertension, vasodilation with hypotension, vomiting
- With intravenous use or oral use Anxiety, arrhythmias, insomnia, restlessness, tachycardia, tremor
- Very rare
- With intravenous use Angle-closure glaucoma
- Frequency not known Increased lacrimation (can have adverse effects on contact lens wear)
- With intravenous use Bradycardia
- With oral use Cold extremities, dry mouth

**PREGNANCY**
- With oral use Manufacturer advises avoid.
- With intravenous use Increased fetal heart rate reported with parenteral ephedrine.
Aminophylline

**INDICATIONS AND DOSE**

**Severe acute asthma in patients not previously treated with theophylline**

- **BY SLOW INTRAVENOUS INJECTION**
  - Child: 5 mg/kg (max. per dose 500 mg), to be followed by intravenous infusion
  - Adult: 250–500 mg (max. per dose 5 mg/kg), to be followed by intravenous infusion

**Severe acute asthma**

- **BY INTRAVENOUS INJECTION**
  - Child 1 month–11 years: 1 mg/kg/hour, adjusted according to plasma-theophylline concentration
  - Child 12–17 years: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
  - Adult: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
  - Elderly: 300 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

**Severe acute exacerbation of chronic obstructive pulmonary disease in patients not previously treated with theophylline**

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 250–500 mg (max. per dose 5 mg/kg), to be followed by intravenous infusion

**Severe acute exacerbation of chronic obstructive pulmonary disease**

- **BY INTRAVENOUS INJECTION**
  - Adult: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
  - Elderly: 300 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

**Chronic asthma**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child (body-weight 40 kg and above): Initially 225 mg twice daily for 1 week, then increased if necessary to 450 mg twice daily, adjusted according to plasma-theophylline concentration

**Reversible airway obstruction**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 350 mg twice daily for 1 week, then increased if necessary to 700 mg twice daily, increase dose according to plasma-theophylline concentration

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose adjustment may be necessary if smoking started or stopped during treatment.

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal weight for height.

**PHARMACOKINETICS**

Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine confers greater solubility in water.

Theophylline is metabolised in the liver. The plasma-theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the half-life of aminophylline are important because the toxic dose is close to the therapeutic dose.

**UNLICENSED USE**

Aminophylline injection not licensed for use in children under 6 months.

**CAUTIONS**

Arrhythmias following rapid intravenous injection, cardiac arrhythmias or other cardiac disease, elderly (increased plasma-theophylline concentration) (in adults)· epilepsy· fever· hypertension· hyperthyroidism· peptic ulcer· risk of hypokalaemia

**INTERACTIONS**

- Appendix 1 (aminophylline).

**SIDE-EFFECTS, FURTHER INFORMATION**

Hypokalaemia Potentially serious hypokalaemia may result from beta2 agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

**Overdose**

Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

For specific details on the management of poisoning, see *Theophylline*, under Emergency treatment of poisoning p. 1209.

**ALLERGY AND CROSS-SENSITIVITY**

Allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis.
Respiratory system

PRESCRIBING AND DISPENSING INFORMATION

With intramuscular use

With intravenous use in adults

With oral use

If aminophylline is given intravenously, a blood sample should be taken 4–6 hours after starting treatment.

With intravenous use Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines).

DIRECTIONS FOR ADMINISTRATION

With intravenous use For intravenous injection, give very slowly over at least 20 minutes (with close monitoring).

With intravenous use in children For intravenous infusion, dilute to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%.

With intravenous use in adults For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride 0.9%.

With intramuscular use Aminophylline is too irritant for intramuscular use.

PRESCRIBING AND DISPENSING INFORMATION

Patients taking oral theophylline or aminophylline should not normally receive a loading dose of intravenous aminophylline.

Consider intravenous aminophylline for treatment of severe and life-threatening acute asthma only after consultation with senior medical staff.

Modified release The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral aminophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

PHYLLOCONTIN CONTINUS® FORTE Phyllocontin Continus® Forte tablets are for smokers and other patients where theophylline half-life is shorter.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

- Aminophylline (Non-proprietary)
- Aminophylline hydrate 225 mg Aminophylline hydrate 225mg modified-release tablets | 56 tablet (£) £2.40 DT price = £2.40
- Phyllocontin Continus (Napp Pharmaceuticals Ltd)
- Aminophylline hydrate 225 mg Phyllocontin Continus 225mg tablets | 56 tablet (£) £4.22 DT price = £4.22
- Aminophylline hydrate 350 mg Phyllocontin Forte Continus 350mg tablets | 56 tablet (£) £4.22 DT price = £4.22

Solution for injection

- Aminophylline (Non-proprietary)
- Aminophylline 25 mg per 1 ml Aminophylline 250mg/10ml solution for injection ampoules | 10 ampoule (PFS) £6.50 DT price = £6.50

Theophylline

INDICATIONS AND DOSE

NUELIN SA® 175MG TABLETS

Reversible airways obstruction | Severe acute asthma | Chronic asthma

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 175–350 mg every 12 hours

Chronic asthma

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 250–500 mg every 12 hours

NUELIN SA® 250 TABLETS

Reversible airways obstruction | Severe acute asthma | Chronic asthma

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 250–500 mg every 12 hours

SLO-PHYLLIN®

Chronic asthma

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Child 2–5 years: 60–120 mg every 12 hours
  - Child 6–11 years: 125–250 mg every 12 hours
  - Child 12–17 years: 250–500 mg every 12 hours

UNIPHYLLIN CONTINUS®

Chronic asthma

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Child 2–11 years: 9 mg/kg every 12 hours (max. per dose 200 mg), dose may be increased in some children with chronic asthma; increased to 10–16 mg/kg every 12 hours (max. per dose 400 mg), may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose
  - Child 12–17 years: 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

Airways disease, obstructive
symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

**Reversible airways obstruction | Severe acute asthma | Chronic asthma**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose adjustment may be necessary if smoking started or stopped during treatment.

**PHARMACOKINETICS**

Theophylline is metabolised in the liver. The plasma-theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the half-life of theophylline are important because the toxic dose is close to the therapeutic dose.

- **UNLICENSED USE**  
  *Slo-Phyllin®* capsules not licensed for use in children under 2 years.

- **CAUTIONS**
  - Cardiac arrhythmias or other cardiac disease—elderly (increased plasma-theophylline concentration).
  - epilepsy—leven, hypertension—hyperthyroidism—peptic ulcer—risk of hypokalaemia

- **INTERACTIONS**
  - Appendix 1 (theophylline).

- **SIDE-EFFECTS**
  - CNS stimulation—convulsions—diarrhoea—gastric irritation—headache—insomnia—nausea—palpitation—tachycardia—vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Hypokalaemia—Potentially serious hypokalaemia may result from beta, agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

**Overdose**

Theophylline in overdose can cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

For details on the management of poisoning, see Theophylline, under Emergency treatment of poisoning p. 1209.

- **PREGNANCY**
  - Neonatal irritability and apnoea have been reported. Theophylline can be taken as normal during pregnancy as it is particularly important that asthma should be well controlled during pregnancy.

- **BREAST FEEDING**
  - Present in milk—irritability in infant reported; modified-release preparations preferable. Theophylline can be taken as normal during breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Reduce dose.

- **MONITORING REQUIREMENTS**
  - In most individuals, a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

- **Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines).**

- **DIRECTIONS FOR ADMINISTRATION**
  - **SLO-PHYLLIN®**
    - In adults—Swallow whole with fluid or swallow enclosed granules with soft food (e.g. yoghurt).
    - In children—Contents of the capsule (enteric-coated granules) may be sprinkled on to a spoonful of soft food (e.g. yoghurt) and swallowed without chewing.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral theophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

- **PATIENT AND CARER ADVICE**
  - **SLO-PHYLLIN®** Patient or carer should be given advice on how to administer theophylline modified release capsules.

**NEBULISER SOLUTIONS**

**HYPERTONIC SODIUM CHLORIDE SOLUTIONS**

- **INDICATIONS AND DOSE**

  **MUCOCLEAR® 3%**

  Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis) | Mild to moderate acute viral bronchiolitis in infants

  - **BY INHALATION OF NEBULISED SOLUTION**
    - Adult: 4 mL 2–4 times a day, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment with hypertonic sodium chloride to reduce the risk of these adverse effects
Peak flow meters

**LOW RANGE PEAK FLOW METERS**

**MEDI® LOW RANGE**


*MEDI peak flow meter low range* (Medicareplus International Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50

**MINI-WRIGHT® LOW RANGE**


*Mini-Wright peak flow meter low range* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.14

**POCKETPEAK® LOW RANGE**


*nSpire Pocket Peak flow meter low range* (nSpire Health Ltd) | 1 device • NHS indicative price = £6.53 • Drug Tariff (Part IXa) price = £6.50

**STANDARD RANGE PEAK FLOW METERS**

**AIRZONE®**


*AirZone peak flow meter standard range* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £4.69 • Drug Tariff (Part IXa) price = £4.50

**MEDI® STANDARD RANGE**


*MEDI peak flow meter standard range* (Medicareplus International Ltd) | 1 device • NHS indicative price = £4.50 • Drug Tariff (Part IXa) price = £4.50

**MICROPEAK®**


*MicroPeak peak flow meter standard range* (Micro Medical Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £4.50

**MINI-WRIGHT® STANDARD RANGE**


*Mini-Wright peak flow meter standard range* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.08 • Drug Tariff (Part IXa) price = £4.50

**PIKO-1®**


*nSpire Piko-1 peak flow meter standard range* (nSpire Health Ltd) | 1 device • NHS indicative price = £9.50 • Drug Tariff (Part IXa) price = £4.50

**PINNACLE®**


*Fyne Dynamics Pinnacle peak flow meter standard range* (Fyne Dynamics Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £4.50

**POCKETPEAK® STANDARD RANGE**


*nSpire Pocket Peak flow meter standard range* (nSpire Health Ltd) | 1 device • NHS indicative price = £6.53 • Drug Tariff (Part IXa) price = £4.50

**VITALOGRAPH®**


*Vitalograph peak flow meter standard range* (Vitalograph Ltd) | 1 device • NHS indicative price = £4.83 • Drug Tariff (Part IXa) price = £4.50

**Spacers**

**SPACERS**

**A2A SPACER®**

For use with all pressurised (aerosol) inhalers.

*A2A Spacer* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £4.15 • Drug Tariff (Part IXa) price = £4.15

*A2A Spacer with medium mask* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £6.68 • Drug Tariff (Part IXa) price = £4.15

*A2A Spacer with small mask* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £6.68 • Drug Tariff (Part IXa) price = £4.15

**ABLE SPACER®**

Small-volume device. For use with all pressurised (aerosol) inhalers.

* Able Spacer* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £4.39 • Drug Tariff (Part IXa) price = £4.39

*Able Spacer with medium mask* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.16 • Drug Tariff (Part IXa) price = £7.16

*Able Spacer with small mask* (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.16 • Drug Tariff (Part IXa) price = £7.16

**AEROCHAMBER PLUS®**

Medium-volume device. For use with all pressurised (aerosol) inhalers.

*AeroChamber Plus* (GlascoSmithKline UK Ltd) | 1 device • NHS indicative price = £4.86 • Drug Tariff (Part IXa) price = £4.86

*AeroChamber Plus with adult mask* (GlascoSmithKline UK Ltd) | 1 device • NHS indicative price = £8.11 • Drug Tariff (Part IXa) price = £8.11

*AeroChamber Plus with child mask* (GlascoSmithKline UK Ltd) | 1 device • NHS indicative price = £8.11 • Drug Tariff (Part IXa) price = £8.11

*AeroChamber Plus with infant mask* (GlascoSmithKline UK Ltd) | 1 device • NHS indicative price = £8.11 • Drug Tariff (Part IXa) price = £8.11

**BABYHALER®**

For paediatric use with *Flisolide®*, and *Ventolin®* inhalers.
Adverse effects of antihistamines are rare, with some patients experiencing sedation, dry mouth, dizziness, and impaired psychomotor function. In allergic rhinitis patients, antihistamines do not appear to impair performance to a greater extent than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

Allergic conditions


Anti-histamines are a key component of the management of allergic conditions, including allergic rhinitis, hay fever, and allergic asthma. They are typically used as first-line therapy for these conditions, and are often combined with other treatments such as nasal corticosteroids and leukotriene antagonists. Antihistamines are effective in reducing symptoms such as sneezing, rhinorrhea, and itching, and can also help to reduce sneezing and nasal congestion associated with seasonal and perennial allergies.

Anti-histamines are available in a variety of formulations, including tablets, capsules, syrup, and nasal sprays. The choice of formulation will depend on the patient's preference and the severity of their symptoms. Anti-histamines are generally well tolerated, but may cause side effects such as drowsiness, dry mouth, and sedation.

In addition to anti-histamines, other treatments for allergic conditions may include topical or systemic corticosteroids, leukotriene antagonists, and monoclonal antibodies. These treatments work by reducing the immune system's response to allergens, and can be used in combination with anti-histamines to achieve the best possible control of symptoms.

Although anti-histamines are effective in managing allergic conditions, they may not be suitable for all patients. Some patients may experience side effects such as drowsiness or sedation, and in some cases, these effects may be sufficiently severe to warrant the use of alternative treatments. In addition, anti-histamines may not be as effective in managing certain types of allergies, such as those caused by insect bites or stings.

Despite these limitations, anti-histamines remain a valuable tool in the management of allergic conditions, and should be considered as part of a comprehensive treatment plan. Regular review and adjustment of treatment may be necessary to ensure the best possible outcome for each patient.
experienced in the treatment of severe persistent asthma. Omalizumab is also indicated as add-on therapy for the treatment of chronic spontaneous urticaria in patients who have had an inadequate response to H<sub>1</sub> antihistamine treatment.

**Allergic emergencies**

**Anaphylaxis**

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by the rapid onset of respiratory and/or circulatory problems and is usually associated with skin and mucosal changes; prompt treatment is required. Patients with pre-existing asthma, especially poorly controlled asthma, are at particular risk of life-threatening reactions. Insect stings are a recognised risk (in particular wasp and bee stings). Latex and certain foods, including eggs, fish, cow’s milk protein, peanuts, sesame, shellfish, soy, and tree nuts may also precipitate anaphylaxis. Medicinal products particularly associated with anaphylaxis include blood products, vaccines, hyposensitising (allergen) preparations, antibacterials, aspirin and other NSAIDs, and neuromuscular blocking drugs. In the case of drugs, anaphylaxis is more likely after parenteral administration; resuscitation facilities must always be available for injections associated with special risk. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens.

**Treatment of anaphylaxis**

Adrenaline/epinephrine provides physiological reversal of the immediate symptoms associated with hypersensitivity reactions such as anaphylaxis and angioedema.

First-line treatment includes:

- securing the airway, restoration of blood pressure (laying the patient flat and raising the legs, or in the recovery position if unconscious or nauseous and at risk of vomiting);
- administering adrenaline/epinephrine (by intramuscular injection in a dose of 0.5 mg/mL adrenaline (1 mg/mL may be appropriate for immediate self-administration); the dose should be repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. Patients receiving beta-blockers require special consideration;
- administering high-flow oxygen and intravenous fluids is also of primary importance;
- administering an antihistamine, such as chlorphenamine maleate, by slow intravenous injection or intramuscular injection is a useful adjunctive treatment, given after adrenaline.
- Administering an intravenous corticosteroid such as hydrocortisone p. 620 (preferably as sodium succinate) is of secondary value in the initial management of anaphylaxis because the onset of action is delayed for several hours, but should be given to prevent further deterioration in severely affected patients.

Continuing respiratory deterioration requires further treatment with bronchodilators including inhaled or intravenous salbutamol p. 239, inhaled ipratropium bromide p. 234, intravenous aminophylline p. 255, or intravenous magnesium sulfate p. 924 [unlicensed indication] (as for acute severe asthma); in addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary.

When a patient is so ill that there is doubt about the adequacy of the circulation, the initial injection of adrenaline/epinephrine may need to be given as a dilute solution by the intravenous route.

Cardiopulmonary arrest may follow an anaphylactic reaction; resuscitation should be started immediately.

On discharge, patients should be considered for further treatment with an oral antihistamine and an oral corticosteroid for up to 3 days to reduce the risk of further reaction. Patients should be instructed to return to hospital if symptoms recur and to contact their general practitioner for follow-up.

Patients who are suspected of having had an anaphylactic reaction should be referred to a specialist for specific allergy diagnosis. Avoidance of the allergen is the principal treatment; if appropriate, an adrenaline/epinephrine auto-injector should be given for self-administration or a replacement supplied.

**Intramuscular adrenaline (epinephrine)**

The intramuscular route is the first choice route for the administration of adrenaline/epinephrine in the management of anaphylaxis. Adrenaline/epinephrine is best given as an intramuscular injection into the anterolateral aspect of the middle third of the thigh; it has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site.

Patients with severe allergy should be instructed in the self-administration of adrenaline/epinephrine p. 211 by intramuscular injection.

Prompt injection of adrenaline/epinephrine is of paramount importance. The adrenaline/epinephrine doses recommended for the emergency treatment of anaphylaxis by appropriately trained healthcare professionals are based on the revised recommendations of the Working Group of the Resuscitation Council (UK).

### Dose of intramuscular injection of adrenaline (epinephrine) for the emergency treatment of anaphylaxis by healthcare professionals

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Volume of adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–5 years</td>
<td>150 micrograms</td>
<td>0.15 mL 1 in 1000 (1 mg/mL) adrenaline&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Child 6–11 years</td>
<td>300 micrograms</td>
<td>0.3 mL 1 in 1000 (1 mg/mL) adrenaline</td>
</tr>
<tr>
<td>Child 12–17 years</td>
<td>500 micrograms</td>
<td>0.5 mL 1 in 1000 (1 mg/mL) adrenaline&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adult</td>
<td>500 micrograms</td>
<td>0.5 mL 1 in 1000 (1 mg/mL) adrenaline</td>
</tr>
</tbody>
</table>

These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse and respiratory function.

1. Use suitable syringe for measuring small volume
2. 300 micrograms (0.3 mL) if child is small or prepubertal

**Intravenous adrenaline (epinephrine)**

Intravenous adrenaline/epinephrine should be given only by those experienced in its use, in a setting where patients can be carefully monitored.

When the patient is severely ill and there is real doubt about the adequacy of the circulation and absorption after intramuscular injection, adrenaline/epinephrine can be given by slow intravenous injection repeated according to response; if multiple doses are required, adrenaline/epinephrine should be given as a slow intravenous infusion stopping when a response has been obtained.

It is important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

The intravenous route is also used for cardiac resuscitation.
Angioedema
Angioedema is dangerous if laryngeal oedema is present. In this circumstance adrenaline/epinephrine injection and oxygen should be given as described under Anaphylaxis; antihistamines and corticosteroids should also be given. Tracheal intubation may be necessary.

Hereditary angioedema
The treatment of hereditary angioedema should be under specialist supervision. Unlike allergic angioedema, adrenaline/epinephrine, corticosteroids, and antihistamines should not be used for the treatment of acute attacks, including attacks involving laryngeal oedema, as they are ineffective and may delay appropriate treatment—intubation may be necessary. The administration of C1-esterase inhibitor p. 273, an endogenous complement blocker derived from human plasma, (in fresh frozen plasma or in partially purified form) can terminate acute attacks of hereditary angioedema; it can also be used for short-term prophylaxis before dental, medical or surgical procedures. Conestat alfa p. 273 and icatibant p. 273 are licensed for the treatment of acute attacks of hereditary angioedema in adults with C1-esterase inhibitor deficiency.

Tranexamic acid p. 104 and danazol p. 678 [unlicensed indication] are used for short-term and long-term prophylaxis of hereditary angioedema. Short-term prophylaxis with tranexamic acid or danazol is started several days before planned procedures (e.g. dental work) and continued for 2–5 days afterwards. Danazol should be avoided in children because of its androgenic effects.

ANTIHISTAMINES > NON-SEDATING

Acrivastine

● INDICATIONS AND DOSE
Symptomatic relief of allergy such as hayfever, chronic idiopathic urticaria

► BY MOUTH
Child 12-17 years: 8 mg 3 times a day
Adult: 8 mg 3 times a day

● CONTRA-INDICATIONS Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe) — elderly

● CAUTIONS Epilepsy

● INTERACTIONS Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

● SIDE-EFFECTS
• Uncommon Antimuscarinic effects — gastro-intestinal disturbances — headache — psychomotor impairment
• Rare Anaphylaxis — angioedema — angle-closure glaucoma (in adults) — arrhythmias — blood disorders — bronchospasm — confusion — convulsions — depression — dizziness — extrapyramidal effects — hypersensitivity reactions — hypotension — liver dysfunction — palpitation — photosensitivity reactions — rashes — sleep disturbances — tremor
• Frequency not known Blurred vision — drowsiness — dry mouth — urinary retention

SIDE-EFFECTS, FURTHER INFORMATION
Non-sedating antihistamines such as acrivastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

If drowsiness occurs, it may diminish after a few days of treatment.

Children and the elderly are more susceptible to side-effects.

● ALLERGY AND CROSS-SENSITIVITY Contra-indicated if history of hypersensitivity to triprolidine.

● PREGNANCY Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

● BREAST FEEDING Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

● RENAL IMPAIRMENT Avoid in severe impairment.

● PATIENT AND CARER ADVICE
Driving and skilled tasks
► In adults Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. driving); excess alcohol should be avoided.
► In children Although drowsiness is rare, nevertheless children and their carers should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
► Benadryl Allergy Relief (McNeil Products Ltd)
Acrivastine 8 mg
Benzyl alcohol, PEG 400, polysorbate 80. Benadryl Allergy Relief 8mg capsules | 24 capsule £4.95

Bilastine

● INDICATIONS AND DOSE
Symptomatic relief of allergic rhinoconjunctivitis and urticaria

► BY MOUTH
Child 12-17 years: 20 mg once daily
Adult: 20 mg once daily

● CONTRA-INDICATIONS Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

● CAUTIONS Epilepsy

● INTERACTIONS Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

● SIDE-EFFECTS
• Common or very common Headache — malaise
• Uncommon Abdominal pain — anxiety — diarrhoea — dizziness — dysphonia — gastritis — increased appetite — insomnia — oral herpes — prolongation of the QT interval — pyrexia — thirst — tinnitus — vertigo — weight gain

SIDE-EFFECTS, FURTHER INFORMATION
Children and the elderly are more susceptible to side-effects.

Non-sedating antihistamines such as bilastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

● PREGNANCY Avoid—limited information available. Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

● BREAST FEEDING Avoid—no information available. Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

● DIRECTIONS FOR ADMINISTRATION Take tablet 1 hour before or 2 hours after food or fruit juice.

● PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer bilastine tablets.
Driving and skilled tasks
Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

### Cetirizine hydrochloride

#### INDICATIONS AND DOSE

**Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria, atopic dermatitis**

- **BY MOUTH**
  - Child 2–5 years: 2.5 mg twice daily
  - Child 6–11 years: 5 mg twice daily
  - Child 12–17 years: 10 mg once daily
  - Adult: 10 mg once daily

- **UNLICENSED USE** Not licensed for use in children under 2 years.
- **CONTRA-INDICATIONS** Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)
- **CAUTIONS** Epilepsy
- **INTERACTIONS** ▶ Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.
- **SIDE-EFFECTS**
  - **Uncommon** Antimuscarinic effects · blurred vision · dry mouth · gastro-intestinal disturbances · headache · psychomotor impairment · urinary retention
  - **Rare** Anaphylaxis · angioedema · angle-closure glaucoma (in adults) · arrhythmias · blood disorders · bronchospasm · confusion · convulsions · depression · dizziness · extrapyramidal effects · hypersensitivity reactions · hypotension · liver dysfunction · palpitation · photosensitivity reactions · rashes · sleep disturbances · tremor
  - **Frequency not known** Drowsiness

**SIDE-EFFECTS, FURTHER INFORMATION**
Non-sedating antihistamines such as cetirizine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

If drowsiness occurs, it may diminish after a few days of treatment.

Children and the elderly are more susceptible to side-effects.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- **RENAL IMPAIRMENT**
  - **in adults** Use half normal dose if eGFR 30–50 mL/minute/1.73 m². Use half normal dose and reduce dose frequency to alternate days if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².
  - **in children** Use half normal dose if estimated glomerular filtration rate 30–50 mL/minute/1.73 m². Use half normal dose and reduce dose frequency to alternate days if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

#### PATIENT AND CARER ADVICE

**Medicines for Children leaflet:** Cetirizine hydrochloride for hay fever [www.medicinesforchildren.org.uk/cetirizine-hay-fever-0](http://www.medicinesforchildren.org.uk/cetirizine-hay-fever-0)

Driving and skilled tasks
Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulary**

Cetirizine Tablets 10 mg may be prescribed. Cetirizine Oral Solution 5 mg/5 mL may be prescribed.

### Desloratadine

#### INDICATIONS AND DOSE

**Symptomatic relief of allergy such as allergic rhinitis, urticaria, chronic idiopathic urticaria**

- **BY MOUTH**
  - Child 1–5 years: 1.25 mg once daily
  - Child 6–11 years: 2.5 mg once daily
  - Child 12–17 years: 5 mg once daily
  - Adult: 5 mg once daily

**PHARMACOKINETICS**

Desloratadine is a metabolite of loratadine.

- **CAUTIONS** Acute porphyrias p. 930 · epilepsy
- **INTERACTIONS** ▶ Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

#### SIDE-EFFECTS

- **Uncommon** Antimuscarinic effects · blurred vision · dry mouth · gastro-intestinal disturbances · headache · psychomotor impairment · urinary retention
- **Rare** Anaphylaxis · angioedema · angle-closure glaucoma (in adults) · arrhythmias · blood disorders · bronchospasm · confusion · convulsions · depression · dizziness · extrapyramidal effects · hypersensitivity reactions · hypotension · liver dysfunction · myalgia · palpitation · photosensitivity reactions · rashes · sleep disturbances · tremor
  - **Very rare** Hallucinations
  - **Frequency not known** Drowsiness
**Fexofenadine hydrochloride**

**INDICATIONS AND DOSE**

Symptomatic relief of seasonal allergic rhinitis  
- **BY MOUTH**  
  - Child 6–11 years: 30 mg twice daily  
  - Child 12–17 years: 120 mg once daily  
  - Adult: 120 mg once daily

Symptomatic relief of chronic idiopathic urticaria  
- **BY MOUTH**  
  - Child 12–17 years: 180 mg once daily  
  - Adult: 180 mg once daily

**PHARMACOKINETICS**  
Fexofenadine is a metabolite of terfenadine.

**CAUTIONS**  
- Epilepsy

**INTERACTIONS**  
- Appendix 1 (antihistamines).  
  Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

**SIDE-EFFECTS**

- **Common**  
  - Antimuscarinic effects: blurred vision  
  - Dry mouth  
  - Gastro-intestinal disturbances  
  - Headache  
  - Psychomotor impairment  
  - Urinary retention

- **Rare**  
  - Anaphylaxis  
  - Angioedema  
  - Angle-closure glaucoma  
  - Arrhythmias  
  - Blood disorders  
  - Bronchospasm  
  - Confusion  
  - Convulsions  
  - Depression  
  - Dizziness  
  - Extrapyramidal effects  
  - Hypersensitivity reactions  
  - Hypotension  
  - Liver dysfunction  
  - Palpitation  
  - Photosensitivity reactions  
  - Rashes  
  - Sleep disturbances  
  - Tremor

- **Frequency not known**  
  - Drowsiness

**FURTHER INFORMATION**

- There can be variation in the licensing of different medicines containing the same drug.

**MEDICINAL FORMS**

**Tablet**

- **Desloratadine (Non-proprietary)**
  - Desloratadine 5 mg: Desloratadine 5mg tablets | 30 tablet POM £6.77 DT price = £0.96
  - **Neoclarityn** (Merck Sharp & Dohme Ltd)
    - Desloratadine 5 mg: Neoclarityn 5mg tablets | 30 tablet POM £6.77 DT price = £0.96

**Oral solution**

- **EXCIPIENTS:** May contain Propylene glycol, sorbitol

- **Desloratadine (Non-proprietary)**
  - Desloratadine 500 microgram per 1 ml: Desloratadine 2.5mg/5ml oral solution sugar free sugar-free | 100 ml POM £6.43 sugar-free  
    150 ml POM £8.00–10.15 DT price = £10.15
  - **Neoclarityn** (Merck Sharp & Dohme Ltd)
    - Desloratadine 500 microgram per 1 ml: Neoclarityn 2.5mg/5ml oral solution sugar-free | 100 ml POM £6.77 sugar-free  
      150 ml POM £10.15 DT price = £10.15

**Levocetirizine hydrochloride**

**INDICATIONS AND DOSE**

Symptomatic relief of allergy such as hay fever, urticaria  
- **BY MOUTH**  
  - Child 6–17 years: 5 mg once daily  
  - Adult: 5 mg once daily

**PHARMACOKINETICS**  
Levocetirizine is an isomer of cetirizine.

**UNLICENSED USE**  
Tablets not licensed for use in children under 6 years.

**CONTRA-INDICATIONS**  
Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

**CAUTIONS**  
- Epilepsy
Respiratory system

PATIENT AND CARER ADVICE
▶ In children
▶ In adults

INTERACTIONS
▶ Oral solution
▶ Xyzal
Levocetirizine hydrochloride (Non-proprietary)
▶ Tablet
containing the same drug.

• INDICATIONS AND DOSE
Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria
▶ BY MOUTH
▶ Child 2–11 years (body-weight up to 31 kg): 5 mg once daily
▶ Child 2–11 years (body-weight 31 kg and above): 10 mg once daily
▶ Child 12–17 years: 10 mg once daily
▶ Adult: 10 mg once daily

• CAUTIONS
Acute porphyrias p. 930
• INTERACTIONS
▶ Appendix 1 (antihistamines).

• SIDE-EFFECTS
▶ Uncommon
Antimuscarinic effects • blurred vision • dry mouth
• gastro-intestinal disturbances • headache • psychomotor impairment • urinary retention
▶ Rare
Anaphylaxis • angioedema • angle-closure glaucoma
(in adults) • arrhythmias • blood disorders • bronchospasm
• confusion • convulsions • depression • dizziness • extrapyramidal effects • hypersensitivity reactions • hypotension • liver dysfunction • palpitation • photosensitivity reactions • rashes • sleep disturbances • tremor
▶ Very rare
Weight gain
▶ Frequency not known
Drowsiness

SIDE-EFFECTS, FURTHER INFORMATION
Non-sedating antihistamines such as levocetirizine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

If drowsiness occurs, it may diminish after a few days of treatment.

Children and the elderly are more susceptible to side-effects.

PREGNANCY
Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

BREAST FEEDING
Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

RENAL IMPAIRMENT
▶ in adults
5 mg on alternate days if eGFR
30–50 mL/minute/1.73 m². 5 mg every 3 days if eGFR
10–30 mL/minute/1.73 m². Avoid if eGFR less than
10 mL/minute/1.73 m².
▶ in children
Reduce dose frequency to alternate days if estimated glomerular filtration rate
30–50 mL/minute/1.73 m². Reduce dose frequency to every 3 days if estimated glomerular filtration rate
10–30 mL/minute/1.73 m². Avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

PATIENT AND CARER ADVICE
Driving and skilled tasks
Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
▶ Levocetirizine hydrochloride (Non-proprietary)
Levocetirizine dihydrochloride 5 mg Levocetirizine 5mg tablets | 30 tablet | £4.39 DT price = £4.34
▶ Xyzal
(UCB Pharma Ltd)
Levocetirizine dihydrochloride 5 mg Xyzal 5mg tablets | 30 tablet | £4.39 DT price = £4.34

Oral solution
▶ Xyzal
(UCB Pharma Ltd)
Levocetirizine dihydrochloride 500 microgram per 1 mL Xyzal 0.5mg/ml oral solution sugar-free | 200 mL | £6.00 DT price = £6.00

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary
Loratadine 10 mg tablets may be prescribed.
Loratadine syrup 5 mg/5 mL may be prescribed.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
▶ Loratadine (Non-proprietary)
Loratadine 10 mg Loratadine 10mg tablets | 14 tablet | G3L no price available
▶ Claritin (Loratadine)
(Bayer Plc)
Loratadine 10 mg Claritin Allergy 10mg tablets | 60 tablet | £8.85
Oral solution
EXCIPIENTS: May contain Propylene glycol

- Loratadine (Non-proprietary)
  - Loratadine 1 mg per 1 ml: Loratadine 5mg/5ml oral solution | 100 ml P £1.89 DT price + £0.89 | 100 ml POM £2.63 DT price + £1.89
  - Claritin (Loratadine) (Bayer Plc)
  - Loratadine 1 mg per 1 ml: Claritin Allergy 5mg/5ml syrups | 70 ml GSK £2.43

Oral lyophillisate
- Claritin (Loratadine) (Bayer Plc)
  - Loratadine 10 mg (Claritin Rapide Allergy 10mg tablets sugar-free | 10 tablet GSK £3.24

Mizolastine

- **INDICATIONS AND DOSE**
  - Symptomatic relief of allergy such as hay fever, urticaria
  - **BY MOUTH**
    - Child 12-17 years: 10 mg once daily
    - Adult: 10 mg once daily

- **CONTRA-INDICATIONS**
  - Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe).
  - Cardiac disease.
  - Hypokalaemia.
  - Susceptibility to QT-interval prolongation

- **CAUTIONS**
  - Epilepsy

- **INTERACTIONS**
  - Common or very common: Anxiety, asthenia, weight gain
  - Uncommon: Antimuscarinic effects, arthralgia, blurred vision, dry mouth, gastro-intestinal disturbances, headache, myalgia, psychomotor impairment, urinary retention
  - Rare: Anaphylaxis, angioedema, angle-closure glaucoma, arrhythmias, blood disorders, bronchospasm, confusion, convulsions, depression, dizziness, extrapyramidal effects, hypersensitivity reactions, hypotension, liver dysfunction, palpitation, photosensitivity reactions, rashes, sleep disturbances, tremor

- **Frequency not known**
  - Drowsiness

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Non-sedating antihistamines such as mizolastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.
  - If drowsiness occurs, it may diminish after a few days of treatment.
  - Children and the elderly are more susceptible to side-effects.

- **PREGNANCY**
  - Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING**
  - Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in significant impairment.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Although drowsiness is rare, nevertheless patients and their carers should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Modified-release tablet**
  - Claritin (Loratadine) (Bayer Pcl)
  - Loratadine 10 mg: Loratadine 60mg/5ml modified-release tablets | 30 tablet POM £6.92 DT price + £6.92

**ANTIHISTAMINES > SEDATING**

- **Alimemazine tartrate**
  - (Trimeprazine tartrate)

- **INDICATIONS AND DOSE**
  - **Urticaria | Pruritus**
    - **BY MOUTH**
      - Child 2–4 years: 2.5 mg 3–4 times a day
      - Child 5–11 years: 5 mg 3–4 times a day
      - Child 12–17 years: 10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day
      - Adult: 10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day
      - Elderly: 10 mg 1–2 times a day

- **UNLICENSED USE**
  - Not licensed for use in children under 2 years.

- **CONTRA-INDICATIONS**
  - Children under 2 years except on specialist advice (safety of such use has not been established).
  - Epilepsy.
  - Hepatic dysfunction.
  - History of narrow angle glaucoma.
  - Hypothyroidism.
  - Most antihistamines should be avoided in acute porphyrias.
  - P. 930 but alimemazine is thought to be safe.
  - Myasthenia gravis.
  - Parkinson's disease.
  - Phaeochromocytoma.
  - Prostatic hypertrophy (in adults).
  - Renal dysfunction.

- **CAUTIONS**
  - Cardiovascular diseases due to tachycardia-inducing and hypotensive effects of phenothiazines.
  - Elderly: exposure to sunlight should be avoided during treatment with high doses.
  - Pyloroduodenal obstruction.
  - Urinary retention.
  - Volume depleted patients who are more susceptible to orthostatic hypotension.

- **INTERACTIONS**
  - Common or very common: Anxiety, asthenia, weight gain
  - Uncommon: Antimuscarinic effects, arthralgia, blurred vision, dry mouth, gastro-intestinal disturbances, headache, myalgia, psychomotor impairment, urinary retention
  - Rare: Anaphylaxis, angioedema, angle-closure glaucoma, arrhythmias, blood disorders, bronchospasm, confusion, convulsions, depression, dizziness, extrapyramidal effects, hypersensitivity reactions, hypotension, liver dysfunction, palpitation, photosensitivity reactions, rashes, sleep disturbances, tremor

- **SIDE-EFFECTS**
  - Common or very common: Anxiety, asthenia, weight gain
  - Uncommon: Antimuscarinic effects, arthralgia, blurred vision, dry mouth, gastro-intestinal disturbances, headache, myalgia, psychomotor impairment, urinary retention
  - Rare: Anaphylaxis, angioedema, angle-closure glaucoma, arrhythmias, blood disorders, bronchospasm, confusion, convulsions, depression, dizziness, extrapyramidal effects, hypersensitivity reactions, hypotension, liver dysfunction, palpitation, photosensitivity reactions, rashes, sleep disturbances, tremor

- **Frequency not known**
  - Drowsiness

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Non-sedating antihistamines such as mizolastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.
  - If drowsiness occurs, it may diminish after a few days of treatment.
  - Children and the elderly are more susceptible to side-effects.

- **PREGNANCY**
  - Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING**
  - Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in significant impairment.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Although drowsiness is rare, nevertheless patients and their carers should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Patients on high dosage may develop photosensitivity and should avoid exposure to direct sunlight.
  - Children and the elderly are more susceptible to side-effects.

  - Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after
Emergency treatment of anaphylactic reactions

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
  - Child 1-5 months: 250 micrograms/kg (max. per dose 2.5 mg), repeated if necessary; maximum 4 doses per day
  - Child 6 months–5 years: 2.5 mg, repeated if necessary; maximum 4 doses per day
  - Child 6-11 years: 5 mg, repeated if necessary; maximum 4 doses per day
  - Child 12-17 years: 10 mg, repeated if necessary; maximum 4 doses per day
  - Adult: 10 mg, repeated if necessary; maximum 4 doses per day


**IMPORTANT SAFETY INFORMATION**

MHRA/CMH ADVICE (MARCH 2008 AND FEBRUARY 2009) OVERTHE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN

Children under 6 years should not be given over-the-counter cough and cold medicines containing chlorphenamine.

- **CONTRA-INDICATIONS** Many antihistamines should be avoided in acute porphyrias. Chlorphenamine is thought to be safe
- **CAUTIONS** Epilepsy · prostatic hypertrophy (in adults) · pyloroduodenal obstruction · susceptibility to angle-closure glaucoma · urinary retention
- **INTERACTIONS**  → Appendix 1 (antihistamines).
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Common or very common** Blurred vision · dry mouth · gastro-intestinal disturbances · headache · psychomotor impairment · urinary retention
    - **Rare** Anaphylaxis · angioedema · angle-closure glaucoma (in adults) · arrhythmias · bronchospasm · confusion · convulsions · depression · dizziness · extrapyramidal effects · hypersensitivity reactions · hypotension · liver dysfunction · palpitation · photosensitivity reactions · sleep disturbances · tremor
    - **Frequency not known** Antimuscarinic effects · blood disorders · exfoliative dermatitis · rashes · tinnitus

**SPECIFIC SIDE-EFFECTS**

- With intramuscular use or intravenous use CNS stimulation · irritant effects · transient hypotension

**SIDE-EFFECTS, FURTHER INFORMATION**

Children and the elderly are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.
- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- **HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.
**INDICATIONS AND DOSE**

Symptomatic relief of allergy such as hay fever, urticaria

- **Pruritus**
  - **By mouth**
  - Adult: 4 mg 3 times a day, usual dose 4–20 mg daily; maximum 32 mg per day

**CONTRA-INDICATIONS**

Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

**CAUTIONS**

Epilepsy, prostatic hypertrophy, pyloroduodenal obstruction, susceptibility to angle-closure glaucoma, urinary retention

**INTERACTIONS**

Appendix 1 (antihistamines)

**SIDE-EFFECTS**

- Rare Anaphylaxis, angioedema, angle-closure glaucoma, arrhythmias, blood disorders, bronchospasm, confusion, convulsions, depression, dizziness, extrapyramidal effects, hypersensitivity reactions, hypotension, liver dysfunction, palpitation, photosensitivity reactions, rashes, sleep disturbances, tremor

**Frequency not known**

Antimuscarinic effects, blurred vision, drowsiness, dry mouth, gastro-intestinal disturbances, headache, psychomotor impairment, urinary retention

**SIDE-EFFECTS, FURTHER INFORMATION**

Elderly patients are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**BREAST FEEDING**

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**HEPATIC IMPAIRMENT**

Avoid in severe liver disease—increased risk of coma.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.
may occur rarely, especially with high doses or in the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitation, and tremor.

- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.

- **PATIENT AND CARER ADVICE**

  - **Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

- **Tablet**

  - **CAUTIONARY AND ADVISORY LABELS**

    - **Cyproheptadine hydrochloride 4 mg** Periactin 4mg tablets | 30 tablet [P] £5.99 DT price = £5.99

- **Hydroxyzine hydrochloride** 22-Feb-2016

  - **DRUG ACTION** Hydroxyzine is a sedating antihistamine which exerts its actions by antagonising the effects of histamine.

- **INDICATIONS AND DOSE**

  - **Pruritus**

    - **BY MOUTH**

      - Child 6 months–5 years: 5–15 mg daily in divided doses, dose adjusted according to weight; maximum 2 mg/kg per day

      - Child 6–17 years (body-weight up to 40 kg): Initially 15–25 mg daily in divided doses, dose increased as necessary, adjusted according to weight; maximum 2 mg/kg per day

      - Child 6–17 years (body-weight 40 kg and above): Initially 15–25 mg daily in divided doses, increased if necessary to 50–100 mg daily in divided doses, dose adjusted according to weight

      - Adult: Initially 25 mg daily, dose to be taken at night; increased if necessary to 25 mg 3–4 times a day

      - Elderly: Initially 25 mg daily, dose to be taken at night; increased if necessary to 25 mg twice daily

- **UNLICENSED USE** Ucerax® preparations not licensed for use in children under 1 year.

- **IMPORTANT SAFETY INFORMATION**

  - **MHRA/CHM ADVICE: RISK OF QT-INTERVAL PROLONGATION AND TORSADE DE POINTEs (APRIL 2015)** Following concerns of heart rhythm abnormalities, the safety and efficacy of hydroxyzine has been reviewed by the European Medicines Agency. The review concludes that hydroxyzine is associated with a small risk of QT-interval prolongation and torsade de pointes; these events are most likely to occur in patients who have risk factors for QT prolongation, e.g. concomitant use of drugs that prolong the QT-interval, cardiovascular disease, family history of sudden cardiac death, significant electrolyte imbalance (low plasma-potassium or plasma-magnesium concentrations), or significant bradycardia. To minimise the risk of such adverse effects, the following dose restrictions have been made and new cautions and contra-indications added:

    - Hydroxyzine is contra-indicated in patients with prolonged QT-interval or who have risk factors for QT-interval prolongation;

    - Avoid use in the elderly due to increased susceptibility to the side-effects of hydroxyzine;

    - Consider the risks of QT-interval prolongation and torsade de pointes before prescribing to patients taking drugs that lower heart rate or plasma-potassium concentration;

    - In adults, the maximum daily dose is 100 mg;

    - In children with body-weight up to 40 kg, the maximum daily dose is 2 mg/kg;

    - In the elderly, the maximum daily dose is 50 mg (if use of hydroxyzine cannot be avoided);

    - The lowest effective dose for the shortest period of time should be prescribed.

- **CONTRA-INDICATIONS** Acquired or congenital QT interval prolongation - avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe) - predisposition to QT interval prolongation

  - **CONTRA-INDICATIONS, FURTHER INFORMATION**

    - QT interval prolongation Risk factors for QT interval prolongation include significant electrolyte imbalance, bradycardia, cardiovascular disease, and family history of sudden cardiac death.

- **CAUTIONS** Bladder outflow obstruction - breathing problems - cardiovascular disease - children - decreased gastrointestinal motility - dementia - elderly - epilepsy - hypertension - hyperthyroidism - myasthenia gravis - prostatic hypertrophy (in adults) - pyloroduodenal obstruction - stenosing peptic ulcer - susceptibility to angle-closure glaucoma - urinary retention

  - **CAUTIONS, FURTHER INFORMATION** Elderly patients are particularly susceptible to side-effects; manufacturers advise avoid or reduce dose.

  - Children have an increased susceptibility to side-effects, particularly CNS effects.

- **INTERACTIONS** → Appendix 1 (antihistamines).

- **SIDE-EFFECTS**

  - **Common or very common** Dry mouth - fatigue - headache

  - **Uncommon** Constipation - dizziness - insomnia - nausea

  - **Rare** Blood disorders - bronchospasm - liver dysfunction - rashes

  - **Frequency not known** Agitation - alopecia - anorexia - anxiety - blurred vision - coma - confusion - convulsions (with high doses) - depression - diarrhoea - drowsiness - dyskinesia (after stopping use) - extrapyramidal effects - flushing - hallucinations - hypotension - impotence - labrynthitis - menstrual disturbances - myalgia - palpitation - priapism - psychomotor impairment - sleep disturbances - tachycardia - tinnitus - tremor (with high doses) - urinary retention - ventricular arrhythmias - vertigo - vomiting

  - **SIDE-EFFECTS, FURTHER INFORMATION** Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

- **ALLERGY AND CROSS-SENSITIVITY** Manufacturer advises hydroxyzine should be avoided in patients with previous hypersensitivity to cetirizine or other piperazine derivatives, and aminophylline.

- **PREGNANCY** Manufacturers advise avoid — toxicity in animal studies with higher doses. Use in the latter part of the third trimester may cause irritability, paradoxical excitability, and tremor in the neonate.
**INDICATIONS AND DOSE**

**Allergic rhinitis**
- **BY MOUTH**
  - Child 3–17 years: 1 mg twice daily
  - Adult: 1 mg twice daily, increased if necessary to 2 mg twice daily, to be taken with food

**Allergic rhinitis in readily sedated patients**
- **BY MOUTH**
  - Adult: Initially 0.5–1 mg once daily, dose to be taken at night

**CONTRA-INDICATIONS** Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

**CAUTIONS**
- Epilepsy
- Prostatic hypertrophy
- Pyloroduodenal obstruction
- Susceptibility to angle-closure glaucoma

**INTERACTIONS**
- Appendix 1 (antihistamines).

**SIDE-EFFECTS**
- **Common or very common**
  - Excitation (in adults)
  - Irritability
  - Nervousness
- **Uncommon**
  - Cystitis
- **Rare**
  - Weight gain
- **Very rare**
  - Stevens-Johnson syndrome

**Frequency not known**
- Anaphylaxis
- Angioedema
- Angle-closure glaucoma
- Antimuscarinic effects
- Arrhythmias
- Blood disorders
- Blurred vision
- Bronchospasm
- Confusion
- Convulsions
- Depression
- Dizziness
- Dry mouth
- Extrapyramidal effects
- Gastrointestinal disturbances
- Headache
- Hypersensitivity reactions
- Hypotension
- Liver dysfunction
- Palpitation
- Photosensitivity reactions
- Psychomotor impairment
- Rash
- Sleep disturbances
- Tremor
- Urinary retention

**SIDE-EFFECTS, FURTHER INFORMATION**

Elderly are more susceptible to side effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**BREAST FEEDING**

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**HEPATIC IMPAIRMENT**

Avoid in severe liver disease—increased risk of coma.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**

Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atarax</strong> (Alliance Pharmaceuticals Ltd)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine hydrochloride 10 mg Atarax 10mg tablets</td>
<td>84 tablet (P) £1.20 DT price = £1.20</td>
</tr>
<tr>
<td>Hydroxyzine hydrochloride 25 mg Atarax 25mg tablets</td>
<td>28 tablet (P) 0.06 DT price = £0.62</td>
</tr>
</tbody>
</table>

**Ketotifen**

**INDICATIONS AND DOSE**

**Symptomatic relief of allergy such as hay fever and urticaria**

**Insomnia associated with urticaria and pruritus**
- **BY MOUTH**
  - Child 2–4 years: 5 mg twice daily, alternatively 5–15 mg once daily, dose to be taken at night
  - Child 5–9 years: 5–10 mg twice daily, alternatively 10–25 mg once daily, dose to be taken at night
  - Child 10–17 years: 10–20 mg 2–3 times a day, alternatively 25 mg once daily, dose to be taken at night, increased if necessary to 25 mg twice daily
  - Adult: 10–20 mg 2–3 times a day
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 25–50 mg (max. per dose 100 mg)

**Emergency treatment of anaphylactic reactions**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 25–50 mg, to be administered as a solution containing 2.5 mg/mL in water for injections; maximum 100 mg per course

**Sedation (short-term use)**
- **BY MOUTH**
  - Child 2–4 years: 15–20 mg
  - Child 5–9 years: 20–25 mg
  - Child 10–17 years: 25–50 mg
  - Adult: 25–50 mg
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 25–50 mg

**Nausea | Vomiting | Vertigo | Labyrinthine disorders | Motion sickness**
- **BY MOUTH**
  - Child 2–4 years: 5 mg, to be taken at bedtime on night before travel, repeat following morning if necessary
  - Child 5–9 years: 10 mg, to be taken at bedtime on night before travel, repeat following morning if necessary

**Promethazine hydrochloride**

**INDICATIONS AND DOSE**

Symptomatic relief of allergy such as hay fever and urticaria

**Insomnia associated with urticaria and pruritus**
- **BY MOUTH**
  - Child 2–4 years: 5 mg twice daily, alternatively 5–15 mg once daily, dose to be taken at night
  - Child 5–9 years: 5–10 mg twice daily, alternatively 10–25 mg once daily, dose to be taken at night
  - Child 10–17 years: 10–20 mg 2–3 times a day, alternatively 25 mg once daily, dose to be taken at night, increased if necessary to 25 mg twice daily
  - Adult: 10–20 mg 2–3 times a day
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 25–50 mg (max. per dose 100 mg)

**Emergency treatment of anaphylactic reactions**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 25–50 mg, to be administered as a solution containing 2.5 mg/mL in water for injections; maximum 100 mg per course

**Sedation (short-term use)**
- **BY MOUTH**
  - Child 2–4 years: 15–20 mg
  - Child 5–9 years: 20–25 mg
  - Child 10–17 years: 25–50 mg
  - Adult: 25–50 mg
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 25–50 mg

**Nausea | Vomiting | Vertigo | Labyrinthine disorders | Motion sickness**
- **BY MOUTH**
  - Child 2–4 years: 5 mg, to be taken at bedtime on night before travel, repeat following morning if necessary
  - Child 5–9 years: 10 mg, to be taken at bedtime on night before travel, repeat following morning if necessary

continued →
**PATIENT AND CARER ADVICE**

- **Hepatic Impairment**
- **Breast Feeding**

**INTERACTIONS**

- Frequency not known

**CONTRA-INDICATIONS**

- Many antihistamines should be avoided in acute porphyrias p. 930 but promethazine is thought to be safe - should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established.

**CAUTIONS**

- Avoid extravasation with intravenous injection
- Avoid extravasation with intramuscular use
- Epilepsy
- Prostatic hypertrophy (in adults)
- Pyloroduodenal obstruction
- Severe coronary artery disease
- Susceptibility to angle-closure glaucoma
- Urinary retention

**INTERACTIONS**

- Appendix 1 (antihistamines).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Rare
  - Anaphylaxis
  - Angioedema
  - Angle-closure glaucoma
  - Arrhythmias
  - Blood disorders
  - Bronchospasm
  - Confusion
  - Convulsions
  - Depression
  - Dizziness
  - Extrapyramidal effects
  - Hypersensitivity reactions
  - Hypotension
  - Liver dysfunction
  - Palpitation
  - Photosensitivity reactions
  - Rashes
  - Sleep disturbances
  - Tremor

- Frequency not known
  - Antimuscarinic effects
  - Blurred vision
  - Drowsiness
  - Dry mouth
  - Gastro-intestinal disturbances
  - Headache
  - Psychomotor impairment
  - Restlessness
  - Urinary retention

**SPECIFIC SIDE-EFFECTS**

- With intramuscular use
  - Injection pain

**SIDE-EFFECTS, FURTHER INFORMATION**

Children and the elderly are more susceptible to side-effects. Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**Pregnancy**

- Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**Breast Feeding**

- Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**Hepatic Impairment**

- Avoid in severe liver disease — increased risk of coma.

**Renal Impairment**

- Use with caution.

**Patient and Carer Advice**

- **Driving and skilled tasks**
  - Drowsiness may affect the performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

**UNLICENSED USE**

- Not licensed for use for sedation in children under 2 years.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009) OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN**

- Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

**Promethazine Hydrochloride Tablets 10 mg or 25 mg may be prescribed.**

**Promethazine Hydrochloride Oral Solution (elixir) 5 mg/5 mL may be prescribed.**

**LESS SUITABLE FOR PRESCRIBING**

- Promethazine is less suitable for prescribing for sedation.

**EXCEPTIONS TO LEGAL CATEGORY**

- Prescription only medicine restriction does not apply to promethazine hydrochloride injection where administration is for saving life in emergency.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, injection, solution for injection ampoules.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS**
  - **2**
  - Promethazine hydrochloride (non-proprietary)
  - Promethazine hydrochloride 10 mg
    - 56 tablet
    - £3.30 DT price = £2.96
  - Phenergan (Sanofi)
    - Promethazine hydrochloride 10 mg
      - 56 tablet
      - £2.96 DT price = £2.96
    - Promethazine hydrochloride 25 mg
      - 56 tablet
      - £4.65 DT price = £4.65
  - Sominex (Actavis UK Ltd)
    - Promethazine hydrochloride 20 mg
      - 20 tablet
      - £1.89
      - 16 tablet
      - £2.69

**Oral solution**

- **CAUTIONARY AND ADVISORY LABELS**
  - **2**
  - Excipients: May contain Sulfites
  - Electrolytes: May contain Sodium
  - Phenergan (Sanofi)
    - Promethazine hydrochloride 1 mg per 1 ml
      - 100 ml
      - £2.85 DT price = £2.85

**Solution for injection**

- Excipients: May contain Sulfites
  - Phenergan (Sanofi)
    - Promethazine hydrochloride 25 mg per 1 ml
      - 10 ampoule
      - £6.74

**VACCINES > ALLERGEN-TYPE VACCINES**

**Bee venom extract**

- **Indications and Dose**
  - Hypersensitivity to bee venom
    - By Subcutaneous injection
    - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**DESENSITISING VACCINES**

- In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
  - Seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
  - Hypersensitivity to wasp and bee venoms.

- Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

**Contra-Indications**

- Consult product literature

**Caution**

- Consult product literature

**Interactions**

- Appendix 1 (bee venom extracts).

**Side-Effects**

- Consult product literature.
Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

- **PREGNANCY** Avoid.
- **PRESCRIBING AND DISPENSING INFORMATION** Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **BNF 73**
  - **Pharmacists** for bee and wasp venom allergy (February 2012) NICE TA246
  - Pharmacists is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:
    - a severe systemic reaction to bee or wasp venom;
    - a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.
  - Treatment with Pharmalgen® should be initiated and monitored in a specialist centre experienced in venom immunotherapy.
  - www.nice.org.uk/TA246
  - **Pharmacists** There can be variation in the licensing of different medicines containing the same drug.

- **MEDICINAL FORMS**
  - **Powder and solution for injection**
    - Bee venom 120 nanogram Pharmalgen Bee Venom 120 nanogram powder and solvent for solution for injection vials | 1 vial (POM) no price available
    - Bee venom 1.2 microgram Pharmalgen Bee Venom 1.2 microgram powder and solvent for solution for injection vials | 1 vial (POM) no price available
    - Bee venom 12 microgram Pharmalgen Bee Venom 12 microgram powder and solvent for solution for injection vials | 1 vial (POM) no price available
    - Bee venom 120 microgram Pharmalgen Bee Venom maintenance set 120 microgram powder and solvent for solution for injection vials | 1 vial (POM) no price available | 4 vial (POM) £150.00

### Grass pollen extract

- **INDICATIONS AND DOSE**
  - **Treatment of seasonal allergic hay fever due to grass pollen in patients who have failed to respond to anti-allergy drugs**
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: (consult product literature)
  - **Treatment of seasonal allergic hay fever due to grass pollen in patients who have failed to respond to anti-allergy drugs (initiated under specialist supervision)**
    - **BY MOUTH**
    - Adult: 1 tablet daily, treatment to be started at least 4 months before start of pollen season and continue for up to 3 years
Tree pollen extract

- **INDICATIONS AND DOSE**
  Treatment of seasonal allergic hay fever due to tree pollen in patients who have failed to respond to anti-allergy drugs
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

- **CONTRA-INDICATIONS** Consult product literature
- **CAUTIONS** Consult product literature
- **INTERACTIONS** Desensitising vaccines should be avoided in patients taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction), or ACE inhibitors (risk of severe anaphylactoid reactions).
- **SIDE-EFFECTS**
  - Hypersensitivity reactions Consult product literature.

**IMPORTANT SAFETY INFORMATION**

**DESENSITISING VACCINES**
In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- hypersensitivity to wasp and bee venoms. Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.
- **CONTRA-INDICATIONS** Consult product literature
- **CAUTIONS** Consult product literature
- **INTERACTIONS** Appendix 1 (wasp venom extracts). Contra-indicated in patients taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction).
- **SIDE-EFFECTS**, **FURTHER INFORMATION** Consult product literature.
- Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), *even when mild*, the patient should be observed until these have resolved completely.
- **PREGNANCY** Avoid. Application should be avoided in pregnant women—consult product literature.
- **PRESCRIBING AND DISPENSING INFORMATION** Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **Pollinex Trees** (Allergy Therapeutics (UK) Ltd)
  - Pollinex Trees No 3 suspension for injection 1ml vials: 1 vial £50.00
  - Pollinex Trees No 2 suspension for injection 1ml vials: 1 vial £50.00
  - Pollinex Trees No 1 suspension for injection 1ml vials: 1 vial £50.00
  - Pollinex Trees suspension for injection treatment and extension course vials: 4 vial £450.00

Wasp venom extract

- **INDICATIONS AND DOSE**
  Hypersensitivity to wasp venom
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**DESENSITISING VACCINES**
In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- hypersensitivity to wasp and bee venoms. Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.
- **CONTRA-INDICATIONS** Consult product literature
- **CAUTIONS** Consult product literature
- **INTERACTIONS** Appendix 1 (wasp venom extracts). Contra-indicated in patients taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction).
- **SIDE-EFFECTS**
  - Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), *even when mild*, the patient should be observed until these have resolved completely.
- **PREGNANCY** Avoid.
- **PRESCRIBING AND DISPENSING INFORMATION** Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- **Pharmalgen®** for bee and wasp venom allergy (February 2012) NICE TA246
  Pharmalgen® is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:
  - a severe systemic reaction to bee or wasp venom;
  - a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.
  Treatment with Pharmalgen® should be initiated and monitored in a specialist centre experienced in venom immunotherapy.
  www.nice.org.uk/TA246

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- **Wasp Venom** (ALK-Abello Ltd)
  Wasp venom 1.2 microgram Pharmalgen Wasp Venom 1.2microgram powder and solvent for solution for injection vials: 1 vial no price available
2.1 Angioedema

Other drugs used for Angioedema Adrenaline/epinephrine, p. 211

DRUGS USED IN HEREDITARY ANGIOEDEMA ▶ COMPLEMENT REGULATORY PROTEINS

C1-esterase inhibitor

- INDICATIONS AND DOSE
BERINERT®
Acute attacks of hereditary angioedema (under expert supervision)
▶ BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
Adult: 20 units/kg

Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (under expert supervision)
▶ BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
Adult: 1000 units for 1 dose, to be administered less than 6 hours before procedure

CINRYZE®
Acute attacks of hereditary angioedema (under expert supervision)
▶ BY SLOW INTRAVENOUS INJECTION
Adult: 1000 units, repeated if necessary for 1 dose, dose may be repeated if necessary

Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (under expert supervision)
▶ BY SLOW INTRAVENOUS INJECTION
Adult: 1000 units for 1 dose, to be administered up to 24 hours before procedure

Long-term prophylaxis of severe, recurrent attacks of hereditary angioedema where acute treatment is inadequate, or when oral prophylaxis is inadequate or not tolerated (under expert supervision)
▶ BY SLOW INTRAVENOUS INJECTION
Adult: 1000 units every 3–4 days, interval between doses to be adjusted according to response

- CAUTIONS Vaccination against hepatitis A and hepatitis B may be required
- SIDE-EFFECTS Fever · headache · thrombosis (with high doses)
- PREGNANCY Manufacturer advises avoid unless essential.
- PRESCRIBING AND DISPENSING INFORMATION C1-esterase inhibitor is prepared from human plasma.

- MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
ELECTROLYTES: May contain Sodium
▶ Berinert P (CSL Behring UK Ltd)
C1-esterase inhibitor 500 unit Berinert 500 unit powder and solvent for solution for injection vials | 1 vial £467.50
C1-esterase inhibitor 1500 unit Berinert 1500 unit powder and solvent for solution for injection vials | 1 vial £1,402.50
▶ Cinryze (Shire Pharmaceuticals Ltd)
C1-esterase inhibitor 500 unit Cinryze 500 unit powder and solvent for solution for injection vials | 2 vial £1,336.00

Conestat alfa

- INDICATIONS AND DOSE
Acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency
▶ BY SLOW INTRAVENOUS INJECTION
Adult (body-weight up to 84 kg): 50 units/kg for 1 dose, to be administered over 5 minutes, dose may be repeated if necessary; maximum 2 doses per day
Adult (body-weight 84 kg and above): 4200 units for 1 dose, to be administered over 5 minutes, dose may be repeated if necessary; maximum 2 doses per day

- CONTRA-INDICATIONS Rabbit allergy
- SIDE-EFFECTS
▶ Common or very common Headache
▶ Uncommon Abdominal discomfort · diarrhoea · nausea · paraesthesia · throat irritation · urticaria · vertigo
- PREGNANCY Use only if potential benefit outweighs risk— toxicity in animal studies.
- BREAST FEEDING Use only if potential benefit outweighs risk—no information available.
- PRE-TREATMENT SCREENING Test for immunoglobulin E (IgE) antibodies against rabbit allergens before starting treatment.
- MONITORING REQUIREMENTS Repeat immunoglobulin E (IgE) antibody testing annually or after 10 treatments—consult product literature.

- MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
▶ Ruconest (Swedish Orphan Biovitrum Ltd)
Conestat alfa 2100 unit Ruconest 2,100 unit powder for solution for injection vials | 1 vial £750.00

DRUGS USED IN HEREDITARY ANGIOEDEMA ▶ SELECTIVE BRADYKININ B2 ANTAGONISTS

Icatibant

- INDICATIONS AND DOSE
Acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency
▶ BY SUBCUTANEOUS INJECTION
Adult: 30 mg for 1 dose, then 30 mg after 6 hours if required, then 30 mg after 6 hours if required; maximum 3 doses per day

- CAUTIONS Ischaemic heart disease · stroke
- SIDE-EFFECTS Dizziness · erythema · headache · injection-site reactions · nausea · pruritus · pyrexia · rash
- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk— toxicity in animal studies.
- BREAST FEEDING Manufacturer advises avoid for 12 hours after administration.
3 Conditions affecting sputum viscosity

Mucolytics for cystic fibrosis

Overview
Mucolytics are prescribed to facilitate expectoration by reducing sputum viscosity. In some patients with chronic obstructive pulmonary disease and a chronic productive cough, mucolytics can reduce exacerbations; mucolytic therapy should be stopped if there is no benefit after a 4-week trial. Steam inhalation with postural drainage is effective in bronchiectasis and in some cases of chronic bronchitis.

Dornase alfa below is used to reduce sputum viscosity in patients with cystic fibrosis.

Nebulised hypertonic sodium chloride (3–7%) is used to mobilise lower respiratory tract secretions in mucus consolidation (e.g. cystic fibrosis). Nebulised hypertonic sodium chloride solution (3%) is used for mild to moderate acute viral bronchiolitis in infants.

Mannitol 25%, administered by inhalation, improves mucus clearance and is licensed for the treatment of cystic fibrosis as an add-on therapy to standard care.

MUCOLYTICS

Carbocisteine

- **INDICATIONS AND DOSE**
  - **Reduction of sputum viscosity**
    - **BY MOUTH**
    - Adult: Initially 2.25 g daily in divided doses, then reduced to 1.5 g daily in divided doses, as condition improves

- **CONTRA-INDICATIONS**
  - Active peptic ulceration

- **CAUTIONS**
  - History of peptic ulceration (may disrupt the gastric mucosal barrier)

- **SIDE-EFFECTS**
  - Rare Gastro-intestinal bleeding
  - Frequency not known Erythema multiforme - Stevens-Johnson syndrome

- **PREGNANCY**
  - Manufacturer advises avoid in first trimester.

- **BREAST FEEDING**
  - No information available.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Flavours of oral liquid formulations may include cherry, raspberry, cinnamon, or rum.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Capsule**
    - Carbocisteine (Non-proprietary)
      - Carbocisteine 375 mg Carbocisteine 375mg capsules | 120 capsule [POM] £18.98 DT price = £11.21
      - Mucodyne (Sanofi)
        - Carbocisteine 375 mg Mucodyne 375mg capsules | 120 capsule [POM] £18.98 DT price = £11.21

MUCOLYTICS

Dornase alfa

*(Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase))*

- **DRUG ACTION**
  - Dornase alfa is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular deoxyribonucleic acid (DNA).

- **INDICATIONS AND DOSE**
  - **Symptomatic treatment of acute exacerbations of chronic bronchitis**
    - **BY MOUTH**
    - Adult: 300 mg twice daily for up to 10 days

    - **CAUTIONS**
      - History of peptic ulceration (may disrupt the gastric mucosal barrier)

    - **SIDE-EFFECTS**
      - Very rare Abdominal pain - diarrhoea - headache - nausea - rash - taste disturbance - urticaria - vomiting

    - **PREGNANCY**
      - Manufacturer advises avoid—no information available.

    - **BREAST FEEDING**
      - Manufacturer advises avoid—no information available.

    - **HEPATIC IMPAIRMENT**
      - Manufacturer advises max. 300 mg daily in mild to moderate impairment. Avoid in severe impairment.

    - **RENAL IMPAIRMENT**
      - Avoid if eGFR less than 25 mL/minute/1.73 m²—no information available.

    - **NATIONAL FUNDING/ACCESS DECISIONS**

      - **Scottish Medicines Consortium (SMC) Decisions**
        - The Scottish Medicines Consortium (October 2007) has advised that erdosteine (Erdotin®) is not recommended for the symptomatic treatment of acute exacerbations of chronic bronchitis.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Capsule**
    - Erdotin (Galen Ltd)
      - Erdosteine 300 mg Erdotin 300mg capsules | 20 capsule [POM] £4.25 DT price = £4.25

3.1 Cystic fibrosis

MUCOLYTICS

Erdostine

- **INDICATIONS AND DOSE**
  - Symptomatic treatment of acute exacerbations of chronic bronchitis

  - **BY MOUTH**
    - Adult: 300 mg twice daily for up to 10 days

  - **CAUTIONS**
    - History of peptic ulceration (may disrupt the gastric mucosal barrier)

  - **SIDE-EFFECTS**
    - Very rare Abdominal pain - diarrhoea - headache - nausea - rash - taste disturbance - urticaria - vomiting

  - **PREGNANCY**
    - Manufacturer advises avoid—no information available.

  - **BREAST FEEDING**
    - Manufacturer advises avoid—no information available.

  - **HEPATIC IMPAIRMENT**
    - Manufacturer advises max. 300 mg daily in mild to moderate impairment. Avoid in severe impairment.

  - **RENAL IMPAIRMENT**
    - Avoid if eGFR less than 25 mL/minute/1.73 m²—no information available.

  - **NATIONAL FUNDING/ACCESS DECISIONS**

    - **Scottish Medicines Consortium (SMC) Decisions**
      - The Scottish Medicines Consortium (October 2007) has advised that erdosteine (Erdotin®) is not recommended for the symptomatic treatment of acute exacerbations of chronic bronchitis.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Capsule**
    - Erdotin (Galen Ltd)
      - Erdosteine 300 mg Erdotin 300mg capsules | 20 capsule [POM] £4.25 DT price = £4.25
Side-effects

Rare
- Chest pain
- Conjunctivitis
- Dyspepsia
- Dysphonia
- Dyspnœa
- Laryngitis
- Pharyngitis
- Pyrexia
- Rash
- Rhinitis
- Urticaria

Pregnancy
No evidence of teratogenicity; manufacturer advises use only if potential benefit outweighs risk.

Breast feeding
Amount probably too small to be harmful—manufacturer advises caution.

Directions for administration
Dornase alfa is administered by inhalation using a jet nebuliser, usually once daily at least 1 hour before physiotherapy; however, alternate-day therapy may be as effective as daily treatment.

For use undiluted with jet nebulisers only; ultrasonic nebulisers are unsuitable.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Nebuliser liquid
- Pulmozyme (Roche Products Ltd)
  - Dornase alfa 1 mg per 1 ml Pulmozyme 2.5mg nebuliser liquid 2.5ml ampoules | 30 ampoule £496.43 DT price + £496.43

Ivacaftor

Indications and dose
Treatment of cystic fibrosis in patients who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (under expert supervision)

- By mouth
- Adult: 150 mg every 12 hours

Dose adjustments due to interactions
Reduce dose to 150 mg twice a week with concomitant use of itraconazole, ketoconazole, posaconazole, voriconazole, telithromycin, and clarithromycin. Reduce dose to 150 mg once daily with concomitant use of fluconazole and erythromycin.

Contra-indications
Organ transplantation (no information available)

Interactions
Appendix 1 (ivacaftor). Avoid grapefruit and Seville oranges.

Side-effects
Common or very common
- Abdominal pain
- Diarrhoea
- Dizziness
- Ear discomfort
- Headache
- Nasal congestion
- Nasopharyngitis
- Oropharyngeal pain
- Pharyngeal erythema
- Pharyngeal oedema
- Rash
- Rhinitis
- Tinnitus
- Upper respiratory-tract infection

Uncommon
- Gynaecomastia
- Nipple disorders
- Vestibular disorder

Pregnancy
Manufacturer advises use only if potential benefit outweighs risk—no information available.

Breast feeding
Manufacturer advises use only if potential benefit outweighs risk—no information available.

Hepatic impairment
Max. 150 mg once daily in moderate impairment; in severe impairment, manufacturer recommends use only if potential benefit outweighs risk—starting dose 150 mg on alternate days, dosing interval adjusted according to clinical response and tolerability.

Renal impairment
Caution in severe impairment.

Pre-treatment screening
If the patient’s genotype is unknown, a validated genotyping method should be performed to confirm the presence of the G551D mutation in at least one allele of the CFTR gene before starting treatment.

Monitoring requirements
Manufacturer advises monitor liver function before treatment, every 3 months during the first year of treatment, then annually thereafter (more frequent monitoring should be considered in patients with a history of transaminase elevations).

Directions for administration
Tablets should be taken with fat-containing food.

Prescribing and dispensing information
Ivacaftor should be prescribed by a physician experienced in the treatment of cystic fibrosis.

Patient and carer advice
Driving and skilled tasks
Manufacturer advises that patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of dizziness. Patients or carers should be given advice on how to administer ivacaftor tablets.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Tablet
Cautory and advisory labels
- Kalydeco (Vertex Pharmaceuticals (UK) Ltd)
- Ivacaftor 150 mg

Kalydeco 150 mg tablets | 56 tablet £14,000.00

Ivacaftor with lumacaftor

Indications and dose
Treatment of cystic fibrosis in patients who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (under expert supervision)

- By mouth
- Adult: 400/250 mg every 12 hours

Dose adjustments due to interactions
Reduce initial dose to 200/125 mg daily for the first week in those also taking a potent CYP3A4 inhibitor (such as clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole).

Dose equivalence and conversion
Dose expressed as x/y mg of lumacaftor/ivacaftor.

Caution
Forced expiratory volume in 1 second (FEV₁) less than 40% of the predicted normal value—additional monitoring required at initiation of treatment—pulmonary exacerbation—no information available

Interactions
Appendix 1 (ivacaftor, lumacaftor).

Side-effects
Common or very common
- Dyspnœa
- Elevated transaminases (clinically significant)
- Flatulence
- Menstrual disturbances
- Metrorrhagia
- Nausea
- Rhinorrhœa
- Vomiting

Uncommon
- Cholestatic hepatitis
- Hepatic encephalopathy
- Hypertension

Breast feeding
Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment
Manufacturer advises reduce dose to 400/250 mg in the morning and 200/125 mg in the evening (600/375 mg total daily dose) in moderate impairment; reduce dose to 200/125 mg every 12 hours (400/250 mg total daily dose) in severe impairment. Manufacturer uses caution with use in severe impairment.

Pre-treatment screening
If the patient’s genotype is unknown, a validated genotyping method should be performed to confirm the presence of the F508del
uncommon on both alleles of the CFTR gene before starting treatment.

- **MONTORING REQUIREMENTS** Manufacturer advises monitor blood pressure periodically during treatment.
- **DIRECTIONS FOR ADMINISTRATION** Tablets should be taken with fat-containing food.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer tablets.

**Missed doses**
Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Lumacaftor with ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (July 2016) NICE TA398 Lumacaftor with ivacaftor is not recommended, within its marketing authorisation, for treating cystic fibrosis in patients who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Patients whose treatment was started before this guidance was published may continue treatment until they (or their carers) and their clinician consider it appropriate to stop.

www.nice.org.uk/TA398

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (May 2016) that lumacaftor with ivacaftor (Orkambi®) is not recommended within NHS Scotland for the treatment of cystic fibrosis in patients who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 25 EXCIPIENTS: May contain Propylene glycol
    - Orkambi (Vertex Pharmaceuticals (UK) Ltd)
      - Ivacaftor 125 mg, Lumacaftor 200 mg Orkambi 200mg/125mg tablets | 112 tablet [Pack] £8,000.00

**Mannitol**

- **INDICATIONS AND DOSE**
  - Treatment of cystic fibrosis as an add-on therapy to standard care
    - **BY INHALATION OF POWDER**
      - Adult: Maintenance 400 mg twice daily, an initiation dose assessment must be carried out under medical supervision, for details of the initiation dose regimen, consult product literature

- **CONTRA-INDICATIONS** Bronchial hyperresponsiveness to inhaled mannitol - impaired lung function (forced expiratory volume in 1 second < 30% of predicted) - non-CF bronchiectasis

- **CAUTIONS** Asthma - haemoptysis

- **INTERACTIONS** → Appendix 1 (mannitol).

- **SIDE-EFFECTS**
  - Common or very common Cough - haemoptysis - headache - pharyngolaryngeal pain - throat irritation - vomiting - wheezing

- **PREGNANCY** Manufacturer advises avoid.

- **BREAST FEEDING** Manufacturer advises avoid.

- **PRE-TREATMENT SCREENING** Patients must be assessed for bronchial hyperresponsiveness to inhaled mannitol before starting the therapeutic dose regimen; an initiation dose assessment must be carried out under medical supervision—for details of the initiation dose regimen, consult product literature.

- **DIRECTIONS FOR ADMINISTRATION** The dose should be administered 5–15 minutes after a bronchodilator and before physiotherapy; the second daily dose should be taken 2–3 hours before bedtime.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer mannitol inhalation powder.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Mannitol dry powder for inhalation for treating cystic fibrosis (November 2012) NICE TA266 Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:
      - who cannot use dornase alfa (rhDNase) because of ineligibility, intolerance or inadequate response to dornase alfa (rhDNase), and
      - whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually), and
      - for whom other osmotic agents are not considered appropriate.
    - www.nice.org.uk/TA266

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium, has advised (November 2013) that mannitol (Bronchitol®) is accepted for restricted use within NHS Scotland for the treatment of cystic fibrosis in adults aged 18 years and over as an add-on therapy to best standard of care. Mannitol is restricted to patients who are not currently using dornase alfa due to lack of response, intolerance, or ineligibility and have rapidly declining lung function and in whom other osmotic agents are considered unsuitable.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Inhalation powder**
    - Mannitol (Non-proprietary)
      - Mannitol 5 mg Osmohale 5mg inhalation powder capsules | 1 capsule [Pack] no price available
      - Mannitol 10 mg Osmohale 10mg inhalation powder capsules | 1 capsule [Pack] no price available
      - Mannitol 20 mg Osmohale 20mg inhalation powder capsules | 1 capsule [Pack] no price available
      - Mannitol 40 mg Osmohale 40mg inhalation powder capsules | 15 capsule [Pack] no price available
    - Bronchitol (Chiesi Ltd)
      - Mannitol 40 mg Bronchitol 40mg inhalation powder capsules with two devices | 280 capsule [Pack] £231.66
      - Bronchitol 40mg inhalation powder capsules with device | 10 capsule [Pack] no price available
4 Cough and congestion

Aromatic inhalations, cough preparations and systemic nasal decongestants

Aromatic inhalations in adults

Inhalations containing volatile substances such as eucalyptus oil are traditionally used and although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting in bronchitis; boiling water should not be used owing to the risk of scalding. Inhalations are also used for the relief of nasal obstruction in acute rhinitis or sinusitis. Eucalyptus with menthol p. 278 inhalation is used to relieve sinusitis affecting the maxillary antrum.

Cough preparations in adults

Cough suppressants

Cough may be a symptom of an underlying disorder, such as asthma, gastro-oesophageal reflux disease, or rhinitis, which should be addressed before prescribing cough suppressants. Cough may be a side-effect of another drug, such as an ACE inhibitor, or it can be associated with smoking or environmental pollutants. Cough can also have a significant habit component. When there is no identifiable cause, cough suppressants may be useful, for example if sleep is disturbed. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Codeine phosphate p. 421 may be effective but it is constipating and can cause dependence; dextromethorphan and pholcodine below have fewer side-effects.

Sedating antihistamines are used as the cough suppressant component of many compound cough preparations on sale to the public; all tend to cause drowsiness which may reflect their main mode of action.

Palliative care

Diamorphine hydrochloride p. 423 and methadone hydrochloride p. 464 have been used to control distressing cough in terminal lung cancer although morphine p. 429 is now preferred. In other circumstances they are contra-indicated because they induce sputum retention and ventilatory failure as well as causing opioid dependence. Methadone hydrochloride linctus should be avoided because it has a long duration of action and tends to accumulate.

Demulcent and expectorant cough preparations

Demulcent cough preparations contain soothing substances such as syrup or glycerol and some patients believe that such preparations relieve a dry irritating cough. Preparations such as simple linctus have the advantage of being harmless and inexpensive; paediatric simple linctus is particularly useful in children.

Expectorants are claimed to promote expulsion of bronchial secretions, but there is no evidence that any drug can specifically facilitate expectoration.

Compound preparations are on sale to the public for the treatment of cough and colds but should not be used in children under 6 years; the rationale for some is dubious. Care should be taken to give the correct dose and to not use more than one preparation at a time.

Systemic nasal decongestants

Nasal decongestants for administration by mouth may not be as effective as preparations for local application but they do not give rise to rebound nasal congestion on withdrawal. Pseudoephedrine hydrochloride p. 1056 is available over the counter; it has few sympathomimetic effects.

Aromatic inhalations in children

The use of strong aromatic decongestants (applied as rubs or to pillows) is not advised for infants under the age of 3 months. Carers of young infants in whom nasal obstruction with mucus is a problem can readily be taught appropriate techniques of suction aspiration but sodium chloride 0.9% p. 914 given as nasal drops is preferred; administration before feeds may ease feeding difficulties caused by nasal congestion.

Cough preparations in children

The use of over-the-counter cough suppressants containing codeine phosphate should be avoided in children under 12 years and in children of any age known to be CYP2D6 ultra-rapid metabolisers. Cough suppressants containing similar opioid analgesics such as dextromethorphan and pholcodine are not generally recommended in children and should be avoided in children under 6 years.

MHRA/CHM advice (March 2008 and February 2009)

Children under 6 years should not be given over-the-counter cough and cold medicines containing the following ingredients:

- brompheniramine, chlorphenamine maleate p. 266, diphenhydramine, doxylamine, promethazine, or triprolidine (antihistamines);
- dextromethorphan or pholcodine (cough suppressants);
- guaifenesin or ipecacuanha (expectorants);
- phenylephrine hydrochloride p. 179, pseudoephedrine hydrochloride, ephedrine hydrochloride p. 254, oxymetazoline, or xylometazoline hydrochloride p. 1057 (decongestants).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to five days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

COUGH AND COLD PREPARATIONS

Pholcodine

- INDICATIONS AND DOSE
  - Dry cough
    - By mouth using linctus
      - Child 6–11 years: 2–5 mg 3–4 times a day
      - Child 12–17 years: 5–10 mg 3–4 times a day
      - Adult: 5–10 mg 3–4 times a day

  IMPORTANT SAFETY INFORMATION
  MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009) OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN

Children under 6 years should not be given over-the-counter cough and cold medicines containing pholcodine (cough suppressant).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to 5 days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

- CONTRA-INDICATIONS
  - Bronchiectasis • bronchiolitis (in children) • chronic bronchitis • chronic obstructive pulmonary disease (in adults) • patients at risk of respiratory failure
Respiratory system

COUGH AND COLD PREPARATIONS

COUGH AND COLD PREPARATIONS

● **Cough and congestion**

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

- **Pholcodine (Non-proprietary)**
  - Pholcodine 1 mg per 1 ml Pholcodine 5 mg/5 ml linctus 200 ml P £1.29 DT price = £1.29 [G33]
  - Pholcodine 5 mg/5 ml linctus sugar-free 200 ml P £1.31 DT price = £1.31 [G33] sugar-free 2000 ml P £13.10 [G33]
  - Pholcodine 2 mg per 1 ml Pholcodine 10 mg/5 ml linctus strong sugar-free 2000 ml P £11.88 DT price = £11.88 [G33]
  - Pholcodine 10 mg/5 ml linctus strong 200 ml P £1.61 [G33]
- **Galenphol (Thornton & Ross Ltd)**
  - Pholcodine 400 microgram per 1 ml Galenphol paediatric 2 mg/5 ml linctus sugar-free 2000 ml P £4.50 DT price = £4.50 [G33]
  - Pholcodine 1 mg per 1 ml Galenphol 5 mg/5 ml linctus sugar-free 2000 ml P £8.50 [G33]
  - Pholcodine 2 mg per 1 ml Galenphol strong 10 mg/5 ml linctus sugar-free 2000 ml P £9.88 DT price = £9.88 [G33]
  - Galenphol-D (Alliance Pharmaceuticals Ltd)
  - Pholcodine 1 mg per 1 ml Pavacol-D 5 mg/5 ml mixture sugar-free 150 ml P £1.69 [G33] sugar-free 300 ml P £2.55 [G33]

**Pholcodine**

Flavours of oral liquid formulations may include anise.

When prepared extemporaneously, the BP states that Pholcodine Linctus, BP consists of pholcodine 5 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 1% and pholcodine. Pholcodine Linctus, Strong, BP consists of pholcodine 10 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 2%.

**PRESCRIBING AND DISPENSING INFORMATION**

Pholcodine is not generally recommended for children. Flavours of oral liquid formulations may include orange. When prepared extemporaneously, the BP states that Pholcodine Linctus, BP consists of pholcodine 5 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 1% and pholcodine. Pholcodine Linctus, Strong, BP consists of pholcodine 10 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 2%.

**INDICATIONS AND DOSAGE**

Cough

- **BY MOUTH**
  - Adult: 5 mL 3–4 times a day, this dose is for Simple Linctus, BP (2.5%)

**SIDE-EFFECTS**

Allergic contact dermatitis

**PRESCRIBING AND DISPENSING INFORMATION**

Not recommended (applied as a rub or to pillows) for infants under 3 months. When prepared extemporaneously, the BP states that free sugar-free

**Other**

**Pholcodine**

- **BY MOUTH**
  - Adult: 5 mL 3–4 times a day, this dose is for Simple Linctus, BP (2.5%)

**SIDE-EFFECTS**

Allergic contact dermatitis

**PRESCRIBING AND DISPENSING INFORMATION**

Not recommended (applied as a rub or to pillows) for infants under 3 months. When prepared extemporaneously, the BP states that benzoin tincture, Compound, BP consists of balsamic acids approx. 4.5%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

CAUTIONARY AND ADVISORY LABELS 15

- **Benzoin tincture (Non-proprietary)**
  - Balsamic acids 16.5 mg per 1 ml Benzoin tincture 500 ml GSL £9.95 DT price = £9.95

**Eucalyptus with menthol**

**INDICATIONS AND DOSE**

Aromatic inhalation for relief of nasal congestion

- **BY INHALATION**
  - Adult: Add one teaspoonful to a pint of hot, not boiling, water and inhale the vapour

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states that Menthol and Eucalyptus Inhalation, BP 1980 consists of racemohol or levomenthol 2 g, eucalyptus oil 10 mL, light magnesium carbonate 7 g, water to 100 mL.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formula

Menthol and Eucalyptus Inhalation BP, 1980 may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Inhalation vapour**

- **Eucalyptus with menthol (Non-proprietary)**
  - Eucalyptus oil 100 microlitre per 1 ml, Menthol 20 mg per 1 ml, Magnesium carbonate light 70 mg per 1 ml Menthol and Eucalyptus inhalation 100 mL GSL £1.36 DT price = £1.36

**RESINS**

**Benzoin tincture**

(Friars’ Balsam)

**INDICATIONS AND DOSE**

Aromatic inhalation for relief of nasal congestion

- **BY INHALATION**
  - Child: Add 5 mL to a pint of hot, not boiling, water and inhale the vapour; repeat after 4 hours if necessary
  - Adult: Add 5 mL to a pint of hot, not boiling, water and inhale the vapour; repeat after 4 hours if necessary

**SIDE-EFFECTS**

Allergic contact dermatitis

**PRESCRIBING AND DISPENSING INFORMATION**

Not recommended (applied as a rub or to pillows) for infants under 3 months. When prepared extemporaneously, the BP states that benzoin tincture, Compound, BP consists of balsamic acids approx. 4.5%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

CAUTIONARY AND ADVISORY LABELS 15

- **Benzoin tincture (Non-proprietary)**
  - Balsamic acids 16.5 mg per 1 ml Benzoin tincture 500 mL GSL £9.95 DT price = £9.95
5  Idiopathic pulmonary fibrosis

Other drugs used for Idiopathic pulmonary fibrosis
Nintedanib, p. 879

ANTIFIBROTICS

Pirfenidone

- **DRUG ACTION** The exact mechanism of action of pirfenidone is not yet understood, but it is believed to slow down the progression of idiopathic pulmonary fibrosis by exerting both antifibrotic and anti-inflammatory properties.

- **INDICATIONS AND DOSE**
  
  **Treatment of mild to moderate idiopathic pulmonary fibrosis (initiated under specialist supervision)**
  
  - **BY MOUTH**
  - Adult: Initially 267 mg 3 times a day for 7 days, then increased to 534 mg 3 times a day for 7 days, then increased to 801 mg 3 times a day
  
  **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  
  Caution with concomitant use with ciprofloxacin—reduce dose of pirfenidone to 534 mg three times daily with high-dose ciprofloxacin (750 mg twice daily). Caution with concomitant use of drugs known to cause photosensitivity—if photosensitivity reaction or rash occurs, dose adjustment or treatment interruption may be required (consult product literature).

- **CONTRA-INDICATIONS** Cigarette smoking

- **CAUTIONS**

  **CAUTIONS, FURTHER INFORMATION**
  
  - Photosensitivity Avoid exposure to direct sunlight—if photosensitivity reaction or rash occurs, dose adjustment or treatment interruption may be required (consult product literature).
  - Treatment interruption If treatment is interrupted for 14 consecutive days or more, the initial 2 week titration regimen should be repeated; if treatment is interrupted for less than 14 consecutive days, the dose can be resumed at the previous daily dose without titration.

- **INTERACTIONS**

  > Appendix 1 (pirfenidone).

- **SIDE-EFFECTS**

  - **Common or very common** Abdominal discomfort · anorexia · arthralgia · constipation · diarrhea · dizziness · dry skin · dysgeusia · dyspepsia · erythema · flatulence · gastritis · gastro-oesophageal reflux disease · headache · hot flush · insomnia · malaise · myalgia · nausea · non-cardiac chest pain · photosensitivity reaction · pruritus · raised hepatic enzymes · rash · somnolence · upper respiratory tract infection · urinary tract infection · vomiting · weight loss
  - **Rare** Raised bilirubin in combination with raised hepatic transaminases

  **SIDE-EFFECTS, FURTHER INFORMATION**

  Gastrointestinal side-effects may require dose reduction or treatment interruption—consult product literature.

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Use with caution in mild to moderate hepatic impairment, particularly if concomitant use of CYP1A2 inhibitors. Avoid use in severe hepatic impairment.

- **RENAL IMPAIRMENT** Avoid use if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**

  - Monitor for weight loss.
  - Test liver function before treatment, then at monthly intervals for the next 6 months, and then every 3 months thereafter; review if abnormal liver function tests—dose reduction, treatment interruption or discontinuation may be required (consult product literature).

- **PATIENT AND CARER ADVICE**

  Driving and skilled tasks Dizziness or malaise may affect performance of skilled tasks (e.g. driving).

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**

  - **Pirfenidone for treating idiopathic pulmonary fibrosis (April 2013)** NICE TA282

  Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis only if:

  - the patient has a forced vital capacity (FVC) between 50% and 80% predicted, and
  - the manufacturer provides pirfenidone with the discount agreed in the patient access scheme. Treatment should be discontinued if there is evidence of disease progression, defined as a decline in predicted FVC of 10% or more within any 12 month period.

  Patients currently receiving pirfenidone that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.

  [www.nice.org.uk/TA282](http://www.nice.org.uk/TA282)

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium has advised (August 2013) that pirfenidone is accepted for restricted use within NHS Scotland for the treatment of mild to moderate idiopathic pulmonary fibrosis. Pirfenidone is restricted for use in patients with a predicted forced vital capacity less than or equal to 80%, and only whilst pirfenidone is available at the price agreed in the patient access scheme.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**

  **CAUTIONARY AND ADVISORY LABELS** 21, 25

  - **Estbriet** (Roche Products Ltd)

    | **Pirfenidone 267 mg** | **Esbriet 267 mg capsules** | **63 capsule &ndash; £501.92** | **252 capsule &ndash; £2,007.70** | **270 capsule &ndash; £2,151.10** |

6  Respiratory depression, respiratory distress syndrome and apnoea

**Respiratory stimulants**

**Overview**

Respiratory stimulants (anaeptic drugs) have a limited place in the treatment of ventilatory failure in patients with chronic obstructive pulmonary disease. They are effective only when given by intravenous injection or infusion and have a short duration of action. Their use has largely been replaced by ventilatory support including nasal intermittent positive pressure ventilation. However, occasionally when ventilatory support is contra-indicated and in patients with hypercapnic respiratory failure who are becoming drowsy or comatose, respiratory stimulants in the short term may
arouse patients sufficiently to co-operate and clear their secretions.

Respiratory stimulants can also be harmful in respiratory failure since they stimulate non-respiratory as well as respiratory muscles. They should only be given under expert supervision in hospital and must be combined with active physiotherapy. There is at present no oral respiratory stimulant available for long-term use in chronic respiratory failure.

RESPIRATORY STIMULANTS

Doxapram hydrochloride

• INDICATIONS AND DOSE
  • Postoperative respiratory depression
    ▶ Initially by intravenous injection
    ▶ Adult: Initially 1–1.5 mg/kg, to be administered over at least 30 seconds, repeated if necessary after intervals of one hour, alternatively (by intravenous infusion) 2–3 mg/minute, adjusted according to response
  • Acute respiratory failure
    ▶ By intravenous infusion
    ▶ Adult: 1.5–4 mg/minute, adjusted according to response, to be given concurrently with oxygen and whenever possible monitor with frequent measurement of blood gas tensions

• CONTRA-INDICATIONS Cerebral oedema · cerebrovascular accident · coronary artery disease · epilepsy and other convulsive disorders · hyperthyroidism · physical obstruction of respiratory tract · severe hypertension · status asthmaticus

• CAUTIONS Give with beta₂ agonist in bronchoconstriction · give with oxygen in severe irreversible airways obstruction or severely decreased lung compliance (because of increased work load of breathing) · hypertension · impaired cardiac reserve · phaeochromocytoma

• INTERACTIONS → Appendix 1 (doxapram).

• SIDE-EFFECTS Arrhythmias · bradycardia · bronchospasm · chest pain · confusion · convulsions · cough · dizziness · dyspnoea · extrasystoles · flushing · hallucination · headache · hyperactivity · hypertension · incontinence · laryngospasm · muscle spasms · nausea · perineal warmth · pyrexia · tachycardia · urinary retention · vomiting

• PREGNANCY No evidence of harm, but manufacturer advises avoid unless benefit outweighs risk.

• HEPATIC IMPAIRMENT Use with caution.

• MONITORING REQUIREMENTS Frequent arterial blood gas and pH measurements are necessary during treatment to ensure correct dosage.

• MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
  • Doxapram hydrochloride (Non-proprietary)
    Doxapram hydrochloride 20 mg per 1 ml  Doxapram 100mg/5ml solution for injection ampoules | 5 ampoule [POM] £110.00

Infusion
  • Doxapram hydrochloride (Non-proprietary)
    Doxapram hydrochloride 2 mg per 1 ml  Doxapram 1g/500ml infusion bags | 1 bag [POM] no price available
1 Dementia

Dementia

27-Sep-2016

Description of condition

Dementia is a progressive and largely irreversible clinical syndrome that is characterised by a widespread impairment of mental function. There are a number of conditions that cause the symptoms of dementia. Alzheimer’s disease accounts for most cases; other common causes include vascular dementia (due to cerebrovascular disease) and dementia with Lewy bodies. The symptoms of dementia include cognitive dysfunction (such as problems with memory, concentration and problem-solving), non-cognitive symptoms (such as psychiatric and behavioural problems) and difficulties with activities of daily living.

Aims of treatment

The aims of treatment are to promote independence, maintain function and treat symptoms.

Non-drug treatment

Patients with all types of mild-to-moderate dementia presenting with cognitive symptoms should be given the opportunity to participate in a structured group cognitive stimulation programme.

Drug treatment

Management of cognitive symptoms

When pharmacological treatments are used, they should be initiated and supervised by a specialist experienced in the management of dementia. The manufacturers of donepezil hydrochloride p. 282, galantamine p. 283, rivastigmine p. 284 and memantine hydrochloride p. 285 recommend that treatment should be reassessed on a regular basis.

Treatment should be continued only when it is considered to be having a worthwhile effect on symptoms.

Donepezil hydrochloride, galantamine and rivastigmine (acetylcholinesterase inhibitors) are recommended for the treatment of cognitive symptoms of mild-to-moderate dementia due to Alzheimer’s disease. Memantine hydrochloride is a suitable alternative for patients with moderate Alzheimer’s disease when acetylcholinesterase inhibitors are contra-indicated or are not tolerated. Memantine hydrochloride is the drug of choice for patients with severe Alzheimer’s disease.

Pharmacological treatments are not recommended for the treatment of cognitive symptoms in cases of vascular dementia.

Management of non-cognitive symptoms

Patients with dementia who develop non-cognitive symptoms (such as delusions or anxiety) or ‘behaviour that challenges’ (such as aggression or agitation) should only be offered a pharmacological intervention if they are severely distressed or if there is an immediate risk of harm to the patient or others. Less severe non-cognitive symptoms are treated with non-pharmacological interventions, such as multisensory stimulation or aromatherapy.

Antipsychotic drugs

Patients with mild-to-moderate non-cognitive symptoms due to Alzheimer’s disease, vascular dementia, mixed dementias or dementia with Lewy bodies should not be prescribed antipsychotic drugs.

Patients with severe non-cognitive symptoms due to Alzheimer’s disease, vascular dementia, mixed dementias or dementia with Lewy bodies which are causing significant distress can be offered treatment with an antipsychotic drug (see Antipsychotic drugs under Psychoses and related disorders p. 358). Careful consideration should be given to the patient’s co-morbid conditions and the benefits and risks of treatment. The MHRA has reported (2009) a clear increased risk of stroke and a small increased risk of death when antipsychotic drugs are used in elderly patients with dementia. The balance of risks and benefits should be carefully assessed, including any previous history of stroke or transient ischaemic attack and any risk factors for cerebrovascular disease including hypertension, diabetes, smoking and atrial fibrillation.

Treatment with antipsychotic drugs should be started with a low dose and titrated upwards, with regular review. In patients who have dementia with Lewy bodies, careful monitoring for severe untoward reactions, such as neuroleptic sensitivity reactions, is recommended.
Acetylcholinesterase inhibitors and memantine

An acetylcholinesterase inhibitor may be used to manage non-cognitive symptoms in patients with mild-to-moderate dementia due to Alzheimer’s disease, if a non-pharmacological approach or an antipsychotic drug is inappropriate or ineffective.

Memantine hydrochloride may be considered in patients with severe symptoms, if a non-pharmacological approach or an antipsychotic drug is inappropriate or ineffective. Memantine hydrochloride may also be used in patients with moderate symptoms in whom acetylcholinesterase inhibitors are contra-indicated.

Patients who have dementia with Lewy bodies should be offered an acetylcholinesterase inhibitor for the treatment of non-cognitive symptoms. Acetylcholinesterase inhibitors are not recommended in patients with vascular dementia.

Management of violence, aggression, and extreme agitation

In cases of dementia associated with severe behavioural disturbance that requires urgent treatment (if violence, aggression and extreme agitation threaten the safety of the patient or others), an antipsychotic drug or a benzodiazepine may be given (see Antipsychotic drugs under Psychoses and related disorders p. 358; see Benzodiazepines under Hypnotics and anxiolytics p. 447). High doses or combinations of drugs should be avoided, and the lowest effective dose should be used. Oral treatment should be offered before parenteral administration. If intramuscular administration is needed for behavioural control, lorazepam p. 317, haloperidol p. 363 or olanzapine p. 373 should be used. Diazepam and chlorpromazine hydrochloride are not recommended. Intravenous administration should be used only in exceptional circumstances.

Useful Resources


www.nice.org.uk/guidance/CG42/

Other drugs used for Dementia Risperidone, p. 377

ANTICHOLINESTERASES › CENTRALLY ACTING

Donepezil hydrochloride

26-Sep-2016

Drug action

Donepezil is a reversible inhibitor of acetylcholinesterase.

Indications and dose

Mild to moderate dementia in Alzheimer’s disease

By mouth

Adult: Initially 5 mg once daily for one month, then increased if necessary up to 10 mg daily, doses to be given at bedtime

Cautions

Asthma · chronic obstructive pulmonary disease · sick sinus syndrome · supraventricular conduction abnormalities · susceptibility to peptic ulcers

Interactions

› Appendix 1 (parasympathomimetics). Caution with concomitant antipsychotic treatment—increased risk of neuroleptic malignant syndrome

Side-effects

› Common or very common

Abnormal dreams · aggression · agitation · anorexia · diarrhoea · dizziness · fatigue · hallucinations · headache · insomnia · muscle cramps · nausea · pruritus · rash · syncope · urinary incontinence · vomiting

› Uncommon

Bradycardia · duodenal ulcers · gastric ulcers · gastro-intestinal haemorrhage · seizures

Rare

AV block · extrapyramidal symptoms · hepatitis · potential for bladder outflow obstruction · sino-atrial block

Very rare

Neuroleptic malignant syndrome

Side-effects, further information

Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

Hepatic impairment

Caution in mild to moderate impairment. No information available for severe impairment.

Directions for administration

Donepezil orodispersible tablet should be placed on the tongue, allowed to disperse, and swallowed.

Patient and carer advice

Patient or carers should be given advise on how to administer donepezil hydrochloride orodispersible tablets.

National funding/access decisions

NICE technology appraisals (TAs)

Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease—updated May 2016

NICE TA217

Donepezil can be used for the treatment of mild to moderate Alzheimer’s disease. Treatment should only be prescribed under the following conditions:

› treatment should be initiated on the advice of a specialist

› ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation

› treatment should continue only if it is considered to have a worthwhile effect on cognitive, global, functional, or behavioural symptoms.

Healthcare professionals should not rely solely on assessment scales to determine the severity of Alzheimer’s disease when the patient has learning or other disabilities, or other communication difficulties.

www.nice.org.uk/TA217

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

› Donepezil hydrochloride (Non-proprietary)

Donepezil hydrochloride 5 mg Donepezil 5mg tablets [28 tablet Pom £59.85 DT price = £1.04

Donepezil hydrochloride 10 mg Donepezil 10mg tablets [28 tablet Pom £83.89 DT price = £1.54

› Aricept (Eisai Ltd)

Donepezil hydrochloride 5 mg Aricept 5mg tablets [28 tablet Pom £85.85 DT price = £1.04

Donepezil hydrochloride 10 mg Aricept 10mg tablets [28 tablet Pom £83.89 DT price = £1.54

Orodispersible tablet

› Donepezil hydrochloride (Non-proprietary)

Donepezil hydrochloride 5 mg Donepezil 5mg orodispersible tablets [28 tablet Pom £59.85

Donepezil 5mg orodispersible tablets sugar free sugar-free [28 tablet Pom £4.15–£50.87 DT price = £6.51

Donepezil hydrochloride 10 mg Donepezil 10mg orodispersible tablets sugar free sugar-free [28 tablet Pom £6.64–£71.31 DT price = £8.27

Donepezil 10mg orodispersible tablets [28 tablet Pom £83.89

› Aricept Evess (Eisai Ltd)

Donepezil hydrochloride 5 mg Aricept Evess 5mg orodispersible tablets sugar-free [28 tablet Pom £59.85 DT price = £6.51

Donepezil hydrochloride 10 mg Aricept Evess 10mg orodispersible tablets sugar-free [28 tablet Pom £83.89 DT price = £8.27

Oral solution

› Donepezil hydrochloride (Non-proprietary)

Donepezil hydrochloride 1 mg per 1 ml Donepezil 1mg/ml oral solution sugar free sugar-free [150 ml Pom £48.00 DT price = £48.00
Galantamine

**DRUG ACTION** Galantamine is a reversible inhibitor of acetylcholinesterase and it also has nicotinic receptor agonist properties.

**INDICATIONS AND DOSE**

Mild to moderately severe dementia in Alzheimer’s disease

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult:** Initially 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for at least 4 weeks; maintenance 8–12 mg twice daily
  - **BY MOUTH USING MODIFIED-RELEASE CAPSULES**
  - **Adult:** Initially 8 mg once daily for 4 weeks, increased to 16 mg once daily for at least 4 weeks; maintenance 16–24 mg daily

**CAUTIONS**

Avoid in gastro-intestinal obstruction · avoid in urinary outlet obstruction · avoid whilst recovering from bladder surgery · avoid whilst recovering from gastro-intestinal surgery · cardiac disease · chronic obstructive pulmonary disease · congestive heart failure · electrolyte disturbances · history of seizures · history of severe asthma · pulmonary infection · sick sinus syndrome · supraventricular conduction abnormalities · susceptibility to peptic ulcers · unstable angina

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · bradycardia · decreased appetite · depression · diarrhoea · dizziness · dyspepsia · fatigue · hallucination · headache · hypertension · malaise · muscle spasm · nausea · syncope · tremor · vomiting · weight loss
- **Uncommon** Arrhythmias · blurred vision · dehydration · first-degree AV block · flushing · hypersonnia · hypotension · muscular weakness · palpitation · paraesthesia · retching · seizures · sweating · taste disturbance · tinnitus
- **Rare** Acute generalized exanthematous pustulosis · erythema multiforme · exacerbation of Parkinson’s disease · hepatitis · Stevens-Johnson syndrome

**INTERACTIONS**

- **Appendix** (parasympathomimetics).
- **By Mouth Using Immediate-Release Medicines**
  - Vigabatrin · anticholinergics
  - Anticholinesterase inhibitors (e.g. donepezil)
  - Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergetic effects and should be started at a low dose and the dose increased according to response and tolerability.
  - Serious skin reactions • Serious skin reactions (including Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) have been reported—manufacturer advises discontinue at the first appearance of skin rash.

**PREGNANCY**

Use with caution—toxicity in animal studies.

**BREAST FEEDING**

Avoid—no information available.

**HEPATIC IMPAIRMENT**

For immediate-release preparations in moderate impairment, initially 4 mg once daily (preferably in the morning) for at least 7 days, then 4 mg twice daily for at least 4 weeks; max. 8 mg twice daily; avoid in severe impairment. For modified-release preparations in moderate impairment, initially 8 mg on alternate days (preferably in the morning) for 7 days, then 8 mg once daily for 4 weeks; max. 16 mg daily; avoid in severe impairment.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 9 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Manufacturer recommends that patients are warned of the signs of serious skin reactions; they should be advised to stop taking galantamine immediately and seek medical advice if symptoms occur.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease—updated May 2016
- NICE TA217

Galantamine can be used for the treatment of mild to moderate Alzheimer’s disease. Treatment should only be prescribed under the following conditions:

- treatment should be initiated on the advice of a specialist
- ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation
- treatment should continue only if it is considered to have a worthwhile effect on cognitive, global, functional, or behavioural symptoms.

Healthcare professionals should not rely solely on assessment scales to determine the severity of Alzheimer’s disease when the patient has learning or other disabilities, or other communication difficulties.

www.nice.org.uk/TA217

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Tablet**

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<thead>
<tr>
<th>Brand name</th>
<th>Dosage</th>
<th>Manufacturer</th>
<th>Price DT (£)</th>
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**Modified-release capsule**

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</thead>
<tbody>
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<td>Galantex XL</td>
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<td>(Shire Pharmaceuticals Ltd)</td>
<td>180.00</td>
</tr>
</tbody>
</table>

**BNF 73**

Dementia 283

4 Nervous system
DRUG ACTION

**Gatalin XL** (Aspire Pharma Ltd)
**Galantamine** (as Galantamine hydrobromide) 8 mg Gatalin XL
8 mg capsules | 28 capsule | £0.82 | 818.24 DT price | £5.18

**Galantamine** (as Galantamine hydrobromide) 16 mg Gatalin XL
16 mg capsules | 28 capsule | £1.64 | 324.48 DT price | £6.90

**Galantamine** (as Galantamine hydrobromide) 24 mg Gatalin XL
24 mg capsules | 28 capsule | £3.79 | 84.09 DT price | £7.80

**Gazylan XL** (Teva UK Ltd)
**Galantamine** (as Galantamine hydrobromide) 8 mg Gazylan XL
8 mg capsules | 28 capsule | £0.82 | 818.24 DT price | £5.18

**Galantamine** (as Galantamine hydrobromide) 16 mg Gazylan XL
16 mg capsules | 28 capsule | £1.64 | 324.48 DT price | £6.90

**Galantamine** (as Galantamine hydrobromide) 24 mg Gazylan XL
24 mg capsules | 28 capsule | £3.79 | 84.09 DT price | £7.80

**Lotprosin XL** (Actavis UK Ltd)
**Galantamine** (as Galantamine hydrobromide) 8 mg Lotprosin XL
8 mg capsules | 28 capsule | £0.82 | 818.24 DT price | £5.18

**Galantamine** (as Galantamine hydrobromide) 16 mg Lotprosin XL
16 mg capsules | 28 capsule | £1.64 | 324.48 DT price | £6.90

**Galantamine** (as Galantamine hydrobromide) 24 mg Lotprosin XL
24 mg capsules | 28 capsule | £3.79 | 84.09 DT price | £7.80

**Luventa XL** (Fontus Health Ltd)
**Galantamine** (as Galantamine hydrobromide) 8 mg Luventa XL
8 mg capsules | 28 capsule | £0.82 | 818.24 DT price | £5.18

**Galantamine** (as Galantamine hydrobromide) 16 mg Luventa XL
16 mg capsules | 28 capsule | £1.64 | 324.48 DT price | £6.90

**Galantamine** (as Galantamine hydrobromide) 24 mg Luventa XL
24 mg capsules | 28 capsule | £3.79 | 84.09 DT price | £7.80

**Reminyl XL** (Shire Pharmaceuticals Ltd)
**Galantamine** (as Galantamine hydrobromide) 8 mg Reminyl XL
8 mg capsules | 28 capsule | £0.82 | 818.24 DT price | £5.18

**Galantamine** (as Galantamine hydrobromide) 16 mg Reminyl XL
16 mg capsules | 28 capsule | £1.64 | 324.48 DT price | £6.90

**Galantamine** (as Galantamine hydrobromide) 24 mg Reminyl XL
24 mg capsules | 28 capsule | £3.79 | 84.09 DT price | £7.80

**Oral solution**
**CAUTIONARY AND ADVISORY LABELS** 3, 21

Galantamine (Non proprietary) 20 mg/ml oral solution non-irritated skin on back, upper arm, or chest, removing
100 ml | £0.04 | 100.00

**Reminyl** (Shire Pharmaceuticals Ltd)
**Galantamine** (as Galantamine hydrobromide) 4 mg per
1 ml Reminyl 4 mg/ml oral solution sugar-free | 100 ml | £0.04 | 120.00

**Rivastigmine**

**Drug action** Rivastigmine is a reversible non-competitive inhibitor of acetylcholinesterases.

**INDICATIONS AND DOSE**

**Mild to moderate dementia in Alzheimer’s disease**

**BY MOUTH**

**Adult:** Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance.

**Transdermal application using patches**

Adult: Apply 4.6 mg/24 hours daily for at least 4 weeks, increased if tolerated to 9.5 mg/24 hours daily for a further 6 months, then increased if necessary to 13.3 mg/24 hours daily, increase to 13.3 mg/24 hours patch if well tolerated and cognitive deterioration or functional decline demonstrated; use caution in patients with body-weight less than 50 kg, if treatment interrupted for more than 3 days, reinitiate from 4.6 mg/24 hours patch

Mild to moderate dementia in Parkinson’s disease

**BY MOUTH**

Adult: Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance.

**Transdermal application using patches**

Adult: Apply 4.6 mg/24 hours daily for at least 4 weeks, increased if tolerated to 9.5 mg/24 hours daily for a further 6 months, then increased if necessary to 13.3 mg/24 hours daily, increase to 13.3 mg/24 hours patch if well tolerated and cognitive deterioration or functional decline demonstrated; use caution in patients with body-weight less than 50 kg, if treatment interrupted for more than 3 days, reinitiate from 4.6 mg/24 hours patch

**Usual dose** 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, reinitiate from 1.5 mg twice daily

**DOSE Equivalence and conversion**

When switching from oral to transdermal therapy, patients taking 3–6 mg by mouth daily should initially switch to 4.6 mg/24 hours patch, then titrate as above. Patients taking 9 mg by mouth daily should switch to 9.5 mg/24 hours patch if oral dose stable and well tolerated; if oral dose not stable or well tolerated. Patients should switch to 4.6 mg/24 hours patch, then titrate as above. Patients taking 12 mg by mouth daily should switch to 9.5 mg/24 hours patch. The first patch should be applied on the day following the last oral dose

**CAUTIONS** Bladder outflow obstruction — conduction abnormalities — duodenal ulcers — gastric ulcers — history of asthma — history of chronic obstructive pulmonary disease — history of seizures — risk of fatal overdose with patch administration errors — sick sinus syndrome — susceptibility to ulcers

**INTERACTIONS** → Appendix 1 (parasympathomimetics).

**SIDE-EFFECTS**

**Common or very common** Abdominal pain — agitation — anorexia — anxiety — bradycardia — confusion — diarrhoea — dizziness — drowsiness — dyspepsia — extrapyramidal symptoms — headache — increased salivation — insomnia — malaise — nausea — sweating — tremor — urinary incontinence — vomiting — weight loss — worsening of Parkinson’s disease

**Uncommon** Atrial fibrillation — AV block — depression — syncope

**Rare** Angina — duodenal ulceration — gastric ulceration — rash — seizures

**Very rare** Gastro-intestinal haemorrhage — hallucinations — hypertension — pancreatitis — tachycardia

**Frequency not known** Aggression — dehydration — hepatitis — restlessness — sick sinus syndrome — skin hypersensitivity reactions

**SIDE-EFFECTS, FURTHER INFORMATION**

Transdermal administration less likely to cause gastrointestinal disturbance.

Treatment should be interrupted if gastro-intestinal side-effects occur and withheld until their resolution — reinitiate dose if necessary.

Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

**Hepatic Impairment** Titrate according to individual tolerability in mild to moderate impairment. Use with caution in severe impairment — no information available.

**Renal Impairment** Titrate according to individual tolerability.

**MONITORING REQUIREMENTS** Monitor body-weight.

**DIRECTIONS FOR ADMINISTRATION**

With transdermal use. Apply patches to clean, dry, non-hairy, non-irritated skin on back, upper arm, or chest, removing after 24 hours and sitting a replacement patch on a different area (avoid using the same area for 14 days).

**Patient and carer advice**

**Exelon® patches** Advise patients and carers of patch administration instructions, particularly to remove the previous day’s patch before applying the new patch — consult product literature.
MEDICINAL FORMS

▶ Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease—updated May 2016

NICE TA217

Rivastigmine can be used for the treatment of mild to moderate Alzheimer's disease. Treatment should only be prescribed under the following conditions:
- treatment should be initiated on the advice of a specialist
- ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation
- treatment should continue only if it is considered to have a worthwhile effect on cognitive, global, functional, or behavioural symptoms.

Healthcare professionals should not rely solely on assessment scales to determine the severity of Alzheimer's disease when the patient has learning or other disabilities, or other communication difficulties.

www.nice.org.uk/TA217

EXELON® PATCHES

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2007) that Exelon® patches should be restricted for use in patients with moderately severe Alzheimer's disease under the conditions of the NICE guidance (September 2007) and when a transdermal patch is an appropriate choice of formulation.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 21, 25

Rivastigmine (as Rivastigmine hydrogen tartrate)

1.5 mg Rivastigmine 1.5mg capsules | 28 capsule PoD £33.25 DT price = £2.58 | 56 capsule PoD £66.51

Rivastigmine (as Rivastigmine hydrogen tartrate)

3 mg Rivastigmine 3mg capsules | 28 capsule PoD £33.25 DT price = £2.85 | 56 capsule PoD £63.18

Rivastigmine (as Rivastigmine hydrogen tartrate)

4.5 mg Rivastigmine 4.5mg capsules | 28 capsule PoD £33.25 DT price = £4.31 | 56 capsule PoD £63.18

Rivastigmine (as Rivastigmine hydrogen tartrate)

6 mg Rivastigmine 6mg capsules | 28 capsule PoD £33.25 DT price = £7.20 | 56 capsule PoD £63.18

Exelon (Novartis Pharmaceuticals UK Ltd)

Rivastigmine (as Rivastigmine hydrogen tartrate) 1.5 mg Exelon 1.5mg capsules | 56 capsule PoD £66.51

Rivastigmine (as Rivastigmine hydrogen tartrate) 3 mg Exelon 3mg capsules | 28 capsule PoD £33.25 DT price = £2.85 | 56 capsule PoD £66.51

Rivastigmine (as Rivastigmine hydrogen tartrate) 4.5 mg Exelon 4.5mg capsules | 28 capsule PoD £33.25 DT price = £4.31 | 56 capsule PoD £66.51

Rivastigmine (as Rivastigmine hydrogen tartrate) 6 mg Exelon 6mg capsules | 28 capsule PoD £33.25 DT price = £7.20 | 56 capsule PoD £66.51

Kerstinop (Aspire Pharma Ltd)

Rivastigmine (as Rivastigmine hydrogen tartrate)

1.5 mg Kerstinop 1.5mg capsules | 28 capsule PoD £33.25 DT price = £2.58

Rivastigmine (as Rivastigmine hydrogen tartrate) 3 mg Kerstinop 3mg capsules | 28 capsule PoD £33.25 DT price = £2.85

Rivastigmine (as Rivastigmine hydrogen tartrate)

4.5 mg Kerstinop 4.5mg capsules | 28 capsule PoD £33.25 DT price = £4.31

Rivastigmine (as Rivastigmine hydrogen tartrate) 6 mg Kerstinop 6mg capsules | 28 capsule PoD £33.25 DT price = £7.20

Nimvastid (Consilient Health Ltd)

Rivastigmine (as Rivastigmine hydrogen tartrate)

1.5 mg Nimvastid 1.5mg capsules | 28 capsule PoD £28.26 DT price = £2.58

Rivastigmine (as Rivastigmine hydrogen tartrate) 3 mg Nimvastid 3mg capsules | 28 capsule PoD £28.26 DT price = £2.85

Rivastigmine (as Rivastigmine hydrogen tartrate)

4.5 mg Nimvastid 4.5mg capsules | 28 capsule PoD £28.26 DT price = £4.31

Rivastigmine (as Rivastigmine hydrogen tartrate) 6 mg Nimvastid 6mg capsules | 28 capsule PoD £28.26 DT price = £7.20

Oral solution

CAUTIONARY AND ADVISORY LABELS 21

Rivastigmine (Non-proprietary)

Rivastigmine (as Rivastigmine hydrogen tartrate) 2 mg per 1 ml

Rivastigmine 2mg/ml oral solution | 120 ml PoD £91.75—94.18

Rivastigmine 2mg/ml oral solution sugar free sugar-free | 120 ml PoD £96.82 DT price = £96.82

Exelon (Novartis Pharmaceuticals UK Ltd)

Rivastigmine (as Rivastigmine hydrogen tartrate) 2 mg per 1 ml

Exelon 2mg/ml oral solution sugar-free | 120 ml PoD £99.14 DT price = £96.82

Transdermal patch

Rivastigmine (Non-proprietary)

Rivastigmine 4.6 mg per 24 hour

Rivastigmine 4.6mg/24hours transdermal patches | 30 patch PoD £77.97 DT price = £77.97

Rivastigmine 9.5 mg per 24 hour

Rivastigmine 9.5mg/24hours transdermal patches | 30 patch PoD £90.30 DT price = £90.30

Exelon 13.3 mg per 24 hour

Rivastigmine 13.3mg/24hours transdermal patches | 30 patch PoD £97.97 DT price = £97.97

Alzest (Dr Reddy's Laboratories (UK) Ltd)

Rivastigmine 4.6 mg per 24 hour

Alzest 4.6mg/24hours transdermal patches | 30 patch PoD £35.10 DT price = £35.10

Rivastigmine 9.5 mg per 24 hour

Alzest 9.5mg/24hours transdermal patches | 30 patch PoD £59.97 DT price = £59.97

Exelon (Novartis Pharmaceuticals UK Ltd)

Rivastigmine 4.6 mg per 24 hour

Rivastigmine 4.6mg/24hours transdermal patches | 30 patch PoD £97.97 DT price = £97.97

Rivastigmine 9.5 mg per 24 hour

Rivastigmine 9.5mg/24hours transdermal patches | 30 patch PoD £77.97 DT price = £77.97

Prometax (Novartis Pharmaceuticals UK Ltd)

Rivastigmine 4.6 mg per 24 hour

Prometax 4.6mg/24hours transdermal patches | 30 patch PoD £77.97 DT price = £77.97

Rivastigmine 9.5 mg per 24 hour

Prometax 9.5mg/24hours transdermal patches | 30 patch PoD £77.97 DT price = £77.97

EraSTIG (Teva UK Ltd)

Rivastigmine 13.3 mg per 24 hour

EraSTIG 13.3mg/24hours transdermal patches | 30 patch PoD £93.80 DT price = £93.80

Voleze (Focus Pharmaceuticals Ltd)

Rivastigmine 4.6 mg per 24 hour

Voleze 4.6mg/24hours transdermal patches | 30 patch PoD £77.97 DT price = £77.97

Rivastigmine 9.5 mg per 24 hour

Voleze 9.5mg/24hours transdermal patches | 30 patch PoD £77.97 DT price = £77.97

DOPAMINERGIC DRUGS > NMDA RECEPTOR ANTAGONISTS

Mempantyl hydrochloride

24-Nov-2016

DRUG ACTION

Memantine is a glutamate receptor antagonist.

INDICATIONS AND DOSE

Moderate to severe dementia in Alzheimer's disease

BY MOUTH

Adult: Initially 5 mg once daily, then increased in steps of 5 mg every week; usual maintenance 20 mg daily; maximum 20 mg per day

CAUTIONS

Epilepsy • history of convulsions • risk factors for epilepsy

INTERACTIONS

Appendix 1 (memantine).

SIDE-EFFECTS

Common or very common Balance disorders • constipation • dizziness • drowsiness • dyspnoea • headache • hypertension
Epilepsy and other seizure disorders

2 Epilepsy and other seizure disorders

Epilepsy

Control of the epilepsies

The object of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Careful adjustment of doses is necessary, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.

When choosing an antiepileptic drug, the presenting epilepsy syndrome should first be considered. If the syndrome is not clear, the seizure type should determine the choice of treatment. Concomitant medication, co-morbidity, age, and sex should also be taken into account.

The dosage frequency is often determined by the plasma-drug half-life, and should be kept as low as possible to encourage adherence with the prescribed regimen. Most antiepileptics, when used in the usual dosage, can be given twice daily. Lamotrigine p. 297, perampanel p. 301, phenobarbital p. 313, and phenytoin p. 302, which have long half-lives, can be given once daily at bedtime. However, with large doses, some antiepileptics may need to be given more frequently to avoid adverse effects associated with high peak plasma-drug concentration.

Management

When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried; the diagnosis should be checked before starting an alternative drug if the first drug showed lack of efficacy. The change from one antiepileptic drug to another should be cautious, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions. If combination therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy. A single antiepileptic drug should be prescribed wherever possible.
MHRA/CHM advice: Antiepileptic drugs: new advice on switching between different manufacturers’ products for a particular drug (November 2013)

The CHM has reviewed spontaneous adverse reactions received by the MHRA and publications that reported potential harm arising from switching of antiepileptic drugs in patients previously stabilised on a branded product to a generic. The CHM concluded that reports of loss of seizure control and/or worsening of side-effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases. The following guidance has been issued to help minimise risk:

- Different antiepileptic drugs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control;
- Antiepileptic drugs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product. These categories are listed below;
- If it is felt desirable for a patient to be maintained on a specific manufacturer’s product this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder);
- This advice relates only to antiepileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);
- Please report on a Yellow Card any suspected adverse reactions to antiepileptic drugs;
- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer);
- Usual dispensing practice can be followed when a specific product is not stated.

**Category 1**
Phenytoin, carbamazepine p. 291, phenobarbital, primidone p. 313. For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer’s product.

**Category 2**
Valproate, lamotrigine, perampanel, retigabine p. 305, rufinamide p. 306, clobazam p. 314, clonazepam p. 315, oxcarbazepine p. 300, eslicarbazepine acetate p. 293, zonisamide p. 311, topiramate p. 309. For these drugs, the need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient and/or carer taking into account factors such as seizure frequency and treatment history.

**Category 3**
Levetiracetam p. 299, lacosamide p. 296, tiagabine p. 309, gabapentin p. 295, pregabalin p. 304, ethosuximide p. 294, vigabatrin p. 313. For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer’s product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors.

**Antiepileptic hypersensitivity syndrome**
Antiepileptic hypersensitivity syndrome is a rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide); rarely cross-sensitivity occurs between some of these antiepileptic drugs. Some other antiepileptics (eslicarbazepine, stiripentol, and zonisamide) have a theoretical risk. The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen. Other systemic signs include liver dysfunction, haematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure. If signs or symptoms of hypersensitivity syndrome occur, the drug should be withdrawn immediately, the patient must not be re-exposed, and expert advice should be sought.

**Interactions**
Interactions between antiepileptics are complex and may increase toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or inhibition; displacement from protein binding sites is not usually a problem. These interactions are highly variable and unpredictable.

**Withdrawal**
Antiepileptic drugs should be withdrawn under specialist supervision. Avoid abrupt withdrawal, particularly of barbiturates and benzodiazepines, because this can precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months.

The decision to withdraw antiepileptic drugs from a seizure-free patient, and its timing, is often difficult and depends on individual circumstances. Even in patients who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.

**Driving**
Patients with epilepsy may drive a motor vehicle (but not a large goods or passenger carrying vehicle) provided that they have been seizure-free for one year or, if subject to attacks only while asleep, have established a 3-year period of asleep attacks without awake attacks. Those affected by drowsiness should not drive or operate machinery.

Guidance issued by the Drivers Medical Unit of the Driver and Vehicle Licensing Agency (DVLA) recommends that patients should be advised not to drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months afterwards.

Patients who have had a first or single epileptic seizure must not drive for 6 months (5 years in the case of large goods or passenger carrying vehicles) after the event; driving may then be resumed, provided the patient has been assessed by a specialist as fit to drive because no abnormality was detected on investigation.

**Pregnancy**
Women of child-bearing potential should discuss with a specialist the impact of both epilepsy, and its treatment, on the outcome of pregnancy.

There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and particularly if the patient takes two or more antiepileptic drugs). Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term developmental disorders. There is also an increased risk of teratogenicity with phenytoin, primidone, phenobarbital, lamotrigine, and carbamazepine. Topiramate carries an increased risk of cleft palate if taken in the first trimester of pregnancy. There is not enough evidence to establish the risk of teratogenicity with other antiepileptic drugs.

Prescribers should also consider carefully the choice of antiepileptic therapy in pre-pubescent girls who may later become pregnant. Women of child-bearing potential who take antiepileptic drugs should be given advice about the
need for an effective contraception method to avoid unplanned pregnancy. Some antiepileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some antiepileptics may be affected by hormonal contraceptives.

Women who want to become pregnant should be referred to a specialist for advice in advance of conception. For some women, the severity of seizure or the seizure type may not pose a serious threat, and drug withdrawal may be considered; therapy may be resumed after the first trimester. If treatment with antiepileptic drugs must continue throughout pregnancy, then monotherapy is preferable at the lowest effective dose.

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen; the risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy. The likelihood of a woman who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern over harm to the fetus. To reduce the risk of neural tube defects, folate supplementation is advised before conception and throughout the first trimester. In the case of sodium valproate p. 306 and valproic acid p. 331 an urgent consultation is required to reconsider the benefits and risks of valproate therapy.

The concentration of antiepileptic drugs in the plasma can change during pregnancy. Doses of phenytoin, carbamazepine, and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring; the dose of other antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. Plasma-drug concentration monitoring during pregnancy is also useful to check compliance. Additionally, in patients taking topiramate or levetiracetam, it is recommended that fetal growth should be monitored. Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol.

Routine injection of vitamin K at birth minimises the risk of neonatal haemorrhage associated with antiepileptics. Withdrawal effects in the newborn may occur with some antiepileptic drugs, in particular benzodiazepines and phenobarbital.

Epilepsy and Pregnancy Register
All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

Breast-feeding
Women taking antiepileptic monotherapy should generally be encouraged to breast-feed; if a woman is on combination therapy or if there are other risk factors, such as premature birth, specialist advice should be sought.

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones. Infants should also be monitored for adverse effects associated with the antiepileptic drug particularly with newer antiepileptics, if the antiepileptic is readily transferred into breast-milk causing high infant serum-drug concentrations (e.g. ethosuximide, lamotrigine, primidone, and zonisamide), or if slower metabolism in the infant causes drugs to accumulate (e.g. phenobarbital and lamotrigine). Serum-drug concentration monitoring should be undertaken in breast-fed infants if suspected adverse reactions develop; if toxicity develops it may be necessary to introduce formula feeds to limit the infant’s drug exposure, or to wean the infant off breast-milk altogether.

Primidone, phenobarbital, and the benzodiazepines are associated with an established risk of drowsiness in breast-fed babies and caution is required.

Withdrawal effects may occur in infants if a mother suddenly stops breast-feeding, particularly if she is taking phenobarbital, primidone, or lamotrigine.

Focal seizures with or without secondary generalisation
Carbamazepine p. 291 and lamotrigine p. 297 are first-line options for treating newly diagnosed focal seizures; oxcarbazepine p. 300, sodium valproate and levetiracetam p. 299 may be used if carbamazepine or lamotrigine are unsuitable or not tolerated. If monotherapy is unsuccessful with two of these first-line antiepileptic drugs, adjunctive treatment may be considered. Options for adjunctive treatment include carbamazepine, clobazam p. 314, gabapentin p. 295, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate p. 309. If adjunctive treatment is ineffective or not tolerated, a tertiary epilepsy specialist should be consulted who may consider eslicarbazepine acetate p. 293, lacosamide p. 296, phenobarbital p. 313, phenytoin p. 302, pregabalin p. 304, tiagabine p. 309, vigabatrin p. 311 and zonisamide p. 311.

Generalised seizures
Tonic-clonic seizures
Sodium valproate is the first-line treatment for newly diagnosed generalised tonic-clonic seizures (except in female patients who are premenopausal, see Valproate below). Lamotrigine is the alternative choice if sodium valproate is not suitable, but may exacerbate myoclonic seizures. In those with established epilepsy with generalised tonic-clonic seizures only, lamotrigine or sodium valproate may be prescribed as the first-line treatment. Carbamazepine and oxcarbazepine may also be considered in newly diagnosed and established tonic-clonic seizures, but may exacerbate myoclonic and absence seizures. Clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate may be used as adjunctive treatment if monotherapy is ineffective or not tolerated.

Absence seizures
Ethosuximide p. 294, or sodium valproate (except in female patients who are premenopausal, see Valproate below), are the drugs of choice in absence seizures and syndromes; lamotrigine p. 297 is a suitable alternative when ethosuximide p. 294 and sodium valproate p. 306 are unsuitable, ineffective or not tolerated. Sodium valproate should be used as the first choice if there is a high risk of generalised tonic-clonic seizures. A combination of any two of these drugs may be used if monotherapy is ineffective. Clobazam p. 314, clonazepam p. 315, levetiracetam p. 299, topiramate p. 309 or zonisamide p. 311 may be considered by a tertiary epilepsy specialist if adjunctive treatment fails. Carbamazepine p. 291, gabapentin p. 295, oxcarbazepine p. 300, phenytoin p. 302, pregabalin p. 304, tiagabine p. 309 and vigabatrin p. 311 are not recommended in absence seizures or syndromes.

Myoclonic seizures
Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably. Sodium valproate is the drug of choice in newly diagnosed myoclonic seizures (except in female patients who are premenopausal, see Valproate below); topiramate and levetiracetam are alternative options if sodium valproate is unsuitable but consideration should be given to the less favourable side-effect profile of topiramate. A combination of two of these drugs may be used if monotherapy is ineffective or not tolerated. If adjunctive treatment fails, a tertiary epilepsy specialist should be consulted and may consider clobazam, clonazepam, zonisamide or piracetam p. 379. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin are not recommended for the treatment of myoclonic seizures.
Sodium valproate and levetiracetam are effective in treating the generalised tonic-clonic seizures that coexist with myoclonic seizures in idiopathic generalised epilepsy.

**Atonic and tonic seizures**
Atonic and tonic seizures are usually seen in childhood, in specific epilepsy syndromes, or associated with cerebral damage or mental retardation. They may respond poorly to the traditional drugs. Sodium valproate is the drug of choice (except in female patients who are premenopausal, see **Valproate** below); lamotrigine can be added as adjunctive treatment. If adjunctive treatment is ineffective or not tolerated, a secondary epilepsy specialist should be consulted, and may consider rufinamide p. 306 or topiramate. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin are not recommended in atonic and tonic seizures.

**Epilepsy syndromes**
Some drugs are licensed for use in particular epilepsy syndromes, such as lamotrigine and rufinamide in Lennox-Gastaut syndrome. The epilepsy syndromes are specific types of epilepsy that are characterised according to a number of features including seizure type, age of onset, and EEG characteristics.

**Antiepileptic drugs**
**Carbamazepine and related antiepileptics**
Carbamazepine is a drug of choice for simple and complex focal seizures and is a first-line treatment option for generalised tonic-clonic seizures. It can be used as adjunctive treatment for focal seizures when monotherapy has been ineffective. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly. Carbamazepine may exacerbate tonic, atonic, myoclonic and absence seizures and is therefore not recommended if these seizures are present.

Oxcarbazepine is licensed as monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures. It can also be considered for the treatment of primary generalised tonic-clonic seizures [unlicensed]. Oxcarbazepine is not recommended in tonic, atonic, absence or myoclonic seizures due to the risk of seizure exacerbation.

Eslicarbazepine acetate p. 293 is licensed for adjunctive treatment in adults with focal seizures with or without secondary generalisation.

**Ethosuximide**
Ethosuximide is a first-line treatment option for absence seizures. It may also be prescribed as adjunctive treatment for absence seizures when monotherapy is ineffective. Ethosuximide is also licensed for myoclonic seizures.

**Gabapentin and pregabalin**
Gabapentin and pregabalin are used for the treatment of focal seizures with or without secondary generalisation. They are not recommended if tonic, atonic, absence or myoclonic seizures are present. Both are also licensed for the treatment of neuropathic pain. Pregabalin is licensed for the treatment of generalised anxiety disorder. Gabapentin is an effective treatment for migraine prophylaxis [unlicensed].

**Lamotrigine**
Lamotrigine is an antiepileptic drug recommended as a first-line treatment for focal seizures and primary and secondary generalised tonic-clonic seizures. It is also licensed for typical absence seizures in children (but efficacy may not be maintained in all children) and is an unlicensed treatment option in adults if first-line treatments have been unsuccessful. Lamotrigine can also be used as adjunctive treatment in atonic or tonic seizures if first-line treatment has failed [unlicensed]. Myoclonic seizures may be exacerbated by lamotrigine and it can cause serious rashes especially in children; dose recommendations should be adhered to closely.

Lamotrigine is used either as sole treatment or as an adjunct to treatment with other antiepileptic drugs. Valproate increases plasma-lamotrigine concentration, whereas the enzyme-inducing antiepileptics reduce it; care is therefore required in choosing the appropriate initial dose and subsequent titration. When the potential for interaction is not known, treatment should be initiated with lower doses, such as those used with valproate.

**Levetiracetam and brivaracetam**
Levetiracetam is used for monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation, and for adjunctive treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures. Levetiracetam may be prescribed alone and in combination for the treatment of myoclonic seizures, and under specialist supervision for absence seizures [both unlicensed].

Brivaracetam p. 290 is used as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation.

**Phenobarbital and primidone**
Phenobarbital p. 313 is effective for tonic-clonic and focal seizures but may be sedative in adults. It may be tried for atypical absence, atonic, and tonic seizures. Rebound seizures may be a problem on withdrawal.

Primidone p. 313 is largely converted to phenobarbital and this is probably responsible for its antiepileptic action. A low initial dose of primidone is essential.

**Phenytoin**
Phenytoin is licensed for tonic-clonic and focal seizures but may exacerbate absence or myoclonic seizures and should be avoided if these seizures are present. It has a narrow therapeutic index and the relationship between dose and plasma–drug concentration is non-linear; small dosage increases in some patients may produce large increases in plasma concentration with acute toxic side-effects. Similarly, a few missed doses or a small change in drug absorption may result in a marked change in plasma–drug concentration. Monitoring of plasma–drug concentration improves dosage adjustment.

When only parenteral administration is possible, fosphenytoin sodium p. 294, a pro-drug of phenytoin, may be convenient to give. Unlike phenytoin (which should only be given intravenously), fosphenytoin sodium may also be given by intramuscular injection.

**Rufinamide**
Rufinamide is licensed for the adjunctive treatment of seizures in Lennox-Gastaut syndrome. It may be considered by a tertiary specialist for the treatment of refractory tonic or atonic seizures [unlicensed].

**Topiramate**
Topiramate can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures with or without secondary generalisation. It can be used as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome and for absence, tonic and atonic seizures under specialist supervision [unlicensed]. It can also be considered as an option in myoclonic seizures [unlicensed]. Topiramate p. 309 is also licensed for prophylaxis of migraine.

**Valproate**
Sodium valproate p. 306 is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in primary generalised tonic-clonic seizures, focal seizures, generalised absences and myoclonic seizures, and can be tried in atypical absence seizures. It is recommended as a first-line option in atonic and tonic seizures. Sodium valproate has widespread metabolic effects.
and monitoring of liver function tests and full blood count is essential. Valproate should not be used in female children, in females of childbearing potential, and pregnant females, unless alternative treatments are ineffective or not tolerated, because of its high teratogenic potential; the benefits and risks of valproate therapy should be carefully reconsidered at regular treatment reviews, see Important safety information in the sodium valproate and valproic acid p. 331 drug monographs.

Valproic acid (as semisodium valproate) is licensed for acute mania associated with bipolar disorder.

Zonisamide
Zonisamide p. 311 can be used alone for the treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy, and as adjunctive treatment for refractory focal seizures with or without secondary generalisation in adults and children aged 6 years and above. It can also be used under the supervision of a specialist for refractory absence and myoclonic seizures [unlicensed indications].

Benzodiazepines
Clobazam p. 314 may be used as adjunctive therapy in the treatment of generalised tonic-clonic and refractory focal seizures. It may be prescribed under the care of a specialist for refractory absence and myoclonic seizures. Clonazepam p. 315 may be prescribed by a specialist for refractory absence and myoclonic seizures, but its sedative side-effects may be prominent.

Other drugs
Acetazolamide p. 1037, a carbonic anhydrase inhibitor, has a specific role in treating epilepsy associated with menstruation. Piracetam p. 379 is used as adjunctive treatment for cortical myoclonus.

Status epilepticus
Convulsive status epilepticus
Immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral thiamine p. 950 should be considered if alcohol abuse is suspected; pyridoxine hydrochloride p. 950 should be given if the status epilepticus is caused by pyridoxine hydrochloride deficiency.

Seizures lasting longer than 5 minutes should be treated urgently with intravenous lorazepam p. 317 (repeated once after 10 minutes if seizures recur or fail to respond). Intravenous diazepam p. 321 is effective but it carries a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. Patients should be monitored for respiratory depression and hypotension.

Where facilities for resuscitation are not immediately available, diazepam can be administered as a rectal solution or midazolam oromucosal solution p. 318 can be given into the buccal cavity.

Important
If, after initial treatment with benzodiazepines, seizures recur or fail to respond 25 minutes after onset, phenytoin sodium, fosphenytoin sodium p. 294, or phenobarbital sodium should be used; contact intensive care unit if seizures continue. If these measures fail to control seizures 45 minutes after onset, anaesthesia with thiopental sodium p. 316, midazolam, or a non-barbiturate anaesthetic such as propofol p. 1175 [unlicensed indication], should be instituted with full intensive care support.

Phenytoin sodium can be given by slow intravenous injection, followed by the maintenance dosage if appropriate.

Alternatively, fosphenytoin sodium (a pro-drug of phenytoin), can be given more rapidly and when given intravenously causes fewer injection-site reactions than phenytoin sodium. Although it can also be given intramuscularly, absorption is too slow by this route for treatment of status epilepticus. Doses of fosphenytoin sodium should be expressed in terms of phenytoin sodium.

Non-convulsive status epilepticus
The urgency to treat non-convulsive status epilepticus depends on the severity of the patient’s condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

Febreile convulsions
Brief febrile convulsions need no specific treatment; antipyretic medication (e.g. paracetamol p. 414), is commonly used to reduce fever and prevent further convulsions but evidence to support this practice is lacking. Prolonged febrile convulsions (those lasting 5 minutes or longer), or recurrent febrile convulsions without recovery must be treated actively (as for convulsive status epilepticus). Long-term anticonvulsant prophylaxis for febrile convulsions is rarely indicated.

Other drugs used for Epilepsy and other seizure disorders Magnesium sulfate, p. 924

Brivaracetam

INDICATIONS AND DOSE
Adjunctive therapy of partial-onset seizures with or without secondary generalisation

→ BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION

Child 16–17 years: Initially 25–50 mg twice daily, adjusted according to response; usual maintenance 25–100 mg twice daily

Adult: Initially 25–50 mg twice daily, adjusted according to response; usual maintenance 25–100 mg twice daily

INTERACTIONS → Appendix 1 (brivaracetam).

SIDE-EFFECTS

Common or very common Anxiety - constipation - decreased appetite - depression - dizziness - insomnia - irritability - malaise - nausea - somnolence - vertigo - vomiting

Uncommon Agitation - agitation - neutropenia - psychotic disorder - suicidal ideation

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—limited information available.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Manufacturer advises consider a starting dose of 25 mg twice daily in chronic liver disease; max. maintenance dose 75 mg twice daily in all stages of impairment.

TREATMENT CESSION Manufacturer advises avoid abrupt withdrawal—reduce daily dose in steps of 50 mg at weekly intervals, then reduce to 20 mg daily for a final week.

DIRECTIONS FOR ADMINISTRATION

With intravenous use For intermittent intravenous infusion, manufacturer advises dilute in Glucose 5% or Sodium Chloride 0.9% or Lactated Ringer’s solution; give over 15 minutes.
Carbamazepine

- **INDICATIONS AND DOSE**

  - **Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures**

    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 100–200 mg 1–2 times a day, increased in steps of 100–200 mg every 2 weeks; usual dose 0.8–1.2 g daily in divided doses; increased if necessary up to 1.6–2 g daily in divided doses
      - Elderly: Reduce initial dose
      - BY RECTUM
      - Adult: Up to 1 g daily in 4 divided doses for up to 7 days, for short-term use when oral therapy temporarily not possible

  - **DOSE EQUIVALENCE AND CONVERSION**
    - Suppositories of 125 mg may be considered to be approximately equivalent in therapeutic effect to tablets of 100 mg but final adjustment should always depend on clinical response (plasma concentration monitoring recommended).

  - **Trigeminal neuralgia**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 100 mg 1–2 times a day, some patients may require higher initial dose, increase gradually according to response; usual dose 200 mg 3–4 times a day, increased if necessary up to 1.6 g daily

  - **Prophylaxis of bipolar disorder unresponsive to lithium**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 400 mg daily in divided doses, increased until symptoms controlled; usual dose 400–600 mg daily; maximum 1.6 g per day

  - **Adjunct in acute alcohol withdrawal**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 800 mg daily in divided doses, then reduced to 200 mg daily for usual treatment duration of 7–10 days, dose to be reduced gradually over 5 days

  - **Diabetic neuropathy**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 100 mg 1–2 times a day, increased gradually according to response; usual dose 200 mg 3–4 times a day, increased if necessary up to 1.6 g daily

  - **Focal and generalised tonic-clonic seizures**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Child 1–11 years: Initially 5 mg/kg once daily, dose to be taken at night, alternatively initially 2.5 mg/kg twice daily, then increased in steps of 2.5–5 mg/kg every 3–7 days as required; maintenance 5 mg/kg 2–3 times a day, increased if necessary up to 20 mg/kg daily
      - Child 12–17 years: Initially 100–200 mg 1–2 times a day, increased to 200–400 mg 2–3 times a day, increased if necessary up to 1.8 g daily, dose should be increased slowly

  - **CARBAGEN® SR**

    - **Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures**
      - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
        - Adult: Initially 100–400 mg daily in 1–2 divided doses, increased in steps of 100–200 mg every 2 weeks, dose should be increased slowly; usual dose 0.8–1.2 g daily in 1–2 divided doses, increased if necessary up to 1.6–2 g daily in 1–2 divided doses
        - Elderly: Reduce initial dose

    - **Trigeminal neuralgia**
      - **BY MOUTH**
        - Adult: Initially 100–200 mg daily in 1–2 divided doses, some patients may require higher initial dose, increase gradually according to response; usual dose 600–800 mg daily in 1–2 divided doses, increased if necessary up to 1.6 g daily in 1–2 divided doses

    - **Prophylaxis of bipolar disorder unresponsive to lithium**
      - **BY MOUTH**
        - Adult: Initially 400 mg daily in 1–2 divided doses, increased until symptoms controlled; usual dose 400–600 mg daily in 1–2 divided doses; maximum 1.6 g per day

    - **Focal and generalised tonic-clonic seizures | Prophylaxis of bipolar disorder**
      - **BY MOUTH**
        - Child 5–11 years: Initially 5 mg/kg daily in 1–2 divided doses, then increased in steps of 2.5–5 mg/kg every 3–7 days as required, dose should be increased slowly; maintenance 10–15 mg/kg daily in
1–2 divided doses, increased if necessary up to 20 mg/kg daily in 1–2 divided doses
- Child 12-17 years: Initially 100–400 mg daily in 1–2 divided doses, then increased to 400–1200 mg daily in 1–2 divided doses, increased if necessary up to 1.8 g daily in 1–2 divided doses, dose should be increased slowly

**TEGRETOL® PROLONGED RELEASE**

**Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures**
- **BY MOUTH**
  - Adult: Initially 100–400 mg daily in 2 divided doses, increased in steps of 100–200 mg every 2 weeks, dose should be increased slowly; usual dose 0.8–1.2 g daily in 2 divided doses, increased if necessary up to 1.6–2 g daily in 2 divided doses
  - Elderly: Reduce initial dose

**Focal and generalised tonic-clonic seizures | Prophylaxis of bipolar disorder**
- **BY MOUTH**
  - Child 5–11 years: Initially 5 mg/kg daily in 2 divided doses, then increased in steps of 2.5–5 mg/kg every 3–7 days as required; maintenance 10–15 mg/kg daily in 2 divided doses, increased if necessary up to 20 mg/kg daily in 2 divided doses
  - Child 12-17 years: Initially 100–400 mg daily in 2 divided doses, dose should be increased slowly; maintenance 400–1200 mg daily in 2 divided doses, increased if necessary up to 1.8 g daily in 2 divided doses

**Trigeminal neuralgia**
- **BY MOUTH**
  - Adult: Initially 100–200 mg daily in 2 divided doses, some patients may require higher initial dose. After initial dose, increase according to response; usual dose 600–800 mg daily in 2 divided doses, increased if necessary up to 1.6 g daily in 2 divided doses, dose should be increased slowly

**Prophylaxis of bipolar disorder unresponsive to lithium**
- **BY MOUTH**
  - Adult: Initially 400 mg daily in 2 divided doses, increased until symptoms controlled; usual dose 400–600 mg daily in 2 divided doses; maximum 1.6 g per day

**UNLICENSED USE** Use in the treatment of alcohol withdrawal is an unlicensed indication. Use in diabetic neuropathy is an unlicensed indication.

**CONTRA-INDICATIONS** Acute porphyrias p. 930 · AV conduction abnormalities (unless paced) · history of bone-marrow depression

**CAUTIONS** Cardiac disease · history of haematological reactions to other drugs · may exacerbate absence and myoclonic seizures · skin reactions · susceptibility to angle-closure glaucoma

**CAUTIONS, FURTHER INFORMATION** Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

Blood, hepatic, or skin disorders · Carbamazepine should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

**INTERACTIONS** → Appendix 1 (carbamazepine).

**SIDE-EFFECTS**
- **Common or very common** Allergic skin reactions · aplastic anaemia · ataxia · blood disorders · blurring of vision · dermatitis · dizziness · drowsiness · dry mouth · eosinophilia · fatigue · haemolytic anaemia · headache · hyponatraemia (leading in rare cases to water intoxication) · leucopenia · nausea · oedema · thrombocytopenia · unsteadiness · urticaria · vomiting
  - **Uncommon** Constipation · diarrhoea · involuntary movements (including nystagmus) · visual disturbances
  - **Rare** Abdominal pain · aggression · agitation · anorexia · cardiac conduction disorders · confusion · delayed multi-organ hypersensitivity disorder · depression · dysarthria · hallucinations · hepatitis · hypertension · jaundice · lymph node enlargement · muscle weakness · paraesthesia · peripheral neuropathy · restlessness · systemic lupus erythematosus · vanishing bile duct syndrome
  - **Very rare** Arthralgia · muscle spasm · acne · alopecia · alterations in skin pigmentation · angle-closure glaucoma · aseptic meningitis · AV block with syncope · circulatory collapse · conjunctivitis · dyspnoea · exacerbation of coronary artery disease · galactorrhoea · gynaecomastia · hearing disorders · hepatic failure · hirsutism · hypercholesterolaemia · impaired male fertility · interstitial nephritis · muscle pain · neuroleptic malignant syndrome · osteomalacia · osteoporosis · pancreatitis · photosensitivity · pneumonia · pemphigus · psychosis · pulmonary hypersensitivity · purpura · renal failure · sexual dysfunction · Stevens-Johnson syndrome · stomatitis · sweating · taste disturbance · thromboembolism · thrombophlebitis · toxic epidermal necrolysis · urinary frequency · urinary retention

**Frequency not known** Suicidal ideation

**SIDE-EFFECTS, FURTHER INFORMATION** Some side-effects (such as headache, ataxia, drowsiness, nausea, vomiting, blurring of vision, dizziness, unsteadiness, and allergic skin reactions) are dose-related, and may be dose-limiting. These side-effects are more common at the start of treatment and in the elderly. Patients should be offered a modified-release preparation to reduce the risk of side-effects; altering the timing of medication may also be beneficial.

**Overdose** For details on the management of poisoning, see Active elimination techniques, under Emergency treatment of poisoning p. 1204.

- **ALLERGY AND CROSS-SENSITIVITY** Antiepileptic hypersensitivity syndrome associated with carbamazepine. See under Epilepsy p. 286 for more information. Caution—cross-sensitivity reported with oxcarbazepine and with phenytoin.

- **PREGNANCY** Doses should be adjusted on the basis of plasma-drug concentration monitoring.

- **BREAST FEEDING** Amount probably too small to be harmful. Monitor infant for possible adverse reactions.

- **HEPATIC IMPAIRMENT** Metabolism impaired in advanced liver disease.

- **RENAL IMPAIRMENT** Use with caution.

- **PRE-TREATMENT SCREENING** Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

- **MONITORING REQUIREMENTS**
  - Plasma concentration for optimum response 4–12 mg/litre (20–50 micromol/litre) measured after 1–2 weeks
  - Manufacturer recommends blood counts and hepatic and renal function tests (but evidence of practical value uncertain).

- **TREATMENT CESSATION** When stopping treatment with carbamazepine for bipolar disorder, reduce the dose gradually over a period of at least 4 weeks.

- **DIRECTIONS FOR ADMINISTRATION** Tegretol® Prolonged Release tablets can be halved but should not be chewed.
Elsicarbazepine acetate

- **INDICATIONS AND DOSE**
  Adjunctive treatment in adults with focal seizures with or without secondary generalisation
  - **BY MOUTH**
    - Adult: Initially 400 mg once daily for 1–2 weeks, then increased to 800 mg once daily (max. per dose 1.2 g)

- **CONTRA-INDICATIONS**
  Second- or third-degree AV block

- **CAUTIONS**
  Elderly • hyponatraemia • PR-interval prolongation

- **INTERACTIONS**
  Appendix 1 (elsicarbazepine). Caution—avoid concomitant administration of drugs that prolong PR interval.

- **SIDE-EFFECTS**
  - Common or very common: Dizziness, drowsiness, fatigue, gastro-intestinal disturbances, headache, impaired coordination, rash • tremor, visual disturbances
  - Uncommon: Agitation, alopecia, anaemia, appetite changes, bradycardia, chest pain, chills, confusion, convulsions, dehydration, dry mouth, dysaesthesia, dysarthria, dystonia, electrolyte imbalance, epistaxis, gingival hyperplasia, hyperactivity, hypertension, hyponatraemia, hypotension, hypothyroidism, impaired memory, insomnia • liver disorders, malaise, menstruation changes, mood changes, movement disorders, myalgia, nail disorder, nocturia, nystagnus, palpitation, parosmia, peripheral neuropathy, peripheral oedema, psychosis, stomatitis, sweating, taste disturbance, tinnitus, urinary tract infection, weight changes
  - Very rare: Leucopenia, pancreatitis, thrombocytopenia

- **Frequency not known**
  PR-interval prolongation, suicidal ideation

- **ALLERGY AND CROSS-SENSITIVITY**
  Antiepileptic hypersensitivity syndrome theoretically associated with elsicarbazepine. See under Epilepsy p. 286 for more information.

- **PREGNANCY**
  The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **HEPATIC IMPAIRMENT**
  Avoid in severe impairment—no information available.

- **RENAL IMPAIRMENT**
  Reduce initial dose to 400 mg every other day for 2 weeks then 400 mg once daily if eGFR 30–60 mL/minute/1.73 m², adjusted according to response. Avoid if eGFR less than 30 mL/minute/1.73 m².

- **PRE-TREATMENT SCREENING**
  Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

- **MONITORING REQUIREMENTS**
  Monitor plasma-sodium concentration in patients at risk of hyponatraemia and discontinue treatment if hyponatraemia occurs.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  Scottish Medicines Consortium (SMC) Decisions
  The Scottish Medicines Consortium has advised (October 2010) that elsicarbazepine (Zebinix®) is accepted for restricted use within NHS Scotland as adjunctive therapy in adults with focal seizures with or without secondary generalisation. It is restricted for use in refractory epilepsy.
Ethosuximide

**INDICATIONS AND DOSE**

**Absence seizures | Atypical absence seizures (adjunct)| Myoclonic seizures**

- **BY MOUTH**
  - Child 1 month–5 years: Initially 5 mg/kg twice daily (max. per dose 125 mg), dose to be increased every 5–7 days; maintenance 10–20 mg/kg twice daily (max. per dose 500 mg), total daily dose may rarely be given in 3 divided doses.
  - Child 6–17 years: Initially 250 mg twice daily, then increased in steps of 250 mg every 5–7 days; usual dose 500–750 mg twice daily, increased if necessary up to 1 g twice daily.
  - Adult: Initially 500 mg daily in 2 divided doses, then increased in steps of 250 mg every 5–7 days; usual dose 1–1.5 g daily in 2 divided doses, increased if necessary up to 2 g daily.

**CAUTIONS** Avoid in acute porphyrias p. 930.

**INTERACTIONS** → Appendix 1 (ethosuximide).

**SIDE-EFFECTS**
- Common or very common: Anorexia · abdominal pain · diarrhoea · gastro-intestinal disturbances · nausea · vomiting · weight loss.
- Uncommon: Agitation · ataxia · dizziness · drowsiness · euphoria · fatigue · headache · hiccup · impaired concentration · irritability.
- Rare: Depression · dyskinesia · gingival hypertrophy · increased libido · myopia · photophobia · psychosis · rash · sleep disturbances · tongue swelling · vaginal bleeding.
- Frequency not known: Agranulocytosis · aplastic anaemia · blood disorders · hyperactivity · increase in seizure frequency · leucopenia · pancytopenia · Stevens-Johnson syndrome · suicidal ideation · systemic lupus erythematosus.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Blood disorders: Blood counts required if features of infection.
- PREGNANCY: The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.
- BREAST FEEDING: Present in milk. Hyperexcitability and sedation reported.
- HEPATIC IMPAIRMENT: Use with caution.
- RENAL IMPAIRMENT: Use with caution.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Ethosuximide for preventing seizures www.medicinesforchildren.org.uk/ethosuximide-for-preventing-seizures

Blood disorders: Patients or their carers should be told how to recognise signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, mouth ulcers, bruising, or bleeding develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 8

- Zebinix (Esai Ltd)
- Eslicarbazine acetate 800 mg Zebinix 800mg tablets | 30 tablet £136.00

**Fosphenytoin sodium**

**INDICATIONS AND DOSE**

**Status epilepticus**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 20 mg(PE)/kg, dose to be administered at a rate of 100–150 mg(PE)/minute, then 4–5 mg(PE)/kg daily in 1–2 divided doses, dose to be administered at a rate of 50–100 mg(PE)/minute, dose to be adjusted according to response and trough plasma-phenytoin concentration.
  - Elderly: Consider 10–25% reduction in dose or infusion rate.

**Prophylaxis or treatment of seizures associated with neurosurgery or head injury**

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 10–15 mg(PE)/kg, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, then 4–5 mg(PE)/kg daily in 1–2 divided doses, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, dose to be adjusted according to response and trough plasma-phenytoin concentration.
  - Elderly: Consider 10–25% reduction in dose or infusion rate.

**Temporary substitution for oral phenytoin**

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Same dose and same dosing frequency as oral phenytoin therapy, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute.
  - Elderly: Consider 10–25% reduction in dose or infusion rate.

**DOSE EQUIVALENCE AND CONVERSION**

Doses are expressed as phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg.

**UNLICENSED USE** Fosphenytoin sodium doses in BNF may differ from those in product literature.

**CONTRA-INDICATIONS** Acute porphyrias p. 930 · second-degree heart block · sino-atrial block · sinus bradycardia · Stokes-Adams syndrome · third-degree heart block.

**CAUTIONS** Heart failure · hypotension · injection solutions alkaline (irritant to tissues) · respiratory depression · resuscitation facilities must be available.

**INTERACTIONS** → Appendix 1 (fosphenytoin).

**SIDE-EFFECTS**
- Common or very common: Alterations in respiratory function · arrhythmias · asthenia · cardiovascular collapse · cardiovascular depression (particularly if injection too...
rapid) · chills · CNS depression (particularly if injection too rapid) · dry mouth · dysarthria · echymosis · euphoria · hypotension · incoordination · pruritus · respiratory arrest · taste disturbance · tinnitus · vasodilatation · visual disturbances

- **Uncommon** Decreased reflexes · hypoacusis · hypoaesthesia · increased reflexes · muscle spasm · muscle weakness · pain · stupor

- **Frequency not known** Confusion · extrapyramidal disorder · hyperglycaemia · purple glove syndrome · tonic seizures · twitching

**SIDE-EFFECTS, FURTHER INFORMATION**

- Cardiovascular reactions Intravenous infusion of fosphenytoin has been associated with severe cardiovascular reactions including asystole, ventricular fibrillation, and cardiac arrest. Hypotension, bradycardia, and heart block have also been reported. The following are recommended:
  - monitor heart rate, blood pressure, and respiratory function for duration of infusion;
  - observe patient for at least 30 minutes after infusion;
  - if hypotension occurs, reduce infusion rate or discontinue;
  - reduce dose or infusion rate in elderly, and in renal or hepatic impairment.

- **ALLERGY AND CROSS-SENSITIVITY** Cross-sensitivity reported with carbamazepine.

- **PREGNANCY** Changes in plasma-protein binding make interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **BREAST FEEDING** Small amounts present in milk, but not known to be harmful.

- **HEPATIC IMPAIRMENT** Consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus).

- **RENAL IMPAIRMENT** Consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus).

- **PRE-TREATMENT SCREENING** HLA-B*1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome).

- **MONITORING REQUIREMENTS**
  - Manufacturer recommends blood counts (but evidence of practical value uncertain).
  - With intravenous use Monitor heart rate, blood pressure, ECG, and respiratory function for during infusion.

- **DIRECTIONS FOR ADMINISTRATION** For intermittent intravenous infusion (Pro–Epanutin ®), give in Glucose 5% or Sodium chloride 0.9%; dilute to a concentration of 1.5–25 mg (phenytoin sodium equivalent (PE))/mL.

- **PRESCRIBING AND DISPENSING INFORMATION** Prescriptions for fosphenytoin sodium should state the dose in terms of phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**ELECTROLYTES:** May contain Phosphate

- **Pro–Epanutin** (Pfizer Ltd)
  - Fosphenytoin sodium 75 mg per 1 ml Pro-Epanutin 750mg/10ml concentrate for solution for injection vials | 10 vial £40.00 (Hospital only)

**INDICATIONS AND DOSE**

**Adjunctive treatment of focal seizures with or without secondary generalisation**

- **BY MOUTH**
  - Child 6–11 years: 10 mg/kg once daily (max. per dose 300 mg) on day 1, then 10 mg/kg twice daily (max. per dose 300 mg) on day 2, then 10 mg/kg 3 times a day (max. per dose 300 mg) on day 3; usual dose 25–35 mg/kg daily in 3 divided doses, some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate. Daily dose maximum to be given in 3 divided doses; maximum 70 mg/kg per day.
  - Child 12–17 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day), some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate.
  - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day).

**Monotherapy for focal seizures with or without secondary generalisation**

- **BY MOUTH**
  - Child 6–11 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day), some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate.
  - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day).

**Peripheral neuropathic pain**

- **BY MOUTH**
  - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; maximum 3.6 g per day.

**Migraine prophylaxis**

- **BY MOUTH**
  - Adult: Initially 300 mg daily, then increased to up to 2.4 g daily in divided doses, adjusted according to response.

**UNLICENSED USE**

- In children Not licensed for use in children under 6 years. Not licensed at doses over 50 mg/kg daily in children under 12 years.
In adults Not licensed for migraine prophylaxis.

**IMPORTANT SAFETY INFORMATION**
The levels of propylene glycol, acetylsalicylic acid and saccharin sodium may exceed the recommended WHO daily intake limits if high doses of gabapentin oral solution (Rossmorn) are given to adolescents or adults with low body-weight (30–50 kg)—consult product literature.

**CAUTIONS**
- Diabetes mellitus
- Elderly
- High doses of oral solution in adolescents and adults with low body-weight
- History of psychotic illness
- Mixed seizures (including absences)

**INTERACTIONS**
- Appendix 1 (gabapentin).

**SIDE-EFFECTS**
- **Common or very common**
  - Abdominal pain
  - Abnormal reflexes
  - Abnormal thoughts
  - Acne
  - Anemia
  - Anorexia
  - Anxiety
  - Arthralgia
  - Ataxia
  - Confusion
  - Constipation
  - Convulsions
  - Cough
  - Depression
  - Diarrhea
  - Dizziness
  - Drowsiness
  - Dry mouth
  - Dry throat
  - Dyspepsia
  - Dyspnoea
  - Emotional lability
  - Fever
  - Flatulence
  - Flu syndrome
  - Gingivitis
  - Headache
  - Hostility
  - Hypertension
  - Increased appetite
  - Increased sweating
  - Insomnia
  - Leucopenia
  - Malaise
  - Movement disorders
  - Myalgia
  - Nausea
  - Nervousness
  - Nystagmus
  - Oedema
  - Paraesthesia
  - Pharyngitis (in adults)
  - Pruritus
  - Rash
  - Rheumatism
  -Speech disorder
  - Tremor
  - Twitching
  - Vasodilatation
  - Vertigo
  - Visual disturbances
  - Vomiting
  - Weight gain

- **Uncommon**
  - Palpitations

- **Frequency not known**
  - Acute renal failure
  - Alopecia
  - Blood glucose fluctuations in patients with diabetes
  - Breast hypertrophy
  - Gynaecomastia
  - Hallucinations
  - Hepatitis
  - Hypersensitivity syndrome
  - Incontinence
  - Pancreatitis
  - Stevens-Johnson syndrome
  - Suicidal ideation
  - Suicidal ideation
  - Nervousness
  - Nystagmus
  - Oedema
  - Paraesthesia
  - Pharyngitis (in adults)
  - Pruritus
  - Rash
  - Rheumatism
  - Speech disorder
  - Tremor
  - Twitching
  - Vasodilatation
  - Vertigo
  - Visual disturbances
  - Vomiting
  - Weight gain

**PREGNANCY**
The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING**
Present in milk—manufacturer advises use only if potential benefit outweighs risk.

**RENAL IMPAIRMENT**
- In adults
  - Reduce dose to 0.6–1.8 g daily in 3 divided doses if eGFR 50–80 mL/minute/1.73 m². Reduce dose to 300–900 mg daily in 3 divided doses if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 300 mg on alternate days (up to max. 600 mg daily) in 3 divided doses if eGFR 15–30 mL/minute/1.73 m². Reduce dose to 300 mg on alternate days (up to max. 600 mg daily) in 3 divided doses if eGFR less than 15 mL/minute/1.73 m²—consult product literature.
- In children
  - Reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m²; consult product literature.

**EFFECT ON LABORATORY TESTS**
False positive readings with some urinary protein tests.

**DIRECTIONS FOR ADMINISTRATION**
Capsules can be opened but the bitter taste is difficult to mask.

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Gabapentin for preventing seizures www.medicinesforchildren.org.uk/gabapentin-for-preventing-seizures

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 3, 5, 8

- **Gabapentin (Non-proprietary)**
  - Gabapentin 600 mg Gabapentin 600mg tablets | 100 tablet £106.00 DT price = £8.50
  - Gabapentin 800 mg Gabapentin 800mg tablets | 100 tablet £138.13 DT price = £28.77
  - **Neurontin (Pfizer Ltd)**
    - Gabapentin 600 mg Neurontin 600mg tablets | 100 tablet £84.80 DT price = £8.50
    - Gabapentin 800 mg Neurontin 800mg tablets | 100 tablet £98.13 DT price = £28.77

**Capsule**

CAUTIONARY AND ADVISORY LABELS 3, 5, 8

- **Gabapentin (Non-proprietary)**
  - Gabapentin 100 mg Gabapentin 100mg capsules | 100 capsule £18.29 DT price = £2.00
  - Gabapentin 300 mg Gabapentin 300mg capsules | 100 capsule £42.40 DT price = £2.91
  - Gabapentin 400 mg Gabapentin 400mg capsules | 100 capsule £49.06 DT price = £4.44
  - **Neurontin (Pfizer Ltd)**
    - Gabapentin 100 mg Neurontin 100mg capsules | 100 capsule £18.29 DT price = £2.00
    - Gabapentin 300 mg Neurontin 300mg capsules | 100 capsule £42.40 DT price = £2.91
    - Gabapentin 400 mg Neurontin 400mg capsules | 100 capsule £49.06 DT price = £4.44

**Oral solution**

CAUTIONARY AND ADVISORY LABELS 3, 5, 8

EXCIPIENTS: May contain Propylene glycol

ELECTROLYTES: May contain Potassium, Sodium

- **Gabapentin (Non-proprietary)**
  - Gabapentin 50 mg per 1 ml Neurontin 250mg/5ml oral solution | 470 ml (P) no price available
  - Gabapentin 50mg/ml oral solution sugar free sugar-free | 150 ml (P) £90.00 DT price = £59.00

**Lacosamide**

**INDICATIONS AND DOSE**
Adjunctive treatment of focal seizures with or without secondary generalisation

- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - Child 16–17 years: Initially 50 mg twice daily, infusion to be administered over 15–60 minutes (for up to 5 days), then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals; maintenance 100 mg twice daily (max. per dose 200 mg twice daily)
  - Adult: Initially 50 mg twice daily, infusion to be administered over 15–60 minutes (for up to 5 days), then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals; maintenance 100 mg twice daily (max. per dose 200 mg twice daily)

**Adjunctive treatment of focal seizures with or without secondary generalisation (alternative loading dose regimen when it is necessary to rapidly attain therapeutic plasma concentrations) (under close medical supervision)**

- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - Child 16–17 years: Loading dose 200 mg, infusion to be administered over 15–60 minutes (for up to 5 days), followed by maintenance 100 mg twice daily, to be given 12 hours after initial dose, then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals
  - Adult: Loading dose 200 mg, infusion to be administered over 15–60 minutes (for up to 5 days), followed by maintenance 100 mg twice daily, to be given 12 hours after initial dose, then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals

**CONTRA-INDICATIONS**
Second- or third-degree AV block
Epilepsy and other seizure disorders 297

Lamotrigine

- INDICATIONS AND DOSE

Monotherapy of focal seizures | Monotherapy of primary and secondary generalised tonic-clonic seizures | Monotherapy of seizures associated with Lennox-Gastaut syndrome

- BY MOUTH

  - Child 2-11 years: Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; increased if necessary up to 500 mg daily, dose titration should be repeated if restarting after interval of more than 5 days
  - Adult: Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; increased if necessary up to 500 mg daily, dose titration should be repeated if restarting after interval of more than 5 days

Adjuvant therapy of focal seizures with valproate | Adjuvant therapy of primary and secondary generalised tonic-clonic seizures with valproate | Adjuvant therapy of seizures associated with Lennox-Gastaut syndrome with valproate

- BY MOUTH

  - Child 2-11 years (body-weight up to 13 kg): Initially 2 mg once daily on alternate days for first 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day
  - Child 2-11 years (body-weight 13 kg and above): Initially 150 micrograms/kg once daily for 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day
  - Child 12-17 years: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days
  - Adult: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days

Hepatic impairment

- Titrate with caution in mild to severe liver impairment.
- Manufacturer advises avoid use in children with severe hepatic impairment.

Breast feeding

- Consult product literature for loading dose if breast feeding.

INTERACTIONS

- Flavours of syrup may include strawberry.

DIRECTIONS FOR ADMINISTRATION

- With intravenous use in children For intravenous infusion, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9%.
- With intravenous use in adults For intravenous infusion (Vimpat®), give intravenously in Glucose 5%, Sodium Chloride 0.9%. May be administered undiluted.
- Prescribing and dispensing information

PATIENT AND CARER ADVICE

- Medicines for Children leaflet: Lacosamide for preventing seizures www.medicinesforchildren.org.uk/lacosamide-for-preventing-seizures

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (January 2009) that lacosamide (Vimpat®) is accepted for restricted use within NHS Scotland as adjunctive treatment for focal seizures with or without secondary generalisation in patients from 16 years. It is restricted for specialist use in refractory epilepsy.

MEDIcular FORMS

- There can be variation in the licensing of different medicines containing the same drug.

Tablet

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 8</th>
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<tbody>
<tr>
<td>Vimpat (UCB Pharma Ltd)</td>
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<tr>
<td>Lacosamide 50 mg</td>
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<td>Lacosamide 100 mg</td>
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Lacosamide 150 mg Vimpat 150mg tablets | 14 tablet £32.44 |
| 56 tablet £129.74 DT price = £129.74 |
Lacosamide 200 mg Vimpat 200mg tablets | 56 tablet £144.16 DT price = £144.16

Oral solution

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<tr>
<td>Vimpat (UCB Pharma Ltd)</td>
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<tr>
<td>Lacosamide 10 mg per 1 ml</td>
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<tr>
<td>200 ml £25.74 DT price = £25.74</td>
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Solution for infusion

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<td>Vimpat (UCB Pharma Ltd)</td>
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Adju*vent therapy of focal seizures (with enzyme inducing drugs) without valproate | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (with enzyme inducing drugs) without valproate | Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (with enzyme inducing drugs) without valproate

» BY MOUTH

- Child 2–11 years: Initially 300 micrograms/kg twice daily for 14 days, then 600 micrograms/kg twice daily for further 14 days, then increased in steps of up to 1 mg/kg every 7–14 days; maintenance 5–15 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 400 mg per day
- Child 12–17 years: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 200–400 mg daily in 2 divided doses, increased if necessary up to 700 mg daily, dose titration should be repeated if restarting after interval of more than 5 days
- Adult: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 200–400 mg daily in 2 divided doses, increased if necessary up to 700 mg daily, dose titration should be repeated if restarting after interval of more than 5 days

Adju*vent therapy of focal seizures (without enzyme inducing drugs) without valproate | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (without enzyme inducing drugs) without valproate | Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (without enzyme inducing drugs) without valproate

» BY MOUTH

- Child 2–11 years: Initially 300 micrograms/kg daily in 1–2 divided doses for 14 days, then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, then increased in steps of up to 600 micrograms/kg every 7–14 days; maintenance 1–10 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day
- Child 12–17 years: Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days
- Adult: Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days

Monotherapy or adju*vent therapy of bipolar disorder (without enzyme inducing drugs) without valproate

» BY MOUTH

- Adult: Initially 25 mg once daily for 14 days, then 50 mg daily in 1–2 divided doses for further 14 days, then 100 mg daily in 1–2 divided doses for further 7 days; maintenance 200 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 400 mg per day

Adju*vent therapy of bipolar disorder with valproate

» BY MOUTH

- Adult: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then 50 mg daily in 1–2 divided doses for further 7 days; maintenance 100 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day

Adju*vent therapy of bipolar disorder (with enzyme inducing drugs) without valproate

» BY MOUTH

- Adult: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased to 100 mg twice daily for further 7 days, then increased to 150 mg twice daily for further 7 days; maintenance 200 mg twice daily, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days

INTERACTIONS

- Common or very common Blurred vision • aggression • agitation • arthralgia • ataxia • back pain • diarrhoea • diplopia • dizziness • drowsiness • dry mouth • headache • insomnia • nausea • nystagmus • rash • tremor • vomiting
- Rare Conjunctivitis
- Very rare Anaemia • blood disorders • confusion • exacerbation of Parkinson’s disease (in adults) • hallucination • hepatic failure • hypersensitivity syndrome • increase in seizure frequency • leucopenia • lupus erythematosus-like reactions • movement disorders • pancytopenia • thrombocytopenia • unsteadiness
- Frequency not known Aseptic meningitis • suicidal ideation

SIDE-EFFECTS, FURTHER INFORMATION

- SkM reactions Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have developed (especially in children); most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.
- ALLERGY AND CROSS-SENSITIVITY Antiepileptic hypersensitivity syndrome associated with lamotrigine. See under Epilepsy p. 286 for more information.
- PREGNANCY Doses should be adjusted on the basis of plasma–drug concentration monitoring.
- BREAST FEEDING Present in milk, but limited data suggest no harmful effect on infant.
- HEPATIC IMPAIRMENT Halve dose in moderate impairment. Quarter dose in severe impairment.
Levetiracetam

**INDICATIONS AND DOSE**

**Monotherapy of focal seizures with or without secondary generalisation**

- **BY MOUTH**, or **BY INTRAVENOUS INFUSION**
  - Child 16-17 years: Initially 250 mg once daily for 1 week, then increased to 250 mg twice daily, then increased in steps of 250 mg twice daily (max. per dose 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks.
  - Adult: Initially 250 mg once daily for 1–2 weeks, then increased to 250 mg twice daily, then increased in steps of 250 mg twice daily (max. per dose 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks.

**Adjunctive therapy of focal seizures with or without secondary generalisation**

- **BY MOUTH**
  - Child 1–5 months: Initially 7 mg/kg once daily, then increased in steps of up to 7 mg/kg twice daily (max. per dose 21 mg/kg twice daily), dose to be increased every 2 weeks.
  - Child 6 months–17 years (body-weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks.
  - Child 12–17 years (body-weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks.
  - Adult: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks.

- **BY INTRAVENOUS INFUSION**
  - Child 4–17 years (body-weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks.
  - Child 12–17 years (body-weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks.
  - Adult: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks.

**Adjunctive therapy of myoclonic seizures and tonic-clonic seizures**

- **BY MOUTH**, or **BY INTRAVENOUS INFUSION**
  - Child 12–17 years (body-weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks.
  - Child 12–17 years (body-weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks.
  - Adult: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks.

**UNLICENSED USE**

- In adults Leviteracetam doses in BNF may differ from those in product literature.

- With oral use in children *Granules* not licensed for use in children under 6 years, for initial treatment in children with body-weight less than 25 kg, or for the administration of doses below 250 mg.

**INTERACTIONS** → Appendix 1 (leviteracetam).
PATIENT AND CARER ADVICE

With oral use

DIRECTIONS FOR ADMINISTRATION

In children

BREAST FEEDING
Present in milk—manufacturer advises avoid.

HEPATIC IMPAIRMENT
In adults Halve dose in severe hepatic impairment if eGFR less than 60 mL/minute/1.73 m². In children Halve dose in severe hepatic impairment if estimated glomerular filtration rate less than 60 mL/minute/1.73 m².

RENAL IMPAIRMENT
In children Reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m² (consult product literature). In adults Maximum 2 g daily if eGFR 50–80 mL/minute/1.73 m². Maximum 1.5 g daily if eGFR 30–50 mL/minute/1.73 m². Maximum 1 g daily if eGFR less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
With intravenous use For intravenous infusion (Keppra®), dilute requisite dose with at least 100 mL glucose 5% or Sodium Chloride 0.9%; give over 15 minutes.

With oral use For administration of oral solution, requisite dose may be diluted in a glass of water.

PRESCRIBING AND DISPENSING INFORMATION
If switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the intravenous dose should be the same as the established oral dose.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Levetiracetam for preventing seizures www.medicinesforchildren.org.uk/levetiracetam-for-preventing-seizures

Levetiracetam 750 mg Keppra 750mg tablets | 60 tablet £84.02 DT price = £4.02
Levetiracetam 1 gram Keppra 1g tablets | 60 tablet £95.34 DT price = £5.61

- Matever (Aspire Pharma Ltd)
Levetiracetam 250 mg Matever 250mg tablets | 60 tablet £28.01 DT price = £2.10
Levetiracetam 500 mg Matever 500mg tablets | 60 tablet £49.32 DT price = £2.76
Levetiracetam 750 mg Matever 750mg tablets | 60 tablet £94.02 DT price = £3.02
Levetiracetam 1 gram Matever 1g tablets | 60 tablet £95.34 DT price = £5.61

Granules

Desitrend (Desitin Pharma Ltd)
Levetiracetam 250 mg Desitrend 250mg granules sachets sugar-free £5.86 60 sachet £22.41
Levetiracetam 500 mg Desitrend 500mg granules sachets sugar-free £12.34 60 sachet £49.16

- Matever (Aspire Pharma Ltd)
Levetiracetam 250 mg Matever 250mg tablets | 60 tablet £28.01 DT price = £2.10
Levetiracetam 500 mg Matever 500mg tablets | 60 tablet £49.32 DT price = £2.76
Levetiracetam 750 mg Matever 750mg tablets | 60 tablet £94.02 DT price = £3.02
Levetiracetam 1 gram Matever 1g tablets | 60 tablet £95.34 DT price = £5.61

- Matever (Aspire Pharma Ltd)
Levetiracetam 250 mg Matever 250mg tablets | 60 tablet £28.01 DT price = £2.10
Levetiracetam 500 mg Matever 500mg tablets | 60 tablet £49.32 DT price = £2.76
Levetiracetam 750 mg Matever 750mg tablets | 60 tablet £94.02 DT price = £3.02
Levetiracetam 1 gram Matever 1g tablets | 60 tablet £95.34 DT price = £5.61

Oxcarbazepine

INDICATIONS AND DOSE

Moxonofor for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures

- BY MOUTH
Child 6–17 years: Initially 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response, dose to be adjusted at weekly intervals; maximum 46 mg/kg per day
Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

Adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures

- BY MOUTH
Child 6–17 years: Initially 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response,
dose to be adjusted at weekly intervals; maintenance
15 mg/kg twice daily; maximum 46 mg/kg per day
▶ Adult: Initially 300 mg twice daily, then increased in
steps of up to 600 mg daily, adjusted according to
response, dose to be adjusted at weekly intervals; usual
dose 0.6–2.4 g daily in divided doses

Treatment of primary generalised tonic-clonic seizures
▶ BY MOUTH
▶ Adult: Initially 300 mg twice daily, then increased in
steps of up to 600 mg daily, adjusted according to
response, dose to be increased at weekly intervals; usual
dose 0.6–2.4 g daily in divided doses

DOSE ADJUSTMENTS DUE TO INTERACTIONS
In adjunctive therapy, the dose of concomitant
antiepileptics may need to be reduced when using high
doses of oxcarbazepine.

● UNLICENSED USE
Not licensed for the treatment of primary
generalised tonic-clonic seizures.

● CAUTIONS
Avoid in acute porphyrias p. 930 • cardiac
conduction disorders • heart failure • hyponatraemia

● INTERACTIONS ➔ Appendix 1 (oxcarbazepine).

● SIDE-EFFECTS
▶ Common or very common
Abdominal pain • acne • agitation
• alopecia • amnesia • anemia • ataxia • confusion
• constipation • depression • diarrhoea • diplopia • dizziness
• drowsiness • headache • hyponatraemia • impaired
concentration • nausea •ystagmus • rash • tremor • visual
disorders • vomiting
▶ Uncommon
Leucopenia • urticaria
▶ Very rare
Arrhythmias • atrioventricular block • hepatitis
• multi-organ hypersensitivity disorders • pancreatitis
• Stevens-Johnson syndrome • systemic lupus
erythematosus • thrombocytopenia • toxic epidermal
necrolysis

Frequency not known
Aplastic anaemia • bone marrow
depression • hypertension • hypothyroidism • neutropenia
• osteoporotic bone disorders • pancytopenia • suicidal
ideation

● ALLERGY AND CROSS-SENSITIVITY
Caution in patients with
hypersensitivity to carbamazepine. Antiepileptic
hypersensitivity syndrome associated with oxcarbazepine.
See under Epilepsy p. 286 for more information.

● PREGNANCY
The dose should be monitored carefully
during pregnancy and after birth, and adjustments made
on a clinical basis.

● BREAST FEEDING
Amount probably too small to be
harmful but manufacturer advises avoid.

● HEPATIC IMPAIRMENT
Caution in severe impairment—no
information available.

● RENAL IMPAIRMENT
▶ In adults
Halve initial dose if eGFR less than
30 ml/minute/1.73 m²; increase according to response at
intervals of at least 1 week.
▶ In children
Halve initial dose if estimated glomerular
filtration rate less than 30 ml/minute/1.73 m², increase
according to response at intervals of at least 1 week.

PRE-TREATMENT SCREENING
Test for HLA-B*1502 allele in
individuals of Han Chinese or Thai origin (avoid unless no
alternative—risk of Stevens-Johnson syndrome in
presence of HLA-B*1502 allele).

MONITORING REQUIREMENTS
▶ Monitor plasma-sodium concentration in patients at risk of
hyponatraemia.
▶ Monitor body-weight in patients with heart failure.

PRESCRIBING AND DISPENSING INFORMATION
Patients may need to be maintained on a specific manufacturer’s
branded or generic oxcarbazepine product.
Switching between formulations Care should be taken when
switching between oral formulations. The need for
continued supply of a particular manufacturer’s product
should be based on clinical judgement and consultation
with the patient or their carer, taking into account factors
such as seizure frequency and treatment history.

● PATIENT AND CARER ADVICE
Medicines for Children: Oxcarbazepine for preventing
seizures www.medicinesforchildren.org.uk/oxcarbazepine-for
preventing-seizures
Blood, hepatic, or skin disorders Patients or their carers
should be told how to recognise signs of blood, liver, or
skin disorders, and advised to seek immediate medical
attention if symptoms such as lethargy, confusion,
muscular twitching, fever, rash, blistering, mouth ulcers,
bruising, or bleeding develop.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines
containing the same drug. Forms available from special-order
manufacturers include: oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 3, 8
▶ Oxcarbazepine (Non-proprietary)
Oxcarbazepine 150 mg
Oxcarbazepine 150mg tablets | 50
tablet [Posm] £11.14 DT price = £8.48
Oxcarbazepine 300 mg
Oxcarbazepine 300mg tablets | 50
tablet [Posm] £22.61 DT price = £16.02
Oxcarbazepine 600 mg
Oxcarbazepine 600mg tablets | 50
tablet [Posm] £45.19 DT price = £38.82
▶ Trileptal (Novartis Pharmaceuticals UK Ltd)
Oxcarbazepine 150 mg
Trileptal 150mg tablets | 50 tablet [Posm]
£12.24 DT price = £8.48
Oxcarbazepine 300 mg
Trileptal 300mg tablets | 50 tablet [Posm]
£24.48 DT price = £16.02
Oxcarbazepine 600 mg
Trileptal 600mg tablets | 50 tablet [Posm]
£48.96 DT price = £38.82

Oral suspension
CAUTIONARY AND ADVISORY LABELS 3, 8
EXCipients: May contain Propylene glycol
▶ Trileptal (Novartis Pharmaceuticals UK Ltd)
Oxcarbazepine 60 mg per 1 ml
Trileptal 60mg/ml oral suspension
sugar-free | 250 ml [Posm] £48.96 DT price = £48.96

Perampanel

● INDICATIONS AND DOSE
Adjunctive treatment of focal seizures with or without
secondary generalised seizures
▶ BY MOUTH
▶ Child 12–17 years: Initially 2 mg once daily, dose to be
taken before bedtime, then increased, if tolerated, in
steps of 2 mg at intervals of at least every 2 weeks,
adjusted according to response; maintenance 4–8 mg
once daily; maximum 12 mg per day
▶ Adult: Initially 2 mg once daily, dose to be taken before
bedtime, then increased, if tolerated, in steps of 2 mg
at intervals of at least every 2 weeks, adjusted
according to response; maintenance 4–8 mg once
daily; maximum 12 mg per day

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Titrate at intervals of at least 1 week with concomitant
carbamazepine, fosphenytoin, oxcarbazepine, or
phenytoin.

● INTERACTIONS ➔ Appendix 1 (perampanel).

● SIDE-EFFECTS
Aggression • anxiety • ataxia • back pain •
blurred vision • changes in appetite • confusion • diplopia •
dizziness • drowsiness • dysarthria • gait disturbance •
irritability • malaise • nausea • suicidal behaviour • suicidal
ideation • vertigo • weight increase

● PREGNANCY
Manufacturer advises avoid.

The dose should be monitored carefully during
pregnancy and after birth, and adjustments made on a
clinical basis.
### 302 Epilepsy and other seizure disorders

**Breastfeeding** Avoid—present in milk in *animal* studies.

**Hepatic Impairment** Increase at intervals of at least 2 weeks, up to max. 8 mg daily in mild or moderate impairment. Avoid in severe impairment.

**Renal Impairment** Avoid in moderate or severe impairment.

**Prescribing and dispensing information**

Switching between formulations: Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients may need to be maintained on a specific manufacturer’s branded or generic perampanel product.

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**Cautionary and advisory labels** 3, 8, 25

- Fycompa (Esai Ltd).

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### Phenytoin

**Indications and dose**

**Tonic-clonic seizures | Focal seizures | Prevention and treatment of seizures during or following neurosurgery or severe head injury**

- **By mouth**
  - Child 1 month–11 years: Initially 1.5–2.5 mg/kg twice daily, then adjusted according to response to 2.5–5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), dose also adjusted according to plasma-phenytoin concentration; maximum 300 mg per day
  - Child 12–17 years: Initially 75–150 mg twice daily, then adjusted according to response to 150–200 mg twice daily (max. per dose 300 mg twice daily), dose also adjusted according to plasma-phenytoin concentration
  - Adult: Initially 3–4 mg/kg daily, alternatively 150–300 mg once daily, alternatively 150–300 mg daily in 2 divided doses, alternatively maintenance 200–500 mg daily, to be taken preferably with or after food, dose to be increased gradually as necessary (with plasma-phenytoin concentration monitoring), exceptionally higher doses may be used

**Status epilepticus | Acute symptomatic seizures associated with head trauma or neurosurgery**

- Initially by slow intravenous injection, or by intravenous infusion
  - Child 1 month–11 years: Loading dose 20 mg/kg, then (by slow intravenous injection or by intravenous infusion) 2.5–5 mg/kg twice daily, to be given with blood pressure and ECG monitoring
  - Child 12–17 years: Loading dose 20 mg/kg, then (by intravenous infusion or by slow intravenous injection) up to 100 mg 3–4 times a day, to be given with blood pressure and ECG monitoring
  - Adult: Loading dose 20 mg/kg (max. per dose 2 g), to be given at a rate not exceeding 1 mg/kg/minute (max. 50 mg per minute), to be given with blood pressure and ECG monitoring, then (by intravenous infusion or by slow intravenous injection or by mouth) maintenance 100 mg every 6–8 hours adjusted according to plasma-concentration monitoring, to be given with blood pressure and ECG monitoring

**Dose equivalence and conversion**

- Preparations containing phenytoin sodium are not bioequivalent to those containing phenytoin base (such as Epanutin Inftabs® and Epanutin® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy. However, if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma-phenytoin concentration monitoring is recommended.

**Unlicensed use**

- With intravenous use: Phenytoin doses in BNF publications may differ from those in product literature.

**Important safety information**

NHS improvement patient safety alert: Risk of death and severe harm from error with injectable phenytoin (November 2016)

Use of injectable phenytoin is error-prone throughout the prescribing, preparation, administration and monitoring processes; all relevant staff should be made aware of appropriate guidance on the safe use of injectable phenytoin to reduce the risk of error.

**Contra-indications**

**General contra-indications**

Acute porphyrias p. 930

**Specific contra-indications**

- With intravenous use: Second- and third-degree heart block - sino-atrial block - sinus bradycardia - Stokes-Adams syndrome

**Caution**

**General cautions**

Enteral feeding (interrupt feeding for 2 hours before and after dose; more frequent monitoring may be necessary)

**Specific cautions**

- With intravenous use: Heart failure - hypotension - injection solutions alkaline (irritant to tissues) - respiratory depression - resuscitation facilities must be available

**Cautions, further information**

Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

Intramuscular phenytoin should not be used (absorption is slow and erratic).

**Interactions**

- Appendix 1 (phenytoin).

**Side-effects**

**General side-effects**

- Common or very common: Acne - anorexia - coarsening of facial appearance - constipation - dizziness - dyskinesia - gingival hypertrophy and tenderness (maintain good oral hygiene) - headache - hirsutism - insomnia - nausea - paraesthesia - rash - transient nervousness - tremor - vomiting
- Rare: Leucopenia - aplastic anaemia - blood disorders - dyskinesia - hepatoxicity - lupus erythematosus - lymphadenopathy - megaloblastic anaemia - osteomalacia - peripheral neuropathy - polyarthritis nodosa - Stevens-Johnson syndrome - thrombocytopenia - toxic epidermal necrolysis
Frequency not known  Hypersensitivity syndrome · interstitial nephritis · pneumonitis · polyarthopathy · suicidal ideation

SPECIFIC SIDE-EFFECTS

Common or very common  
With intravenous use  Alterations in respiratory function · arrhythmias · cardiovascular collapse · cardiovascular depression (particularly if injection too rapid) · CNS depression (particularly if injection too rapid) · hypotension · respiratory arrest

Frequency not known  
With intravenous use Purple glove syndrome · tonic seizures

SIDE-EFFECTS, FURTHER INFORMATION

Hepatotoxicity  Discontinue immediately and do not re-administer.

Rash  Discontinue; if mild re-introduce cautiously but discontinue immediately if recurrence.

Use in adolescents  Phenytoin may cause coarsening of the facial appearance, acne, hirsutism, and gingival hyperplasia and so may be particularly undesirable in adolescent patients.

Bradycardia and hypotension  
With intravenous use  Reduce rate of administration if bradycardia or hypotension occurs.

Overdose  Symptoms of phenytoin toxicity include nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia.

ALLERGY AND CROSS-SENSITIVITY

Cross-sensitivity reported with carbamazepine. Antiepileptic hypersensitivity syndrome associated with phenytoin. See under Epilepsy p. 286 for more information.

PREGNANCY  Changes in plasma-protein binding make interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction. Doses should be adjusted on the basis of plasma-drug concentration monitoring.

BREAST FEEDING  Small amounts present in milk, but not known to be harmful.

HEPATIC IMPAIRMENT  Reduce dose to avoid toxicity.

PRE-TREATMENT SCREENING  HLA* 1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome).

MONITORING REQUIREMENTS

In adults  The usual total plasma-phenytoin concentration for optimum response is 10–20 mg/litre (or 40–80 micromol/litre). In pregnancy, the elderly, and certain disease states where protein binding may be reduced, careful interpretation of total plasma-phenytoin concentration is necessary; it may be more appropriate to measure free plasma-phenytoin concentration.

In children  Therapeutic plasma-phenytoin concentrations reduced in first 3 months of life because of reduced protein binding. Though plasma concentration for optimum response: neonate—3 months, 6–15 mg/litre (25–60 micromol/litre); child 3 months–18 years, 10–20 mg/litre (40–80 micromol/litre).

Manufacturer recommends blood counts (but evidence of practical value uncertain).

With intravenous use  Monitor ECG and blood pressure.

DIRECTIONS FOR ADMINISTRATION

With intravenous use in children  Before and after administration flush intravenous line with Sodium Chloride 0.9%. For intravenous injection, give into a large vein at rate not exceeding 1 mg/kg/minute (max. 50 mg/minute). For intravenous infusion, dilute to a concentration not exceeding 10 mg/ml with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation.

With intravenous use in adults  For intravenous infusion (Epanutin®), give intermittently in Sodium chloride 0.9%. Flush intravenous line with Sodium chloride 0.9% before and after infusion; dilute in 50–100 ml infusion fluid (final concentration not to exceed 10 mg/ml) and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation. To avoid local venous irritation each injection or infusion should be preceded and followed by an injection of sterile physiological saline through the same needle or catheter.

PRESCRIBING AND DISPENSING INFORMATION

Switching between formulations  Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

PATIENT AND CARER ADVICE  

Medicines for Children leaflet: Phenytoin for preventing seizures  www.medicinesforchildren.org.uk/phenytoin-for-preventing-seizures

Blood or skin disorders  Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

MEDITCINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, Chewable tablet, Capsule, Oral suspension, Solution for injection.

Tablet  

<table>
<thead>
<tr>
<th>Cautionary and Advisory Labels 8</th>
<th>Phenytoin (Non-proprietary)</th>
<th>Phenytoin sodium 100 mg</th>
<th>Epanutin (Pfizer Ltd)</th>
<th>Phenytoin 50 mg</th>
<th>£13.18</th>
<th>200 tablet (Pom)</th>
<th>£38.48</th>
<th>2500 tablet (Pom)</th>
<th>£48.79</th>
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<tr>
<td>Capsule</td>
<td>Phenytoin (Non-proprietary)</td>
<td>Phenytoin sodium 25 mg</td>
<td>Epanutin (Pfizer Ltd)</td>
<td>Phenytoin sodium 25 mg capsules</td>
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<td>28 capsule (Pom)</td>
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<td>Oral suspension</td>
<td>Phenytoin (Non-proprietary)</td>
<td>Phenytoin sodium 50 mg</td>
<td>Epanutin (Pfizer Ltd)</td>
<td>Phenytoin sodium 50 mg capsules</td>
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<td>28 capsule (Pom)</td>
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<tr>
<td>Solution for injection</td>
<td>Phenytoin (Non-proprietary)</td>
<td>Phenytoin sodium 50 mg per 1 ml</td>
<td>Epanutin (Pfizer Ltd)</td>
<td>Phenytoin sodium 50 mg per 1 ml solution for injection ampoules</td>
<td>£15.50–24.40</td>
<td>5 ampoule (Pom)</td>
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<td>Phenytoin sodium 50 mg per 1 ml</td>
<td>Epanutin (Pfizer Ltd)</td>
<td>Phenytoin sodium 50 mg per 1 ml</td>
<td>Epanutin Ready-Mixed Parenteral 250mg/5ml solution for injection ampoules</td>
<td>£48.79</td>
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</table>

PATIENT AND CARER ADVICE  

Medicines for Children leaflet: Phenytoin for preventing seizures  www.medicinesforchildren.org.uk/phenytoin-for-preventing-seizures

Blood or skin disorders  Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).
Pregabalin

- **INDICATIONS AND DOSE**
  - **Peripheral and central neuropathic pain**
    - **BY MOUTH**
    - Adult: Initially 150 mg daily in 2–3 divided doses, then increased if necessary to 300 mg daily in 2–3 divided doses, dose to be increased at 3–7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses, dose to be increased after 7 days
  - **Adjunctive therapy for focal seizures with or without secondary generalisation**
    - **BY MOUTH**
    - Adult: Initially 25 mg twice daily, then increased in steps of 50 mg daily, dose to be increased at 7 day intervals, increased to 300 mg daily in 2–3 divided doses for 7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses

- **SIDE-EFFECTS**
  - **Common or very common**
    - Agitation
    - Confusion
    - Constipation
    - Diplopia
    - Disturbances in muscle control and movement
    - Dizziness
    - Drowsiness
    - Dry mouth
    - Euphoria
    - Flatulence
    - Impaired attention
    - Impaired memory
    - Insomnia
    - Irritability
    - Malaise
    - Oedema
    - Paraesthesia
    - Sexual dysfunction
    - Speech disorder
    - Visual disturbances
  - **Uncommon**
    - Abdominal distension
    - Abnormal dreams
    - Agitation
    - Arthralgia
    - Chills
    - Cognitive impairment
    - Depersonalisation
    - Depression
    - Dry eye
    - Dysphoria
    - Dysuria
    - First-degree AV block
    - Flushing
    - Gastro-esophageal reflux disease
    - Hallucinations
    - Hyperacusis
    - Hypersalivation
    - Hypertension
    - Hypoglycaemia
    - Hypotension
    - Hypothyroidism
    - Myalgia
    - Nasal dryness
    - Nasopharyngitis
    - Panic attacks
    - Rash
    - Stupor
    - Sweating
    - Syncope
    - Tachycardia
    - Taste disturbance
    - Thirst
    - Thrombocytopaenia
    - Urinary incontinence
  - **Rare**
    - Arrhythmia
    - Acute myocardial infarction
    - Bradycardia
    - Breast discharge
    - Breathing difficulty
    - Cough
    - Dysphoria
    - Epistaxis
    - Hyperglycaemia
    - Hypokalaemia
    - Leucopenia
    - Menstrual disturbances
    - Neutropenia
    - Oliguria
    - Pancreatitis
    - Parosmia
    - Renal failure
    - Thrombomylsis
    - Rhinitis
    - Urticaria
    - Weight loss
  - **Frequency not known**
    - Aggression
    - Congestive heart failure
    - Convulsions
    - Diarrhoea
    - Encephalopathy
    - Headache
    - Keratitis
    - Nausea
    - Pruritus
    - QT-interval prolongation
    - Stevens-Johnson syndrome
    - Suicidal ideation
    - Urinary retention

- **UNLICENSED USE**
  - Pregabalin doses in BNF may differ from those in product literature.

- **CAUTIONS**
  - Conditions that may precipitate encephalopathy, severe congestive heart failure

- **INTERACTIONS**
  - Appendix 1 (pregabalin).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions**
    - The Scottish Medicines Consortium has advised (July 2007) that pregabalin (Lyrica®) is not recommended for the treatment of central neuropathic pain.
    - The Scottish Medicines Consortium has advised (April 2009) that pregabalin (Lyrica®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in adults who have not achieved adequate pain relief with, or have not tolerated, first- or second-line treatments; discontinue treatment if sufficient benefit is not achieved within 8 weeks of reaching the maximum tolerated dose.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS 3, 8**
  - **Pregabalin (Non-proprietary)**
    - Pregabalin 25 mg | 56 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 50 mg | 56 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 75 mg | 56 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 100 mg | 84 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 150 mg | 56 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 200 mg | 84 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 250 mg | 56 capsule Pm | £6.40 DT price = £6.40
  - **Alzain** (Dr Reddy’s Laboratories (UK) Ltd)
    - Pregabalin 25 mg | 56 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 50 mg | 56 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 75 mg | 56 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 100 mg | 84 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 150 mg | 56 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 200 mg | 84 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 250 mg | 56 capsule Pm | £8.64 DT price = £8.64
    - Pregabalin 300 mg | 56 capsule Pm | £8.64 DT price = £8.64
  - **Lecenta** (Actavis UK Ltd)
    - Pregabalin 25 mg | 56 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 50 mg | 56 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 75 mg | 56 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 100 mg | 84 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 150 mg | 56 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 200 mg | 84 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 250 mg | 56 capsule Pm | £6.39 DT price = £6.39
    - Pregabalin 300 mg | 56 capsule Pm | £6.39 DT price = £6.39
  - **Lyrica** (Pfizer Ltd)
    - Pregabalin 25 mg | 56 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 50 mg | 56 capsule Pm | £6.40 DT price = £6.40
    - Pregabalin 75 mg | 56 capsule Pm | £6.40 DT price = £6.40
Retigabine

INDICATIONS AND DOSE

Adjuvant treatment of drug-resistant focal seizures with or without secondary generalisation when other appropriate drug combinations have proved inadequate or have not been tolerated

- **BY MOUTH**
  - Adult: Initially up to 300 mg daily in 3 divided doses, then increased in steps of up to 150 mg every week, adjusted according to response; maintenance 0.6–1.2 g daily
  - Elderly: Initially 150 mg daily in 3 divided doses, then increased in steps of up to 150 mg every week, adjusted according to response; maximum 900 mg per day

CAUTIONS

- Known QT-interval prolongation • risk of urinary retention

CAUTIONS, FURTHER INFORMATION

- QT-interval prolongation Patients with known QT-interval prolongation, or with the following risk factors for QT interval prolongation, should be carefully monitored while taking retigabine: cardiac failure, ventricular hypertrophy, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval.

INTERACTIONS

- Appendix 1 (retigabine).

SIDE-EFFECTS

- Common or very common: Amnesia • anxiety • blurred vision • confusion • constipation • diplopia • discoloration of lips • discoloration of nails • discoloration of skin • dizziness • dry mouth • dysuria • haematuria • impaired attention • impaired coordination • impaired speech • increased appetite • malaise • myoclonus • nausea • paraesthesia • peripheral oedema • psychosis • tremor • vertigo • visual impairment • weight gain

- Uncommon: Dypsopias • dysphagia • hypokinesia • nephrolithiasis • rash • suicidal ideation • sweating • urinary retention

- **PREGNANCY** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **HEPATIC IMPAIRMENT** Reduce dose by 50% in moderate to severe impairment; increase by 50 mg every week according to response up to maximum 600 mg daily (450 mg in elderly).

- **RENAL IMPAIRMENT** Reduce dose by 50% if eGFR less than 50 mL/minute/1.73 m²; increase by 50 mg every week according to response up to maximum 600 mg daily (450 mg in elderly).

MONITORING REQUIREMENTS

- Ophthalmological monitoring A comprehensive ophthalmological examination (including visual acuity test, slit-lamp examination, and dilated fundoscopy) should be performed at initiation of treatment and at least every 6 months thereafter during treatment. Changes in vision or retinal pigment should lead to re-assessment of the benefits and risks of continuing treatment—discontinue unless no other treatment options are available. Monitoring should be increased if treatment is continued.

- Monitor for discolouration of ocular tissue and visual impairment.

- Monitor for blue-grey discoloration of nails, lips and skin—continue treatment only if potential benefit outweighs risk.

PRESCRIBING AND DISPENSING INFORMATION

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

- Patients may need to be maintained on a specific manufacturer’s branded or generic retigabine product.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Retigabine for the adjunctive treatment of partial onset seizures in epilepsy (July 2011) NICE TA232

Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, and topiramate has not provided an adequate response, or has not been tolerated.

www.nice.org.uk/TA232

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (June 2011) that retigabine (Trobalt®) is accepted for restricted use within NHS Scotland as adjunctive therapy in adults with focal seizures with or without secondary generalisation. It is restricted for use in refractory epilepsy.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 8, 14, 25

- **Trobalt** (GlaxoSmithKline UK Ltd)
  - **Retigabine 50 mg** Trobalt 50 mg tablets | 21 tablet | £4.87 | £4.87 | 84 tablet | £19.46
  - **Retigabine 100 mg** Trobalt 100 mg tablets | 21 tablet | £9.73 | £9.73 | 42 tablet | no price available | £38.93
  - **Retigabine 200 mg** Trobalt 200 mg tablets | 84 tablet | £7.76 | £7.76 | 300 tablet | £116.78
  - **Retigabine 400 mg** Trobalt 400 mg tablets | 84 tablet | £127.68 | £127.68 | Trobalt tablets starter pack | 63 tablet | £24.33

Pregabalin 20 mg per 1 ml Pregabalin 20 mg/ml oral solution sugar-free | 473 ml | £9.48 | £9.48

Lyrica (Pfizer Ltd) Pregabalin 20 mg per 1 ml Lyrica 20 mg/ml oral solution sugar-free | 473 ml | £9.48 | £9.48
Rufinamide

**INDICATIONS AND DOSE**

Adjuvant treatment of seizures in Lennox-Gastaut syndrome

- **BY MOUTH**

  - Child 4–17 years (body-weight up to 30 kg): Initially 100 mg twice daily, then increased in steps of 100 mg twice daily (max. per dose 500 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
  
  - Child 4–17 years (body-weight 30–49 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 900 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
  
  - Child 4–17 years (body-weight 50–69 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 1.2 g twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
  
  - Child 4–17 years (body-weight 70 kg and above): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 1.6 g twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
  
  - Adult (body-weight 30–49 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 900 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
  
  - Adult (body-weight 50–69 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 1.2 g twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
  
  - Adult (body-weight 70 kg and above): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 1.6 g twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days

Adjuvant treatment of seizures in Lennox-Gastaut syndrome with valproate

- **BY MOUTH**

  - Child 4–17 years (body-weight up to 30 kg): Initially 100 mg twice daily, then increased in steps of 100 mg twice daily (max. per dose 300 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days

**INTERACTIONS**

- Appendix 1 (rufinamide).

**SIDE-EFFECTS**

Abdominal pain, acne, anorexia, anxiety, back pain, blurred vision, constipation, diarrhoea, diplopia, dizziness, drowsiness, dyspepsia, epistaxis, fatigue, gait disturbances, headache, hyperactivity, hypersensitivity syndrome, impaired coordination, increase in seizure frequency, influenza-like symptoms, insomnia, nausea, nyctagmus, oligomenorrhea, rash, rhinitis, tremor, vomiting, weight loss

**ALLERGY AND CROSS-SENSITIVITY**

Antiepileptic hypersensitivity syndrome associated with rufinamide. See under Epilepsy p. 286 for more information.

**PREGNANCY**

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Caution and careful dose titration in mild to moderate impairment. Avoid in severe impairment.

**DIRECTIONS FOR ADMINISTRATION**

Tablets may be crushed and given in half a glass of water.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients may need to be maintained on a specific manufacturer’s branded or generic rufinamide product.

**PATIENT AND CARER ADVICE**

Counselling on antiepileptic hypersensitivity syndrome is advised.

Medicines for Children leaflet: Rufinamide for preventing seizures www.medicinesforchildren.org.uk/rufinamide-for-preventing-seizures

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2008) that rufinamide (Inovelon®) is accepted for restricted use within NHS Scotland as adjuvant therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 8, 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inovelon</strong> (Eisai Ltd)</td>
</tr>
<tr>
<td><strong>Rufinamide 100 mg</strong> Inovelon 100mg tablets</td>
</tr>
<tr>
<td><strong>Rufinamide 200 mg</strong> Inovelon 200mg tablets</td>
</tr>
<tr>
<td><strong>Rufinamide 400 mg</strong> Inovelon 400mg tablets</td>
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</tbody>
</table>

**Oral suspension**

<table>
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<tr>
<th>CAUTIONARY AND ADVISORY LABELS 8, 21</th>
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<tr>
<td><strong>Inovelon</strong> (Eisai Ltd)</td>
</tr>
<tr>
<td><strong>Rufinamide 40 mg per 1 ml</strong> Inovelon 40mg/ml oral suspension sugar-free</td>
</tr>
</tbody>
</table>

**Sodium valproate**

**INDICATIONS AND DOSE**

All forms of epilepsy

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

  - Child 1 month–11 years: Initially 10–15 mg/kg daily in 1–2 divided doses (max. per dose 600 mg); maintenance 25–30 mg/kg daily in 2 divided doses, doses up to 60 mg/kg daily in 2 divided doses may be used in infantile spasms; monitor clinical chemistry and haematological parameters if dose exceeds 40 mg/kg daily

  - Child 12–17 years: Initially 600 mg daily in 1–2 divided doses, increased in steps of 150–300 mg every 3 days; maintenance 1–2 g daily in 2 divided doses; maximum 2.5 g per day

  - Adult: Initially 600 mg daily in 1–2 divided doses, then increased in steps of 150–300 mg every 3 days; maintenance 1–2 g daily, alternatively maintenance 20–30 mg/kg daily; maximum 2.5 g per day
Initiation of valproate treatment

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 10 mg/kg, (usually 400–800 mg), followed by (by intravenous infusion or by intravenous injection) up to 2.5 g daily in 2–4 divided doses, alternatively (by continuous intravenous infusion) up to 2.5 g daily; (by intravenous injection or by intravenous infusion or by continuous intravenous infusion) usual dose 1–2 g daily, alternatively (by intravenous injection or by intravenous infusion or by continuous intravenous infusion) usual dose 20–30 mg/kg daily, intravenous injection to be administered over 3–5 minutes

Continuation of valproate treatment

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: If switching from oral therapy to intravenous therapy give the same dose as current oral daily dose, give over 3–5 minutes by intravenous injection or in 2–4 divided doses by intravenous infusion

Migraine prophylaxis

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 200 mg twice daily, then increased if necessary to 1.2–1.5 g daily in divided doses

**EPILIM CHRONOSPHERE®**

**All forms of epilepsy**

- **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**EPILIM CHRONO®**

**All forms of epilepsy**

- **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**EPISENTA® CAPSULES**

**All forms of epilepsy**

- **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**Mania**

- **BY MOUTH**
  - Adult: Initially 750 mg daily in 1–2 divided doses, adjusted according to response, usual dose 1–2 g daily in 1–2 divided doses, doses greater than 45 mg/kg daily require careful monitoring

**EPISENTA® GRANULES**

**All forms of epilepsy**

- **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**Mania**

- **BY MOUTH**
  - Adult: Initially 750 mg daily in 1–2 divided doses, adjusted according to response, usual dose 1–2 g daily in 1–2 divided doses, doses greater than 45 mg/kg daily require careful monitoring

**EPIVAL®**

**All forms of epilepsy**

- **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**SIDE-EFFECTS**


- **Very rare** Acne – gynaecomastia – hepatic dysfunction – hirsutism – increase in bleeding time – pancreatitis

- **Frequency not known** Hypersensitivity reactions – suicidal ideation

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Hepatic dysfunction** Withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control.

- **Pancreatitis** Discontinue treatment if symptoms of pancreatitis develop.

**CONCEPTION AND CONTRACEPTION** Valproate is associated with teratogenic risks and should not be used in females of child-bearing potential unless there is no safer alternative—this should be fully considered and discussed before prescribing for females of child-bearing age. Exclude pregnancy before treatment—effective contraception advised in females of child-bearing potential. In females planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: VALPROATE AND RISK OF ABNORMAL PREGNANCY OUTCOMES**

Infants exposed to valproate in utero are at a high risk of serious developmental disorders (up to 30–40% risk) and congenital malformations (approx. 11% risk). Valproate should not be used in female children, females of childbearing potential or during pregnancy unless alternative treatments are ineffective or not tolerated.

**CONTRA-INDICATIONS**

Acute porphyrias p. 930 • known or suspected mitochondrial disorders (higher rate of acute liver failure and liver-related deaths) • personal or family history of severe hepatic dysfunction

**CAUTIONS** Systemic lupus erythematosus

**CAUTIONS, FURTHER INFORMATION**

Consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

**Liver toxicity**

LIVER dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).
PREGNANCY Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valproate should not be used during pregnancy unless there is no safer alternative and only after a careful discussion of the risks. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Neonatal bleeding (related to hypofibrininaemia) reported. Neonatal hepatotoxicity also reported.

Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy.

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING Present in milk—risk of haematological disorders in breast-fed newborns and infants.

HEPATIC IMPAIRMENT Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months). Avoid in active liver disease.

RENAL IMPAIRMENT Reduce dose.

MONITORING REQUIREMENTS
- Plasma-valproate concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful.
- Monitor liver function before therapy and during first 6 months especially in patients most at risk.
- Measure full blood count and ensure no undue potential for bleeding before starting and before surgery.

EFFECT ON LABORATORY TESTS False-positive urine tests for ketones.

TREATMENT CESSATION Avoid abrupt withdrawal; if treatment with valproate is stopped, reduce the dose gradually over at least 4 weeks.

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Epilim®), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute Epilim® with solvent provided then dilute with infusion fluid.

EPIVAL® Tablets may be halved but not crushed or chewed.

EPISENTA® CAPSULES Contents of capsule may be mixed with soft food or drink that is cold or at room temperature and swallowed immediately without chewing.

EPILIM® SYRUP May be diluted, preferably in Syrup BP; use within 14 days.

EPISENTA® GRANULES Granules may be mixed with soft food or drink that is cold or at room temperature and swallowed immediately without chewing.

EPILIM CHRONOSSPHERE® Granules may be mixed with soft food or drink that is cold or at room temperature, and swallowed immediately without chewing.

PRESCRIBING AND DISPENSING INFORMATION

Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic oral sodium valproate product.

EPILIM CHRONOSSPHERE® Prescribe dose to the nearest whole 50-mg sachet.

PATIENT AND CARER ADVICE
Risk of abnormal pregnancy outcomes A patient guide and card should be provided to all female patients.

Medicines for Children leaflet: Sodium valproate for preventing seizures www.medicinesforchildren.org.uk/sodium-valproate-for-preventing-seizures

Blood or hepatic disorders Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop.

Pancreatitis Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop.

MHRA advice: Valproate and the risk of abnormal pregnancy outcomes Female patients and their carers should be counselled on the risk of valproate treatment during pregnancy. Ensure female patients are provided with relevant resources, to support their understanding of the risks. In particular the prescriber must ensure the patient understands:
- the risks associated with valproate during pregnancy;
- the need to use effective contraception;
- the need for regular review of treatment;
- the need to rapidly consult if she is planning a pregnancy or becomes pregnant.

EPISENTA® CAPSULES Patients and carers should be counselled on the administration of capsules.

EPISENTA® GRANULES Patients and carers should be counselled on the administration of granules.

EPILIM CHRONOSSPHERE® Patients and carers should be counselled on the administration of granules.

MEDICINAL CHRONOSPHERE There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, suppository.

Tablet

CAUTIONARY AND ADVISORY LABELS 8, 10, 21

- Epilim® (Sanofi) ▼
  Sodium valproate 100 mg Epilim 100mg crushable tablets | 100 tablet (Pom) £5.60 DT price = £5.60

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 8, 10, 21, 25

- Epilim Chrono® (Sanofi) ▼
  Sodium valproate 200 mg Epilim Chrono 200 tablets | 100 tablet (Pom) £11.65 DT price = £11.65
  Sodium valproate 300 mg Epilim Chrono 300 tablets | 100 tablet (Pom) £17.47 DT price = £17.47
  Sodium valproate 500 mg Epilim Chrono 500 tablets | 100 tablet (Pom) £29.10 DT price = £29.10

- Epival® CR (Chanelle Medical UK Ltd) ▼
  Sodium valproate 300 mg Epival CR 300mg tablets | 100 tablet (Pom) £12.13 DT price = £17.47
  Sodium valproate 500 mg Epival CR 500mg tablets | 100 tablet (Pom) £20.21 DT price = £29.10

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 5, 8, 10, 25

- Sodium valproate (non-proprietary) ▼
  Sodium valproate 200 mg Sodium valproate 200mg gastro-resistant tablets | 100 tablet (Pom) £7.70 DT price = £4.75

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 8, 10, 21, 25

- Episenta® (Desitin Pharma Ltd) ▼
  Sodium valproate 150 mg Episenta 150mg modified-release capsules | 100 capsule (Pom) £7.00
  Sodium valproate 300 mg Episenta 300mg modified-release capsules | 100 capsule (Pom) £13.00 DT price = £13.00
Tiagabine

**INDICATIONS AND DOSE**

Adjunctive treatment for focal seizures with or without secondary generalisation that are not satisfactorily controlled by other antiepileptics (with enzyme-inducing drugs)

- **BY MOUTH**
  - Child 12–17 years: Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every week; maintenance 30–45 mg daily in 2–3 divided doses
  - Adult: Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every week; maintenance 15–30 mg daily in 2–3 divided doses

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea, dizziness, emotional lability, impaired concentration, nervousness, speech impairment, tiredness, tremor
- **Rare** Bruising, confusion, depression, drowsiness, non-convulsive status epilepticus, psychosis, suicidal ideation, visual disturbances
- **Frequency not known** Leucopenia

**PREGNANCY** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**HEPATIC IMPAIRMENT** In mild to moderate impairment reduce dose, prolong the dose interval, or both. Avoid in severe impairment.

**PATIENT AND CARER ADVICE** Medicines for Children leaflet: Tiagibine for preventing seizures www.medicinesforchildren.org.uk/tiagabine-for-preventing-seizures

Driving and skilled tasks

May impair performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

<table>
<thead>
<tr>
<th>Name</th>
<th>Form</th>
<th>Strength</th>
<th>Manufacturer</th>
<th>Price DT (£)</th>
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<td>Tablet</td>
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**Topiramate**

**INDICATIONS AND DOSE**

Monotherapy of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation

- **BY MOUTH**
  - Child 6–17 years: Initially 0.5–1 mg/kg once daily (max. per dose 25 mg) for 1 week, dose to be taken at night, then increased in steps of 250–500 micrograms/kg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 50 mg twice daily (max. per dose 7.5 mg/kg twice daily), if child cannot tolerate titration regimens recommended above then smaller steps or longer interval between steps may be used; maximum 500 mg per day
  - Adult: Initially 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 100–200 mg daily in 2 divided doses, adjusted according to response, doses of 1 g daily have been used in refractory epilepsy; maximum 500 mg per day

**CONTRAINDICATIONS** Avoid in acute porphyrias p. 930

**CAUTIONS, FURTHER INFORMATION**

Tiagabine should be avoided in absence, myclonic, tonic and atomic seizures due to risk of seizure exacerbation.

**INTERACTIONS** Appendix 1 (tiagabine).

**Additional Notes**

- **Modified-release granules**
  - **Sodium valproate**
    - powdered and solvent for injection
    - Episenta (Desitin Pharma Ltd)
    - Sodium valproate 40 mg per 1 ml
    - Episenta 500 mg modified-release granules
    - Sodium valproate 1 gram
  - **Sodium valproate**
    - powder and solvent for injection
    - Episenta (Desitin Pharma Ltd)
    - Sodium valproate 1000 mg granules
  - **Solution for injection**
    - Sodium valproate 100 mg per 1 ml
    - Episenta (Desitin Pharma Ltd)
    - Sodium valproate 1000 mg liquid
  - **Powder and solvent for solution for injection**
    - Sodium valproate 400 mg
    - Episenta (Desitin Pharma Ltd)
    - Sodium valproate 1500 mg
  - **Epilim Chronosphere MR**
    - modified-release granules
    - Episenta (Desitin Pharma Ltd)
    - Sodium valproate 1500 mg
  - **Sodium valproate**
    - powder and solvent for injection vials
    - Episenta (Desitin Pharma Ltd)
    - Sodium valproate 1500 mg

**CAUTIONARY AND ADVISORY LABELS**

8, 10, 21, 25

**INDICATIONS AND DOSE**

Topiramate

**INDICATIONS AND DOSE**

Topiramate
Adjunctive treatment of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation | Adjunctive treatment for seizures associated with Lennox-Gastaut syndrome

**BY MOUTH**

- Child 2–17 years: Initially 1–3 mg/kg once daily (max. per dose 25 mg) for 1 week, dose to be taken at night, then increased in steps of 0.5–1.5 mg/kg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 2.5–4.5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), if child cannot tolerate recommended titration regimen then smaller steps or longer intervals between steps may be used; maximum 400 mg per day
- Adult: Initially 25–50 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 200–400 mg daily in 2 divided doses; maximum 400 mg per day

**Migraine prophylaxis**

**BY MOUTH**

- Adult: Initially 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25 mg every week; usual dose 50–100 mg daily in 2 divided doses; maximum 200 mg per day

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, agitation, alopecia, anaemia, anxiety, appetite changes, arthralgia, cognitive impairment, confusion, constipation, depression, diarrhoea, dizziness, drowsiness, dry mouth, dyspepsia, dysphonia, epistaxis, gastritis, impaired attention, impaired coordination, irritability, malaise, mood changes, movement disorders, muscle spasm, muscular weakness, myalgia, nausea, nephrolithiasis, nystagmus, paraesthesia, pruritus, rash, seizures, sleep disturbance, speech disorder, taste disturbance, tinnitus, tremor, urinary disorders, visual disturbances, vomiting

- **Uncommon** Abdominal distension, altered sense of smell, blepharospasm, blood disorders, bradycardia, dry eye, flatulence, flushing, gingival bleeding, glossodynia, haematuria, halitosis, hearing loss, hypokalaemia, hypotension, increased lacrimation, influenza-like symptoms, leucopenia, metabolic acidosis, mydriasis, neutropenia, palpitation, pancreatitis, panic attack, peripheral neuropathy, photophobia, postural hypotension, psychosis, reduced sweating, salivation, sexual dysfunction, skin discoloration, suicidal ideation, thirst, thrombocytopenia, urinary calculus

- **Rare** Abnormal skin odour, calcinosis, hepatitis, hepatitis, periorbital oedema, Raynaud’s syndrome, Stevens-Johnson syndrome, unilateral blindness

- **Very rare** Angle-closure glaucoma

- **Frequency not known** Encephalopathy, hyperammonaemia, maculopathy, toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Acute myopia with secondary angle-closure glaucoma Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the lens and iris have also been reported. If raised intra-ocular pressure occurs:
  - seek specialist ophthalmological advice;
  - use appropriate measures to reduce intra-ocular pressure;
  - stop topiramate as rapidly as feasible

**PREGNANCY** Increased risk of cleft palate if taken in the first trimester of pregnancy. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. It is recommended that the fetal growth should be monitored.

**BREAST FEEDING** Manufacturer advises avoid—present in milk.

**HEPATIC IMPAIRMENT** Use with caution in moderate to severe impairment—clearance may be reduced.

**RENAL IMPAIRMENT**

- In adults Half usual starting and maintenance dose if eGFR less than 70 mL/minute/1.73 m²—reduced clearance and longer time to steady-state plasma concentration.
- In children Half usual starting and maintenance dose if estimated glomerular filtration less than 70 mL/minute/1.73 m²—reduced clearance and longer time to steady-state plasma concentration. Use with caution.

**DIRECTIONS FOR ADMINISTRATION**

**TOPAMAX® CAPSULES** Swallow whole or sprinkle contents of capsule on soft food and swallow immediately without chewing.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history. Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic topiramate product.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Topiramate for preventing seizures www.medicinesforchildren.org.uk/topiramate-for-preventing-seizures

**TOPAMAX® CAPSULES** Patients or carers should be given advice on how to administer Topamax™ capsules.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

**Topiramate (Non-proprietary)**

- **Topiramate 25 mg** Topiramate 25mg tablets | 60 tablet | £7.62 DT price = £1.85
- **Topiramate 50 mg** Topiramate 50mg tablets | 60 tablet | £12.83 DT price = £2.09
- **Topiramate 100 mg** Topiramate 100mg tablets | 60 tablet | £15.20 DT price = £2.74
- **Topiramate 200 mg** Topiramate 200mg tablets | 60 tablet | £19.99 DT price = £4.00
- **Topamax** (Janssen-Cilag Ltd)
  - **Topiramate 25 mg** Topamax 25mg tablets | 60 tablet | £19.29 DT price = £1.85
  - **Topiramate 50 mg** Topamax 50mg tablets | 60 tablet | £31.69 DT price = £2.09
  - **Topiramate 100 mg** Topamax 100mg tablets | 60 tablet | £56.76 DT price = £2.74
  - **Topiramate 200 mg** Topamax 200mg tablets | 60 tablet | £110.23 DT price = £4.00

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**

**Topiramate (Non-proprietary)**

- **Topiramate 15 mg** Topiramate 15mg capsules | 60 capsule | £28.11 DT price = £25.35
- **Topiramate 25 mg** Topiramate 25mg capsules | 60 capsule | £25.95 DT price = £14.63
Vigabatrin

INDICATIONS AND DOSE

Adjunctive treatment of focal seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics (under expert supervision)

BY MOUTH

Child 1–23 months: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 75 mg/kg)

Child 2–11 years: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 1.5 g)

Child 12–17 years: Initially 250 mg twice daily, to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 1–1.5 g twice daily

Adult: Initially 1 g once daily, alternatively initially 1 g daily in 2 divided doses, then increased in steps of 500 mg every week, adjusted according to response; usual dose 2–3 g daily; maximum 3 g per day

BY RECTUM

Child 1–23 months: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 75 mg/kg)

Child 2–11 years: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 1.5 g)

Child 12–17 years: Initially 250 mg twice daily, to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 1–1.5 g twice daily

UNLICENSED USE

Granules not licensed for rectal use. Tablets not licensed to be crushed and dispersed in liquid. Vigabatrin doses in BNF publications may differ from those in product literature.

CONTRA-INDICATIONS

Visual field defects

CAUTIONS

Elderly · history of behavioural problems · history of depression · history of psychosis

CAUTIONS, FURTHER INFORMATION

Vigabatrin may worsen absence, myoclonic, tonic and atonic seizures.

Visual field defects · Vigabatrin is associated with visual field defects. The onset of symptoms varies from 1 month to several years after starting. In most cases, visual field defects have persisted despite discontinuation, and further deterioration after discontinuation cannot be excluded. Product literature advises visual field testing before treatment and at 6-month intervals. Patients and their carers should be warned to report any new visual symptoms that develop and those with symptoms should be referred for an urgent ophthalmological opinion. Gradual withdrawal of vigabatrin should be considered.

INTERACTIONS

Appendix 1 (vigabatrin).

SIDE-EFFECTS

Common or very common · Abdominal pain · aggression · agitation · blurred vision · depression · diplopia · dizziness · drowsiness · excitation (in children) · fatigue · headache · impaired concentration · impaired memory · irritability · nausea · nervousness · nystagmus · oedema · paresthesia · paranoia · speech disorder · tremor · visual field defects · vomiting · weight gain

Uncommon · Ataxia · mania · occasional increase in seizure frequency (especially if myoclonic) · psychosis · rash

Rare · Peripheral retinal neuropathy · retinal disorders · suicidal ideation

Very rare · Hepatitis · optic atrophy · optic neuritis

Frequency not known · Movement disorders in infantile spasms

SIDE-EFFECTS, FURTHER INFORMATION

Encephalopathic symptoms including marked sedation, stupor, and confusion with non-specific slow wave EEG can occur rarely—reduce dose or withdraw.

Visual field defects · About one-third of patients treated with vigabatrin have suffered visual field defects; counselling and careful monitoring for this side-effect are required.

PREGNANCY

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING

Present in milk—manufacturer advises avoid.

RENAL IMPAIRMENT

In adults · Consider reduced dose or increased dose interval if eGFR less than 60 mL/minute/1.73 m².

In children · Consider reduced dose or increased dose interval if estimated glomerular filtration rate less than 60 mL/minute/1.73 m².

MONITORING REQUIREMENTS

Closely monitor neurological function.

DIRECTIONS FOR ADMINISTRATION

With oral use · The contents of a sachet should be dissolved in water or a soft drink immediately before taking. Tablets may be crushed and dispersed in liquid.

With rectal use · Dissolve contents of sachet in small amount of water and administer rectally [unlicensed use].

PATIENT AND CARER ADVICE

Patients and their carers should be warned to report any new visual symptoms that develop.

Medicines for Children leaflet: Vigabatrin for preventing seizures www.medicinesforchildren.org.uk/vigabatrin-for-preventing-seizures

MEDITINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 8

Vigabatrin 500 mg Sabril 500mg tablets | 100 tablet | £44.41 DT price = £44.41

Powder

CAUTIONARY AND ADVISORY LABELS 3, 8, 13

Vigabatrin 500 mg Sabril 500mg oral powder sachets sugar-free | 50 sachet | £24.60 DT price = £24.60

Zonisamide

INDICATIONS AND DOSE

Monotherapy for treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy

BY MOUTH

Adult: Initially 100 mg once daily for 2 weeks, then increased in steps of 100 mg every 2 weeks, usual maintenance dose 300 mg once daily; maximum 500 mg per day

continued →
Adjunctive treatment for refractory focal seizures with or without secondary generalisation

- **BY MOUTH**
  - Child 6–17 years (body-weight 20–54 kg): Initially 1 mg/kg once daily for 7 days, then increased in steps of 1 mg/kg every 7 days, usual maintenance 6–8 mg/kg once daily (max. per dose 500 mg once daily), dose to be increased at 2-week intervals in patients who are **not** receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4
  - Child 6–17 years (body-weight 55 kg and above): Initially 1 mg/kg once daily for 7 days, then increased in steps of 1 mg/kg every 7 days, usual maintenance 300–500 mg daily, dose to be increased at 2-week intervals in patients who are **not** receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4
  - Adult: Initially 50 mg daily in 2 divided doses for 7 days, then increased to 100 mg daily in 2 divided doses, then increased in steps of 100 mg every 7 days, usual maintenance 300–500 mg daily in 1–2 divided doses, dose to be increased at 2-week intervals in patients who are **not** receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

- **CAUTIONS** Elderly · low body-weight or poor appetite — monitor weight throughout treatment (fatal cases of weight loss reported in children) · metabolic acidosis — monitor serum bicarbonate concentration in children and those with other risk factors (consider dose reduction or discontinuation if metabolic acidosis develops) · risk factors for renal stone formation (particularly predisposition to nephrolithiasis)

- **CAUTIONS, FURTHER INFORMATION**
  - Avoid overheating and ensure adequate hydration especially in children, during strenuous activity or if in warm environment (fatal cases of heat stroke reported in children).

- **INTERACTIONS** → Appendix 1 (zonisamide),
  - in adults Caution with concomitant use of drugs that increase risk of hyperthermia, metabolic acidosis, or nephrolithiasis
  - in children Caution with concomitant use of drugs that increase risk of nephrolithiasis. Contra-indicated with use of drugs that increase risk of hyperthermia or metabolic acidosis.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · agitation · alopecia · anorexia · ataxia · confusion · constipation · depression · diarrhoea · diplopia · dizziness · drowsiness · ecchymosis · fatigue · impaired attention · impaired memory · insomnia · irritability · nausea · nystagmus · paraesthesia · peripheral oedema · pruritus · psychosis · pyrexia · rash (consider withdrawal) · speech disorder · tremor · weight loss
  - **Uncommon** Aggression · cholecystitis · cholelithiasis · dyspepsia · hypokalaemia · pneumonia · seizures · suicidal ideation · urinary calculus · urinary tract infection · vomiting
  - **Very rare** Amnesia · aspiration · blood disorders · coma · dyspnoea · hallucinations · heat stroke · hepatitis · hydromephrosis · impaired sweating · metabolic acidosis · myasthenic syndrome · neuroleptic malignant syndrome · pancreatitis · renal failure · renal tubular acidosis · rhabdomyolysis · Stevens-Johnson syndrome · toxic epidermal necrolysis

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in sulfonamide hypersensitivity. Antiepileptic hypersensitivity syndrome theoretically associated with zonisamide. See under Epilepsy p. 286 for more information.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises women of childbearing potential should use adequate contraception during treatment and for 4 weeks after last dose.

- **PREGNANCY** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **BREAST FEEDING** Manufacturer advises avoid for 4 weeks after last dose.

- **HEPATIC IMPAIRMENT** Initially increase dose at 2-week intervals if mild or moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Initially increase dose at 2-week intervals; discontinue if renal function deteriorates.

- **TREATMENT CESSATION** Avoid abrupt withdrawal (consult product literature for recommended withdrawal regimens in children).

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.
  - Patients may need to be maintained on a specific manufacturer’s branded or generic zonisamide product.

- **PATIENT AND CARER ADVICE**
  - Children and their carers should be made aware of how to prevent and recognise overheating and dehydration. Medicines for Children leaflet: Zonisamide for preventing seizures www.medicinesforchildren.org.uk/zonisamide-for-preventing-seizures

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (February 2014) that zonisamide (Zonegran®) is accepted for restricted use within NHS Scotland as adjunctive treatment of focal seizures, with or without secondary generalisation, in adolescents and children aged 6 years and above. It is restricted to use on advice from specialists in paediatric neurology or epilepsy.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  - **Zonisamide (Non-proprietary)**
    - Zonisamide 25 mg Zonisamide 25mg capsules 14 capsule £8.38–£8.96 DT price = £8.84
    - Zonisamide 50 mg Zonisamide 50mg capsules 56 capsule £46.69–£47.81 DT price = £47.17
    - Zonisamide 100 mg Zonisamide 100mg capsules 56 capsule £59.58–£63.73 DT price = £62.88
  - **Zonegran (Eisai Ltd)**
    - Zonisamide 25 mg Zonegran 25mg capsules 14 capsule £8.82 DT price = £8.84
    - Zonisamide 50 mg Zonegran 50mg capsules 56 capsule £47.04 DT price = £47.17
    - Zonisamide 100 mg Zonegran 100mg capsules 56 capsule £62.72 DT price = £62.88
Phenobarbital
(Phenobarbitone)

- **INDICATIONS AND DOSE**
  - **All forms of epilepsy except typical absence seizures**
    - **BY MOUTH**
      - Child 1 month–11 years: Initially 1–1.5 mg/kg twice daily, then increased in steps of 2 mg/kg daily as required; maintenance 2.5–4 mg/kg 1–2 times a day
      - Child 12–17 years: 60–180 mg once daily
      - Adult: 60–180 mg once daily, dose to be taken at night
  - **Status epilepticus**
    - **BY INTRAVENOUS INJECTION**
      - Adult: 10 mg/kg (max. per dose 1 g), dose to be administered at a rate not more than 100 mg/minute, injection to be diluted 1 in 10 with water for injections
    - **BY SLOW INTRAVENOUS INJECTION**
      - Child 1 month–11 years: Initially 20 mg/kg, dose to be administered at a rate no faster than 1 mg/kg/minute, then 2.5–5 mg/kg 1–2 times a day
      - Child 12–17 years: Initially 20 mg/kg (max. per dose 1 g), dose to be administered at a rate no faster than 1 mg/kg/minute, then 300 mg twice daily
  - **DOSE EQUIVALENCE AND CONVERSION**
    - For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect.

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930 · children · debilitated · elderly · history of alcohol abuse · history of drug abuse · respiratory depression (avoid if severe)

- **INTERACTIONS**
  - **Common or very common**
    - Agranulocytosis · allergic skin reactions · ataxia · behavioural disturbances · cholasteasis · depression · drowsiness · hallucinations · hepatitis · hyperactivity particularly in the elderly and in children · hypotension · impaired cognition · impaired memory · irritability · lethargy · megaloblastic anaemia (may be treated with folic acid) · nyctagmus · osteomalacia · paradoxic excitation (in adults) · respiratory depression · thrombocytopenia
  - **Very rare**
    - Antiepileptic Hypersensitivity Syndrome · Stevens-Johnson syndrome · suicidal ideation · toxic epidermal necrolysis
  - **Frequency not known**
    - Hyperkinesia (in children)

- **OVERDOSE**
  - For details on the management of poisoning, see Active poisonings

- **ALLERGY AND CROSS-SENSITIVITY**
  - Antiepileptic hypersensitivity syndrome associated with phenobarbital. See under Epilepsy p. 286 for more information.

- **PREGNANCY**
  - The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **BREAST FEEDING**
  - Avoid if possible; drowsiness may occur.

- **HEPATIC IMPAIRMENT**
  - May precipitate coma. Avoid in severe impairment.

- **RENAL IMPAIRMENT**
  - Use with caution.

- **MONITORING REQUIREMENTS**
  - Plasma-phenobarbital concentration for optimum response is 15–40 mg/litre (60–180 micromol/litre);

  - however, monitoring the plasma-drug concentration is less useful than with other drugs because tolerance occurs.

- **TREATMENT CESSION**
  - Avoid abrupt withdrawal (dependence with prolonged use).

- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use For administration by mouth, tablets may be crushed.
  - With intravenous use in adults Solution for injection must be diluted before intravenous administration.
  - With intravenous use in children For intravenous injection, dilute to a concentration of 20 mg/mL with Water for Injections; give over 20 minutes (no faster than 1 mg/kg/minute).

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Some hospitals supply alcohol-free formulations of varying phenobarbital strengths.
  - Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients should be maintained on a specific manufacturer’s product.

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Phenobarbital for preventing seizures www.medicinesforchildren.org.uk/phenobarbital-for-preventing-seizures

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution

  **Tablet**

  - CAUTIONARY AND ADVISORY LABELS 2, 8
    - **Phenobarbital (Non-proprietary)**
      - Phenobarbital 15 mg Phenobarbital 15mg tablets | 28 tablet [Pres] £24.95 DT price = £18.26 [CD]
      - Phenobarbital 30 mg Phenobarbital 30mg tablets | 28 tablet [Pres] £5.99 DT price = £20.00 [CD]
      - Phenobarbital 60 mg Phenobarbital 60mg tablets | 28 tablet [Pres] £7.99 DT price = £6.03 [CD]

  **Oral solution**

  - CAUTIONARY AND ADVISORY LABELS 2, 8
    - **Phenobarbital (Non-proprietary)**
      - Phenobarbital 3 mg per 1 ml Phenobarbital 15mg/5ml elixir | 500 ml [Pres] £83.00 DT price = £83.00 [CD]

  **Solution for injection**

  - EXCIPIENTS: May contain Propylene glycol
    - **Phenobarbital (Non-proprietary)**
      - Phenobarbital sodium 30 mg per 1 ml Phenobarbital sodium 30mg/1ml solution for injection ampoules | 10 ampoule [Pres] £76.87–£81.42 [CD]
      - Phenobarbital sodium 60 mg per 1 ml Phenobarbital sodium 60mg/1ml solution for injection ampoules | 10 ampoule [Pres] £81.73 [CD]
      - Phenobarbital sodium 200 mg per 1 ml Phenobarbital sodium 200mg/1ml solution for injection ampoules | 10 ampoule [Pres] £66.63 [CD]
Clobazam

**INDICATIONS AND DOSE**

**Adjunct in epilepsy**

> **BY MOUTH**
> Child 6–17 years: Initially 5 mg daily, dose to be increased if necessary at intervals of 5 days, maintenance 0.3–1 mg/kg daily, daily doses of up to 30 mg may be given as a single dose at bedtime, higher doses should be divided; maximum 60 mg per day
> Adult: 20–30 mg daily, then increased if necessary up to 60 mg daily

**Anxiety (short-term use)**

> **BY MOUTH**
> Adult: 20–30 mg daily in divided doses, alternatively 20–30 mg once daily, dose to be taken at bedtime; increased if necessary up to 60 mg daily in divided doses, dose only increased in severe anxiety (in hospital patients), for debilitated patients, use elderly dose
> Elderly: 10–20 mg daily

**UNLICENSED USE**

Not licensed for use in children under 6 years.

**IMPORTANT SAFETY INFORMATION**

Do not confuse with clonazepam.

**CONTRA-INDICATIONS**

Chronic psychosis (in adults) - hyperkinesis - not for use alone to treat anxiety associated with depression (in adults) - obsessional states - phobic states - respiratory depression

**CAUTIONS**

Muscle weakness - organic brain changes - personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

**CAUTIONS, FURTHER INFORMATION**

The effectiveness of clobazam may decrease significantly after weeks or months of continuous therapy.

**SIDE-EFFECTS**

> Common or very common Amnesia - ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression
> Uncommon Changes in libido (in adults) - dizziness - dystarthritis - gastrointestinal disturbances - gynaecomastia - headache (in adults) - hypotension (in adults) - incontinence - salivation changes - slurred speech (in adults) - tremor - urinary retention (in adults) - vertigo (in adults) - visual disturbances
> Rare Apnoeas - blood disorders - changes in libido (in children) - headache (in children) - hypotension (in adults) - muscle weakness - onesidedness - paradoxical increase in aggression - psychosis - respiratory depression

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | Primidone (Non-proprietary) | Primidone 50 mg Pr mimidone 50mg tablets | 100 tablet | £106.74–£112.37 DT price = £106.77
| | Primidone 250 mg Pr mimidone 250mg tablets | 90 tablet | no price available | 100 tablet | £99.65–£121.94 DT price = £114.49

**Oral suspension**

| CAUTIONARY AND ADVISORY LABELS | Primidone (Non-proprietary) | Primidone 25 mg per 1 ml Liskantin Saft 125mg/5ml oral suspension | 250 ml | no price available

**HYPNOTICS, SEDATIVES AND ANXIOLYTICS**

**CAUTIONS**

Avoid in acute porphyria p. 930 · children · debilitated · elderly · history of alcohol abuse · history of drug abuse · respiratory depression (avoid if severe)

**CAUTIONS, FURTHER INFORMATION**

Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

**INTERACTIONS**

Appendix 1 (primidone).

**SIDE-EFFECTS**

> Common or very common Agranulocytosis · allergic skin reactions · ataxia · behavioural disturbances · cholestasis · depression · drowsiness · hallucinations · hepatitis · hyperactivity (in children) · hyperactivity particularly in the elderly (in adults) · hypotension · imposed cognition · impaired memory · irritability · lethargy · megaloblastic anaemia (may be treated with folic acid) · nausea · nystagmus · osteomalacia · paradoxical excitement (in adults) · respiratory depression · thrombocytopenia · visual disturbances
> Uncommon Dizziness · headache · vomiting
> Rare Arthralgia · lupus erythematosus · psychosis
> Very rare Antiepileptic Hypersensitivity Syndrome · Stevens-Johnson syndrome · suicidal ideation · toxic epidermal necrolysis
> Frequency not known Dupuytren’s contracture

**ALLERGY AND CROSS-SENSITIVITY**

Antiepileptic hypersensitivity syndrome associated with primidone. See under Epilepsy p. 286 for more information.

**PREGNANCY**

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**HEPATIC IMPAIRMENT**

Reduce dose. May precipitate coma.

**RENAL IMPAIRMENT**

Use with caution.

**MONITORING REQUIREMENTS**

Monitor plasma concentrations of derived phenobarbital; plasma concentration for optimum response is 15–40 mg/litre (60–180 micromol/litre).

**TREATMENT CESSATION**

Avoid abrupt withdrawal (dependence with prolonged use).

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

**ESSENTIAL TREATMENT CESSATION**

Monitor plasma concentrations of derived phenobarbital;
Children • jaundice • respiratory depression • skin reactions • urinary retention (in children) • vertigo (in children)

- Frequency not known Delusions (in children) • excitement (in children) • hallucinations (in children) • irritability (in children) • psychosis (in children) • restlessness (in children)

- Breast Feeding Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.

- Hepatic Impairment Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

- Renal Impairment Start with small doses in severe impairment.

- Monitoring Requirements
  - In children: Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified, because the target concentration ranges are arbitrary and often vary between individuals. However, plasma drug concentrations may be measured in children with worsening seizures, status epilepticus, suspected noncompliance, or suspected toxicity. Similarly, haematological and biochemical monitoring should not be undertaken unless clinically indicated.

- Prescribing and Dispensing Information
  - Switching between formulations: Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

  Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic clobazam product.

- Patient and Carer Advice
  - Medicines for Children leaflet: Clobazam for preventing seizures. www.medicinesforchildren.org.uk/clobazam-preventing-seizures-0

- National Funding/Access Decisions
  - NHS restrictions: Clobazam is not prescribable under the NHS except for epilepsy and endorsed ‘SLS’.

- Medicinal Forms
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension

Tablet

**Clobazam (Non-proprietary)**

- Clobazam 10 mg Clobazam 10mg tablets | 30 tablet PPh £3.56 [CD4-1]
- Frisium (Sanofi) Clobazam 10 mg Frisium 10mg tablets | 30 tablet PPh £2.51 [CD4-1]

Oral suspension

**Clobazam (Non-proprietary)**

- Clobazam 1 mg per 1 ml Clobazam 5mg/5ml oral suspension sugar-free | 150 ml PPh £90.00 DT price = £90.00 [CD4-1]
- Clobazam 2 mg per 1 ml Clobazam 10mg/5ml oral suspension sugar-free | 150 ml PPh £95.00 DT price = £90.00 [CD4-1]
- Perizam (Rosemont Pharmaceuticals Ltd) Perizam 1mg/ml oral suspension sugar-free | 150 ml PPh £90.00 DT price = £90.00 [CD4-1]
- Perizam 2mg/ml oral suspension sugar-free | 150 ml PPh £95.00 DT price = £90.00 [CD4-1]

**Frisium**

- Frisium 10 mg Frisium 10mg tablets | 30 tablet PPh £2.51 [CD4-1]

**Tapclob** (Martindale Pharmaceuticals Ltd)

- Tapclob 1 mg per 1 ml Tapclob 5mg/5ml oral suspension sugar-free | 150 ml PPh £95.00 DT price = £90.00 [CD4-1]
- Tapclob 2 mg per 1 ml Tapclob 10mg/5ml oral suspension sugar-free | 150 ml PPh £95.00 DT price = £90.00 [CD4-1]
- Tapclob 5 mg per 1 ml Tapclob 25mg/5ml oral suspension sugar-free | 150 ml PPh £158.34 [CD4-1]

**Clobazam 10 mg** Clobazam 10mg tablets | 30 tablet PPh £3.56 [CD4-1]

**Clobazam 2 mg** Clobazam 2mg/ml oral suspension sugar-free | 150 ml PPh £95.00 DT price = £90.00 [CD4-1]

**NHS restrictions** Clobazam is not prescribable under the NHS except for epilepsy and endorsed ‘SLS’.

**Clonazepam**

- **INDICATIONS AND DOSE**
  - **All forms of epilepsy**
    - **By mouth**
      - Child 1-11 months: Initially 250 micrograms once daily for 4 nights, dose to be increased over 2-4 weeks, usual dose 0.5-1 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary
      - Child 1-4 years: Initially 250 micrograms once daily for 4 nights, dose to be increased over 2-4 weeks, usual dose 1-3 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary
      - Child 5-11 years: Initially 500 micrograms once daily for 4 nights, dose to be increased over 2-4 weeks, usual dose 3-6 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary
      - Child 12-17 years: Initially 1 mg once daily for 4 nights, dose to be increased over 2-4 weeks, usual dose 4-8 mg daily, dose usually taken at night; may be given in 3-4 divided doses if necessary

  **All forms of epilepsy | Myoclonus**
    - **By mouth**
      - Adult: Initially 1 mg once daily for 4 nights, dose to be increased over 2-4 weeks, usual dose 4-8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3-4 divided doses if necessary
      - Elderly: Initially 500 micrograms once daily for 4 nights, dose to be increased over 2-4 weeks, usual dose 4-8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3-4 divided doses if necessary

  **Panic disorders (with or without agoraphobia) resistant to antidepressant therapy**
    - **By mouth**
      - Adult: 1-2 mg daily

- **Unlicensed Use** Clonazepam doses in BNF may differ from those in product literature. Use for panic disorders (with or without agoraphobia) resistant to antidepressant therapy is an unlicensed indication.

**Important Safety Information**

- **Contra-Indications** Coma, current alcohol abuse, current drug abuse, respiratory depression

- **Caution** Acute porphyrias p. 930 • airways obstruction • brain damage • cerebellar ataxia • depression • spinal ataxia • suicidal ideation

**Cautions, Further Information**

The effectiveness of clonazepam may decrease significantly after weeks or months of continuous therapy.

**Side-Effects**

- Common or very common: Amnesia • bronchial hypersecretion in infants and small children • co-ordination disturbances • confusion • dependence • dizziness • drowsiness • fatigue • muscle hypotonia • nystagmus • poor concentration • restlessness • salivary hypersecretion in infants and small children • withdrawal symptoms (in children)

- Rare: Aggression • anxiety • blood disorders • dystartha • gastro-intestinal symptoms • headache • paradoxical...
effects - pruritus - respiratory depression - reversible hair loss - sexual dysfunction - skin pigmentation changes - suicidal ideation (in adults) - urinary incontinence - urticaria - visual disturbances on long-term treatment

- **Very rare** Increase in seizure frequency

- **BREAST FEEDING** Present in milk, and should be avoided if possible during breast-feeding.

  All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.

- **HEPATIC IMPAIRMENT** Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

- **RENAI IMPAIRMENT** Start with small doses in severe impairment.

- **MONITORING REQUIREMENTS**

  - In children Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified, because the target concentration ranges are arbitrary and often vary between individuals. However, plasma drug concentrations may be measured in children with worsening seizures, status epilepticus, suspected noncompliance, or suspected toxicity. Similarly, haematological and biochemical monitoring should not be undertaken unless clinically indicated.

- **PRESCRIBING AND DISPENCING INFORMATION**

  Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

  Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic oral clonazepam product.

- **PATIENT AND CARER ADVICE**

  Medicines for Children leaflet: Clonazepam for preventing seizures www.medicinesforchildren.org.uk/clonazepam-preventing-seizures-0

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: orodispersible tablet, oral suspension, oral solution, oral drops

  **Tablet**

  CAUTIONARY AND ADVISORY LABELS 2, 8

  - **Clonazepam (Non-proprietary)**
    - Clonazepam 2 mg Clonazepam 2mg tablets 100 tablet [PoM] £33.41 DT price = £31.47 [CD4-8]
    - Clonazepam 500 microgram Clonazepam 500microgram tablets 100 tablet [PoM] £30.11 DT price = £28.35 [CD4-1]

  **Oral solution**

  CAUTIONARY AND ADVISORY LABELS 2, 8

  EXCIPIENTS: May contain Ethanol

  - **Clonazepam (Non-proprietary)**
    - Clonazepam 100 microgram per 1 ml Clonazepam 500micrograms/5ml oral solution sugar free sugar-free 150 ml [PoM] £83.40 DT price = £66.95 [CD4-8]
    - Clonazepam 400 microgram per 1 ml Clonazepam 2mg/5ml oral solution sugar free sugar-free 150 ml [PoM] £108.36 DT price = £108.36 [CD4-1]

  **Oral drops**

  - **Clonazepam (Non-proprietary)**
    - Clonazepam 2.5 mg per 1 ml Rivotril 2.5mg/1ml drops sugar-free 90 ml [PoM] no price available [CD4-1]

  **Oral lyophilisate**

  - **Clonazepam (Non-proprietary)**
    - Clonazepam 500 microgram Klonopin 0.5mg oral lyophilisates sugar-free 60 tablet [PoM] no price available [CD4-1]

### 2.1 Status epilepticus

- **Other drugs used for Status epilepticus** Diazepam, p. 321 - Fosphenytoin sodium, p. 294 - Phenobarbital, p. 313 - Phenytoin, p. 302

#### ANTIEPILEPTICS  ▶ BARBITURATES

### Thiopental sodium

(Thiopentone sodium)

- **INDICATIONS AND DOSE**

  **Status epilepticus (only if other measures fail)**

  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: 75–125 mg for 1 dose, to be administered as a 2.5% (25 mg/mL) solution

  **Induction of anaesthesia**

  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: Initially 100–150 mg, to be administered over 10–15 seconds usually as a 2.5% (25 mg/mL) solution, followed by 100–150 mg after 0.5–1 minute if required, dose to be given in fit and premedicated adults; debilitated patients or adults over 65 years may require a lower dose or increased administration time, alternatively initially up to 4 mg/kg (max. per dose 500 mg)

  **Anaesthesia of short duration**

  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: Initially 100–150 mg, to be administered over 10–15 seconds usually as a 2.5% (25 mg/mL) solution, followed by 100–150 mg after 0.5–1 minute if required, dose to be given in fit and premedicated adults; debilitated patients or adults over 65 years may require a lower dose or increased administration time, alternatively initially up to 4 mg/kg (max. per dose 500 mg)

  **Reduction of raised intracranial pressure if ventilation controlled**

  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: 1.5–3 mg/kg, repeated if necessary

#### IMPORTANT SAFETY INFORMATION

Thiopental sodium should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 · myotonic dystrophy

- **CAUTIONS** Acute circulatory failure (shock) · avoid intra-arterial injection · cardiovascular disease · elderly · fixed cardiac output · hypovolaemia · reconstituted solution is highly alkaline (extravasation causes tissue necrosis and severe pain)

- **INTERACTIONS** Appendix 1 (anaesthetics, general).

- **SIDE-EFFECTS** Arrhythmias · cough · headache · hypersensitivity reactions · hypotension · laryngeal spasm · myocardial depression · rash · sneezing

- **PREGNANCY** May depress neonatal respiration when used during delivery.

- **BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

- **HEPATIC IMPAIRMENT** Use with caution—reduce dose.

- **RENAI IMPAIRMENT** Caution in severe impairment.
PATIENT AND CARER ADVICE

Driving and skilled tasks
Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Powder for solution for injection

- Thiopental sodium (Non-proprietary)
- Thiopental sodium 500 mg: Thiopental 500 mg powder for solution for injection vials | 25 vial Pack £172.50

HYPNOTICS, SEDATIVES AND ANXIOLYTICS > BENZODIAZEPINES

Lorazepam

INDICATIONS AND DOSE

Short-term use in anxiety

- BY MOUTH
  - Adult: 1–4 mg daily in divided doses, for debilitated patients, use elderly dose
  - Elderly: 0.5–2 mg daily in divided doses

Short-term use in insomnia associated with anxiety

- BY MOUTH
  - Adult: 1–2 mg daily, to be taken at bedtime

Acute panic attacks

- BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION
  - Adult: 25–30 micrograms/kg every 6 hours if required; usual dose 1.5–2.5 mg every 6 hours if required, intravenous injection to be administered into a large vein, only use intramuscular route when oral and intravenous routes not possible

Conscious sedation for procedures

- BY MOUTH
  - Adult: 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation
  - BY SLOW INTRAVENOUS INJECTION
  - Adult: 50 micrograms/kg, to be administered 30–45 minutes before operation
  - BY INTRAMUSCULAR INJECTION
  - Adult: 50 micrograms/kg, to be administered 60–90 minutes before operation

Premedication

- BY MOUTH
  - Adult: 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation
  - BY SLOW INTRAVENOUS INJECTION
  - Adult: 50 micrograms/kg, to be administered 30–45 minutes before operation
  - BY INTRAMUSCULAR INJECTION
  - Adult: 50 micrograms/kg, to be administered 60–90 minutes before operation

Status epilepticus | Febrile convulsions | Convulsions caused by poisoning

- BY SLOW INTRAVENOUS INJECTION
  - Child 1 month-11 years: 100 micrograms/kg (max. per dose 4 mg) for 1 dose, then 100 micrograms/kg after 10 minutes (max. per dose 4 mg) if required for 1 dose, to be administered into a large vein
  - Child 12-17 years: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein

UNLICENSED USE


IMPORTANT SAFETY INFORMATION

ANAESTHESIA

Benzodiazepines should only be administered for anaesthesia by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

CONTRA-INDICATIONS

- Avoid injections containing benzyl alcohol in neonates · chronic psychosis (in adults) · CNS depression · compromised airway · hyperkinesis · not for use alone to treat depression (or anxiety associated with depression) (in adults) · obsessional states · phobic states · respiratory depression

CAUTIONS

- Personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence · muscle weakness · organic brain changes · parenteral administration

CAUTIONS, FURTHER INFORMATION

- Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

- Special precautions for parenteral administration When given parenterally, facilities for managing respiratory depression with mechanical ventilation must be available. Close observation required until full recovery from sedation.

SIDE-EFFECTS

- Common or very common Amnesia · ataxia (in children) · ataxia (especially in the elderly)(in adults) · confusion (in children) · confusion (especially in the elderly)(in adults) · dependence · drowsiness the next day · lightheadedness the next day · muscle weakness · paradoxical increase in aggression

- Uncommon Changes in libido (in adults) · dizziness · dysarthria · gastro-intestinal disturbances · gynaecomastia · headache (in adults) · hypotension (in adults) · incontinence · salivation changes · slurred speech (in adults) · tremor · urinary retention (in adults) · vertigo (in adults) · visual disturbances

- Rare Apnoea · blood disorders · changes in libido (in children) · headache (in children) · hypotension (in children · jaundice · respiratory depression · skin reactions · urinary retention (in children) · vertigo (in children)

- Frequency not known Delusions (in children) · excitement (in children) · hallucinations (in children) · irritability (in children) · marked respiratory depression, particularly with high dose and intravenous use (facilities for its treatment are essential) · pain (on intravenous injection) · psychosis (in children) · restlessness (in children) · thrombophlebitis (on intravenous injection)

BREAST FEEDING

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

HEPATIC IMPAIRMENT

Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

RENAL IMPAIRMENT

Start with small doses in severe impairment.
318 Epilepsy and other seizure disorders

Nervous system

MEDICINAL FORMS

With intravenous use in adults

With intramuscular use in adults

With intravenous use in children

DIRECTIONS FOR ADMINISTRATION

Adult:

BY SLOW INTRAVENOUS INJECTION

BY BUCCAL ADMINISTRATION

Status epilepticus

Midazolam

EXCIPIENTS: May contain Benzyl alcohol, propylene glycol

Lorazepam (Non-proprietary)

CAUTIONARY AND ADVISORY LABELS

2, 19

extends to afterwards. For intravenous benzodiazepines the risk about the risks of undertaking skilled tasks (e.g. driving) afterwards. For intravenous benzodiazepines the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection

Table

CAUTIONARY AND ADVISORY LABELS 2, 19

Lorazepam (Non-proprietary)

Lorazepam 1 mg Lorazepam 1mg tablets | 28 tablet m | £6.75 DT price = £2.35 (C04-J) | 30 tablet m no price available (C04-J)

Lorazepam 2.5 mg Lorazepam 2.5mg tablets | 28 tablet m | £12.50 DT price = £2.95 (C04-J) | 30 tablet m no price available (C04-J)

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol, propylene glycol

Ativan (Pfizer Ltd)

Lorazepam 4 mg per 1 ml Ativan 4mg/1ml solution for injection ampoules | 10 ampoule m | £3.54 (C04-J)

Midazolam

INDICATIONS AND DOSE

Status epilepticus

BY BUCCAL ADMINISTRATION

Child 1-2 months: 300 micrograms/kg (max. per dose 2.5 mg), then 300 micrograms/kg after 10 minutes (max. per dose 2.5 mg) if required

Child 3-11 months: 2.5 mg, then 2.5 mg after 10 minutes if required

Child 1-4 years: 5 mg, then 5 mg after 10 minutes if required

Child 5-9 years: 7.5 mg, then 7.5 mg after 10 minutes if required

Child 10-17 years: 10 mg, then 10 mg after 10 minutes if required

Adult: 10 mg, then 10 mg after 10 minutes if required

Conscious sedation for procedures

BY SLOW INTRAVENOUS INJECTION

Adult: Initially 2–2.5 mg, to be administered 5–10 minutes before procedure at a rate of approximately 2 mg/minute, increased in steps of 1 mg

if required, usual total dose is 3.5–5 mg; maximum 7.5 mg per course

Elderly: Initially 0.5–1 mg, to be administered 5–10 minutes before procedure at a rate of approximately 2 mg/minute, increased in steps of 0.5–1 mg if required; maximum 3.5 mg per course

Sedative in combined anaesthesia

INITIALLY BY INTRAVENOUS INJECTION

Adult: 30–100 micrograms/kg, repeated if necessary, alternatively (by continuous intravenous infusion) 30–100 micrograms/kg/hour

Elderly: Lower doses needed

Premedication

BY DEEP INTRAMUSCULAR INJECTION

Adult: 70–100 micrograms/kg, to be administered 20–60 minutes before induction, for debilitated patients, use elderly dose

Elderly: 25–50 micrograms/kg, to be administered 20–60 minutes before induction

BY INTRAVENOUS INJECTION

Adult: 1–2 mg, repeated if necessary, to be administered 5–30 minutes before procedure, for debilitated patients, use elderly dose

Elderly: 0.5 mg, repeated if necessary, initial dose to be administered 5–30 minutes before procedure, repeat dose slowly as required

Induction of anaesthesia (but rarely used)

BY SLOW INTRAVENOUS INJECTION

Adult: 150–200 micrograms/kg daily in divided doses (max. per dose 5 mg), dose to be given at intervals of 2 minutes, maximum total dose 600 micrograms/kg, for debilitated patients, use elderly dose

Elderly: 50–150 micrograms/kg daily in divided doses (max. per dose 5 mg), dose to be given at intervals of 2 minutes, maximum total dose 600 micrograms/kg

Sedation of patient receiving intensive care

INITIALLY BY SLOW INTRAVENOUS INJECTION

Adult: Initially 30–300 micrograms/kg, dose to be given in steps of 1–2.5 mg every 2 minutes, then (by slow intravenous injection or by continuous intravenous infusion) 30–200 micrograms/kg/hour, reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia, lower doses may be adequate if opioid analgesic also used

Confusion and restlessness in palliative care (adjunct to antipsychotic)

BY SUBCUTANEOUS INFUSION

Adult: Initially 10–20 mg/24 hours, adjusted according to response; usual dose 20–60 mg/24 hours

Convulsions in palliative care

BY CONTINUOUS SUBCUTANEOUS INFUSION

Adult: Initially 20–40 mg/24 hours

UNLICENSED USE Oromucosal solution not licensed for use in children under 3 months. Oromucosal solution not licensed for use in adults over 18 years. Unlicensed oromucosal formulations are also available and may have different doses—refer to product literature.

IMPORTANT SAFETY INFORMATION

ANAESTHESIA

Benzodiazepines should only be administered for anaesthesia by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

PRESCRIBING OF MIDAZOLAM IN PALLIATIVE CARE

The use of high-strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be considered in palliative care and other situations where a higher strength may be more appropriate to administer the prescribed dose, and
CONTRA-INDICATIONS  CNS depression • compromised airway • severe respiratory depression

CAUTIONS  Cardiac disease • children (particularly if cardiovascular impairment) • concentration of midazolam in children under 15 kg not to exceed 1 mg/mL • debilitated patients (reduce dose) (in children) • hypothermia • hypovolaemia (risk of severe hypotension) • neonates • risk of airways obstruction and hyperventilation in children under 6 months (monitor respiratory rate and oxygen saturation) • vasoconstriction

CAUTIONS, FURTHER INFORMATION
- Recovery when used for sedation  Midazolam has a fast onset of action, recovery is faster than for other benzodiazepines such as diazepam, but may be significantly longer in the elderly, in patients with a low cardiac output, or after repeated dosing.

SIDE-EFFECTS  Amnesia • anaphylaxis • ataxia • blood disorders • bronchospasm • cardiac arrest • changes in libido (in adults) • confusion • convulsions (more common in neonates) • depression of consciousness • dizziness • drowsiness • dry mouth • dysarthria • euphoria • fatigue (in children) • gastrointestinal disturbances • hallucinations • headache • heart rate changes • hiccups • hypotension • incontinence • increased appetite • injection-site reactions • involuntary movements • jaundice • laryngospasm • muscle weakness • paradoxical aggression (especially in children and elderly) • paradoxical excitement (especially in children and elderly) • respiratory arrest (particularly with high doses or on rapid injection) • respiratory depression (may be severe with sedative and peri-operative use—facilities for its treatment are essential) • respiratory depression (particularly with high doses or on rapid injection) • restlessness (with sedative and peri-operative use) (in children) • salivation changes • sedation (may be severe with sedative and perioperative use) (in children) • skin reactions • visual disturbances

SIDE-EFFECTS, FURTHER INFORMATION
- Sedation  Midazolam is associated with profound sedation when high doses are given or when it is used with certain other drugs.

Overdose
There have been reports of overdosage when high strength midazolam has been used for conscious sedation. The use of high-strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be restricted to general anaesthesia, intensive care, palliative care, or other situations where the risk has been assessed. It is advised that flumazenil is available when midazolam is used, to reverse the effects if necessary.

BREAST FEEDING  Small amount present in milk—avoid breast-feeding for 24 hours after administration (although amount probably too small to be harmful after single doses).

HEPATIC IMPAIRMENT  Use with caution particularly in sedative doses; can precipitate coma. For status epilepticus and febrile convulsions: use with caution in mild to moderate impairment; avoid in severe impairment.

RENAI IMPAIRMENT  Use with caution in chronic renal failure.

DIRECTIONS FOR ADMINISTRATION  For intravenous infusion (Hypnovel®), give continuously in Glucose 5% or Sodium chloride 0.9%.

PRESCRIBING AND DISPENSING INFORMATION
Palliative care
For further information on the use of midazolam in palliative care, see www.palliativedrugs.com/formulary/en/midazolam.html.

PATIENT AND CARER ADVICE
Patients or carers should be given advice on how to administer midazolam oromucosal solution.

Medicines for Children leaflet: Midazolam for stopping seizures www.medicinesforchildren.org.uk/midazolam-for-stopping-seizures

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oromucosal solution, solution for injection, infusion, solution for infusion

Oromucosal solution
CAUTIONARY AND ADVISORY LABELS 2
- Buccolam (Shire Pharmaceuticals Ltd)
  Midazolam (as Midazolam hydrochloride) 5 mg per
  1 ml Buccolam 7.5 mg/1.5 ml oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £89.00 DT price = £89.00 (C03)
  Buccolam 10 mg/2 ml oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £91.50 DT price = £91.50 (C03)
  Buccolam 5 mg/1 ml oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £89.50 DT price = £89.50 (C03)
  Buccolam 2.5 mg/0.5 ml oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £82.00 DT price = £82.00 (C03)

Solution for injection
- Midazolam (Non-proprietary)
  Midazolam (as Midazolam hydrochloride) 1 mg per
  1 ml Midazolam 5 mg/5 ml solution for injection ampoules | 10 ampoule (Pom) £6.00 (C03)
  Midazolam 2 mg/2 ml solution for injection ampoules | 10 ampoule (Pom) £5.00 (C03)
  Midazolam (as Midazolam hydrochloride) 2 mg per
  1 ml Midazolam 10 mg/5 ml solution for injection ampoules | 10 ampoule (Pom) £9.80 (C03) | 10 ampoule (Pom) no price available (Hospital only) (C03)
  Midazolam (as Midazolam hydrochloride) 5 mg per
  1 ml Midazolam 50 mg/10 ml solution for injection ampoules | 10 ampoule (Pom) £78.00 (C03)
  Midazolam 10 mg/2 ml solution for injection ampoules | 10 ampoule (Pom) £7.97 DT price = £6.90 (C03)
  Hypnovel (Roche Products Ltd)
  Midazolam (as Midazolam hydrochloride) 5 mg per 1 ml
  Hypnovel 10 mg/2 ml solution for injection ampoules | 10 ampoule (Pom) £7.11 DT price = £6.90 (C03)

Solution for infusion
- Midazolam (Non-proprietary)
  Midazolam (as Midazolam hydrochloride) 1 mg per
  1 ml Midazolam 50 mg/50 ml solution for infusion vials | 1 vial (Pom) £9.56–£11.00 (C03)
  Midazolam (as Midazolam hydrochloride) 2 mg per
  1 ml Midazolam 100 mg/50 ml solution for infusion vials | 1 vial (Pom) £9.05–£12.50 (C03)
3 Mental health disorders

3.1 Anxiety

Other drugs used for Anxiety Duloxetine, p. 345 · Escitalopram, p. 342 · Lorazepam, p. 317 · Moclobemide, p. 340 · Oxprenolol hydrochloride, p. 141 · Paroxetine, p. 344 · Pericyazine, p. 364 · Perphenazine, p. 364 · Pregabalin, p. 304. Trazodone hydrochloride, p. 347 · Trifluoperazine, p. 366 · Venlafaxine, p. 345

Buspirone hydrochloride

**INDICATIONS AND DOSE**

**Anxiety (short-term use)**

- **BY MOUTH**
  - Adult: 5 mg 2–3 times a day, increased if necessary up to 45 mg daily, dose to be increased at intervals of 2–3 days; usual dose 15–30 mg daily in divided doses

**CONTRA-INDICATIONS** Acute porphyrias p. 930 · epilepsy

**CAUTIONS** Does not alleviate symptoms of benzodiazepine withdrawal

**CAUTIONS, FURTHER INFORMATION**

A patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone.

**INTERACTIONS** → Appendix 1 (anxiolytics and hypnotics).

**SIDE-EFFECTS**

- **Common or very common** Dizziness · excitement · headache · fatigue · palpitation · seizures · sweating · tachycardia
- **Rare** Chest pain · confusion · drowsiness · dry mouth · nervousness
- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.
- **HEPATIC IMPAIRMENT** Reduce dose in mild to moderate disease. Avoid in severe disease.
- **RENAL IMPAIRMENT** Reduce dose. Avoid if eGFR less than 20 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

May affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Buspirone hydrochloride (Non-proprietary)**
  - **Buspirone hydrochloride 5 mg** Buspirone 5mg tablets | 30 tablet (PO) £3.30 307 price = £3.38
  - **Buspirone hydrochloride 10 mg** Buspirone 10mg tablets | 30 tablet (PO) £5.62 307 price = £4.20

**HYPOSTONICS, SEDATIVES AND ANXIOLYTICS**

**Benzodiazepines**

**CONTRA-INDICATIONS** Acute pulmonary insufficiency · marked neuromuscular respiratory weakness · sleep apnoea syndrome · unstable myasthenia gravis

**CAUTIONS** Avoid prolonged use (and abrupt withdrawal thereafter) · debilitated patients (reduce dose)(in adults) · elderly (reduce dose) · history of alcohol dependence or abuse · history of drug dependence or abuse · myasthenia gravis · respiratory disease

**CAUTIONS, FURTHER INFORMATION**

- **Paradoxical effects** A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**INTERACTIONS** → Appendix 1 (anxiolytics and hypnotics).

**SIDE-EFFECTS**

**Overdose**

Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma. For details on the management of poisoning, see Benzodiazepines, under Emergency treatment of poisoning p. 1204.

**PREGNANCY** Risk of neonatal withdrawal symptoms when used during pregnancy. Avoid regular use and use only if there is a clear indication such as seizure control. High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

**RENAL IMPAIRMENT** Increased cerebral sensitivity to benzodiazepines.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including benzodiazepines, see Drugs and driving under Guidance on prescribing p. 1.

**Alprazolam**

**INDICATIONS AND DOSE**

**Short-term use in anxiety**

- **BY MOUTH**
  - Adult: 250–500 micrograms 3 times a day, increased if necessary up to 3 mg daily, for debilitated patients, use elderly dose
  - Elderly: 250 micrograms 2–3 times a day, increased if necessary up to 3 mg daily

**CONTRA-INDICATIONS** Chronic psychosis · hyperkinesia · not for use alone to treat depression (or anxiety associated with depression) · obsessional states · phobic states · respiratory depression

**CAUTIONS** Muscle weakness · organic brain changes · personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

**SIDE-EFFECTS**

- **Common or very common** Amnesia · ataxia (especially in the elderly) · confusion (especially in the elderly) · dependence · drowsiness the next day · lightheadedness the next day · muscle weakness · paradoxical increase in aggression
- **Uncommon** Changes in libido · dizziness · dysthria · gastro-intestinal disturbances · gynaecomastia · headache · hypotension · incontinence · salivation changes · slurred speech · tremor · urinary retention · vertigo · visual disturbances
- **Rare** Apnoea · blood disorders · jaundice · respiratory depression · skin reactions
Chlordiazepoxide hydrochloride

**INDICATIONS AND DOSE**

**Short-term use in anxiety**

- **BY MOUTH**
  - Adult: 10 mg 3 or 4 times a day, increased if necessary to 60–100 mg daily in divided doses, for debilitated patients, use elderly dose.
  - Elderly: 5 mg 3 times a day, increased if necessary to 30–50 mg daily in divided doses.

**Treatment of alcohol withdrawal in moderate dependence**

- **BY MOUTH**
  - Adult: 10–30 mg 4 times a day, dose to be gradually reduced over 5–7 days, consult local protocols for titration regimens.

**Treatment of alcohol withdrawal in severe dependence**

- **BY MOUTH**
  - Adult: 10–50 mg 4 times a day and 10–40 mg as required for the first 2 days, dose to be gradually reduced over 7–10 days, consult local protocols for titration regimens; maximum 250 mg per day.

**CONTRA-INDICATIONS** Chronic psychosis · hyperkinesia · not for use alone to treat depression (or anxiety associated with depression) · obsessional states · phobic states · respiratory depression.

**CAUTIONS** Muscle weakness · organic brain changes · personality disorder (within the fearful group—dependent, avoidant, obsessive—compulsive) may increase risk of dependence.

**SIDE-EFFECTS**

- **Common or very common** Amnesia · ataxia (especially in the elderly) · confusion (especially in the elderly) · dependence · drowsiness the next day · lightheadedness the next day · muscle weakness · paradoxical increase in aggression.
- **Uncommon** Changes in libido · dizziness · dysarthria · gastrointestinal disturbances · gynaecomastia · headache · hypotension · incontinence · salivation changes · slurred speech · tremor · urinary retention · vertigo · visual disturbances.

**Rare** Apnoea · blood disorders · jaundice · respiratory depression · skin reactions.

**HEPATIC IMPAIRMENT** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**RENAL IMPAIRMENT** Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer. Avoid in severe impairment.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks** May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NHS restrictions** Alprazolam tablets are not prescribable under the NHS.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- **Xanax** (Pfizer Ltd)
  - Alprazolam 250 microgram tablets 60 tablet [Pom] £3.18 [CD4-1]  
  - Alprazolam 500 microgram tablets 60 tablet [Pom] £6.09 [CD4-1]

**Chlordiazepoxide hydrochloride (Non-proprietary)**

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 2**

- **Chlordiazepoxide hydrochloride 5 mg** Chlordiazepoxide 5 mg capsules 28 capsule [Pom] no price available [CD4-1] 100 capsule [Pom] £11.50 DT price = £11.50 [CD4-1]

**Chlordiazepoxide hydrochloride 10 mg** Chlordiazepoxide 10 mg capsules 28 capsule [Pom] no price available [CD4-1] 100 capsule [Pom] £17.80 DT price = £17.80 [CD4-1]

- **Librium** (Meda Pharmaceuticals Ltd)
  - Chlordiazepoxide hydrochloride 5 mg Librium capsules 100 capsule [Pom] £5.38 DT price = £11.50 [CD4-1]

**Chlordiazepoxide hydrochloride 10 mg** Librium 10 mg capsules 100 capsule [Pom] £7.46 DT price = £17.80 [CD4-1]

**Diazepam**

**INDICATIONS AND DOSE**

**Muscle spasm of varied aetiology**

- **BY MOUTH**
  - Adult: 2–15 mg daily in divided doses, then increased if necessary to 60 mg daily, adjusted according to response, dose only increased in spastic conditions.

**Acute muscle spasm**

- **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
  - Adult: 10 mg, then 10 mg after 4 hours if required, intravenous injection to be administered into a large vein at a rate of no more than 5 mg/minute.

**Tetanus**

- **BY INTRAVENOUS INJECTION**
  - Child: 100–300 micrograms/kg every 1–4 hours

**Adult:** 100–300 micrograms/kg every 1–4 hours

- **BY INTRAVENOUS INFUSION, OR BY NASODUODENAL TUBE**
  - Child: 3–10 mg/kg, adjusted according to response, to be given over 24 hours

**Adult:** 3–10 mg/kg, adjusted according to response, to be given over 24 hours

**BNF 73 Anxiety 321 2016-11-21**
Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm
▶ By mouth
- Child 1–11 months: Initially 250 micrograms/kg twice daily
- Child 1–4 years: Initially 2.5 mg twice daily
- Child 5–11 years: Initially 5 mg twice daily
- Child 12–17 years: Initially 10 mg twice daily; maximum 40 mg per day

Anxiety
▶ By mouth
- Adult: 2 mg 3 times a day, then increased if necessary to 15–30 mg daily in divided doses, for debilitated patients, use elderly dose
- Elderly: 1 mg 3 times a day, then increased if necessary to 7.5–15 mg daily in divided doses

Insomnia associated with anxiety
▶ By mouth
- Adult: 5–15 mg daily, to be taken at bedtime

Severe acute anxiety | Control of acute panic attacks | Acute alcohol withdrawal
▶ By intramuscular injection, or by slow intravenous injection
- Adult: 10 mg, then 10 mg after at least 4 hours if required, intravenous injection to be administered into a large vein, at a rate of not more than 5 mg/minute

Acute drug-induced dystonic reactions
▶ By intravenous injection
- Adult: 5–10 mg, then 5–10 mg after at least 10 minutes as required, to be administered into a large vein, at a rate of not more than 5 mg/minute

Acute anxiety and agitation
▶ By rectum
- Adult: 500 micrograms/kg, then 500 micrograms/kg after 12 hours as required
- Elderly: 250 micrograms/kg, then 250 micrograms/kg after 12 hours as required

Premedication
▶ By mouth
- Adult: 5–10 mg, to be given 1–2 hours before procedure, for debilitated patients, use elderly dose
- Elderly: 2.5–5 mg, to be given 1–2 hours before procedure

▶ By intravenous injection
- Adult: 100–200 micrograms/kg, to be administered into a large vein at a rate of not more than 5 mg/minute, immediately before procedure

Sedation in dental procedures carried out in hospital
▶ By mouth
- Adult: Up to 20 mg, to be given 1–2 hours before procedure

Conscious sedation for procedures, and in conjunction with local anaesthesia
▶ By mouth
- Adult: 5–10 mg, to be given 1–2 hours before procedure, for debilitated patients, use elderly dose
- Elderly: 2.5–5 mg, to be given 1–2 hours before procedure

Sedative cover for minor surgical and medical procedures
▶ By intravenous injection
- Adult: 10–20 mg, to be administered into a large vein over 2–4 minutes, immediately before procedure

Status epilepticus | Febrile convulsions | Convulsions due to poisoning
▶ By intravenous injection
- Neonate: 300–400 micrograms/kg, then 300–400 micrograms/kg after 10 minutes if required, to be given over 3–5 minutes

Child 1 month–11 years: 300–400 micrograms/kg (max. per dose 10 mg), then 300–400 micrograms/kg after 10 minutes if required, to be given over 3–5 minutes
- Child 12–17 years: 10 mg, then 10 mg after 10 minutes if required, to be given over 3–5 minutes
- Adult: 10 mg, then 10 mg after 10 minutes if required, administered at a rate of 1 mL (5 mg) per minute
▶ By rectum
- Neonate: 1.25–2.5 mg, then 1.25–2.5 mg after 10 minutes if required
- Child 1 month–1 year: 5 mg, then 5 mg after 10 minutes if required
- Child 2–11 years: 5–10 mg, then 5–10 mg after 10 minutes if required
- Child 12–17 years: 10–20 mg, then 10–20 mg after 10 minutes if required
- Adult: 10–20 mg, then 10–20 mg after 10–15 minutes if required
- Elderly: 10 mg, then 10 mg after 10–15 minutes if required

Life-threatening acute drug-induced dystonic reactions
▶ By intravenous injection
- Child 1 month–11 years: 100 micrograms/kg, repeated if necessary, to be given over 3–5 minutes
- Child 12–17 years: 5–10 mg, repeated if necessary, to be given over 3–5 minutes

Dyspnœa associated with anxiety in palliative care
▶ By mouth
- Adult: 5–10 mg daily

Pain of muscle spasm in palliative care
▶ By mouth
- Adult: 5–10 mg daily

- **Unlicensed use** Diazepam Desitin®, Diazepam Rectubes®, and Stesolid Rectal Tubes® not licensed for use in children under 1 year.

**Important safety information**

**Anaesthesia**

Benzodiazepines should only be administered for anaesthesia by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

**Contra-indications** Avoid injections containing benzyl alcohol in neonates • chronic psychosis (in adults) • CNS depression • compromised airway • hyperkinesia • not for use alone to treat depression (or anxiety associated with depression) (in adults) • obsessional states • phobic states • respiratory depression

**Caution**

**General cautions** Muscle weakness • organic brain changes • parenteral administration (close observation required until full recovery from sedation) • personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

**Specific cautions** With intravenous use High risk of venous thrombophlebitis with intravenous use (reduced by using an emulsion formulation)

**Caution, Further information**

**Side-effects**

**General side-effects**

- Common or very common Amnesia • ataxia (in children) • ataxia (especially in the elderly) (in adults) • confusion (in...
children) - confusion (especially in the elderly) (in adults) - decrease in muscle strength - paradoxical increase in aggression

- **Uncommon** Changes in libido (in adults) - dizziness - dysarthria - gastrointestinal disturbances - gynaecomastia - headache (in adults) - hypotension (in adults) - incontinence - salivation changes - slurred speech (in adults) - tremor - urinary retention (in adults) - vertigo (in adults) - visual disturbances.

- **Rare** Apnoea - blood disorders - changes in libido (in children) - headache (in children) - hypotension (in children) - jaundice - respiratory depression - skin reactions - urinary retention (in children) - vertigo (in children)

- **Frequency not known** Delusions (in children) - excitement (in children) - hallucinations (in children) - hypotonia (when used for muscle spasm) - irritability (in children) - marked respiratory depression, particularly with high dose (facilities for its treatment are essential) - psychosis (in children) - restlessness (in children)

### SPECIFIC SIDE-EFFECTS

- With intravenous use
  - Pain - thrombophlebitis - venous thrombosis (in adults)

### PREGNANCY

Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol. 

- Epilepsy and Pregnancy Register: All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

### BREASTFEEDING

Present in milk, and should be avoided if possible during breast-feeding.

### HEPATIC IMPAIRMENT

Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half lives are safer, such as temazepam or oxazepam.

Avoid in severe impairment.

### RENAL IMPAIRMENT

Start with small doses in severe impairment.

### DIRECTIONS FOR ADMINISTRATION

- With intravenous use
  - Diazepam is adsorbed by plastics of infusion bags and giving sets. Emulsion formulation preferred for intravenous injection.

- With intravenous use in children
  - For continuous intravenous infusion of diazepam emulsion, dilute to a concentration of max. 400 micrograms/mL with Glucose 5% or 10%; max. 6 hours between addition and completion of infusion. For continuous intravenous infusion of diazepam solution, dilute to a concentration of max. 50 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%.

- With intravenous use in adults
  - For intravenous infusion (solution) (Diazepam, Wockhardt), give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to a concentration of not more than 10 mg in 200 mL. For intravenous infusion (emulsion) (Diazemuls®), give continuously in Glucose 5% or 10%. May be diluted to a max. concentration of 200 mg in 500 mL; max. 6 hours between addition and completion of administration. May be given via drip tubing in Glucose 5% or 10% or Sodium chloride 0.9%.

- With intramuscular use or intravenous use in adults
  - Solution for injection should not be diluted, except for intravenous infusion.

- With intramuscular use in adults
  - Only use intramuscular route when oral and intravenous routes not possible.

### PRESCRIBING AND DISPENSING INFORMATION

- **Palliative care**
  - In adults: For further information on the use of diazepam in palliative care, see www.palliatiervedrugs.com/formulary/en/diazepam.html.

- **PATIENT AND CARER ADVICE**

  - **Driving and skilled tasks**
    - May impair judgement and increase reaction time, and so affect ability to drive or perform skilled tasks; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair performance on the following day.

    - Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of undertaking skilled tasks (e.g. driving) afterwards. For intravenous benzodiazepines the risk extends to at least 24 hours after administration.

    - Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

    - Medicines for Children leaflet: Diazepam for muscle spasm www.medicinesforchildren.org.uk/diazepam-for-muscle-spasm

    - Medicines for Children leaflet: Diazepam (rectal) for stopping seizures www.medicinesforchildren.org.uk/diazepam-rectal-stopping-seizures-0

### PROFESSION SPECIFIC INFORMATION

- **Dental practitioners’ formulary**
  - Diazepam Tablets may be prescribed.
  - Diazepam Oral Solution 2 mg/5 mL may be prescribed.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, suppository.

#### Tablet

- **CAUTIONARY AND ADVISORY LABELS** 2, 19

  - **Diazepam (Non-proprietary)**

    - Diazepam 2 mg (Actavis UK Ltd) 28 tablet (POM) £1.10 DT price = £0.75 (CD4-1) 100 tablet (POM) £160.71 (CD4-1)

    - Diazepam 5 mg (Actavis UK Ltd) 28 tablet (POM) £1.12 DT price = £0.78 (CD4-1) 100 tablet (POM) £210.71 (CD4-1)

    - Diazepam 10 mg (Actavis UK Ltd) 28 tablet (POM) £4.99 DT price = £0.93 (CD4-1) 500 tablet (POM) £113.04 (CD4-1)

#### Oral suspension

- **CAUTIONARY AND ADVISORY LABELS** 2, 19

  - **Diazepam (Non-proprietary)**

    - Diazepam 1 mg per 1 ml (Actavis UK Ltd) 5mg/5ml oral suspension | 100 ml (POM) £5.60-£6.60 (CD4-1)

    - Diazepam 400 microgram per 1 ml (Actavis UK Ltd) 2mg/5ml oral suspension | 100 ml (POM) £31.75-£39.00 DT price = £31.75 (CD4-1)

#### Oral solution

- **CAUTIONARY AND ADVISORY LABELS** 2, 19

  - **Diazepam (Non-proprietary)**

    - Diazepam 400 microgram per 1 ml (Actavis UK Ltd) 2mg/5ml oral solution sugar free price = £31.75-£40.49 DT price = £31.75 (CD4-1)

#### Solution for injection

- **CAUTIONARY AND ADVISORY LABELS** 2, 19

  - **Diazepam (Non-proprietary)**

    - Diazepam 5 mg per 1 ml (Actavis UK Ltd) 10mg/2ml solution for injection ampoules | 10 ampoule (POM) £5.50 DT price = £5.50 (CD4-1)

#### Emulsion for injection

- **Diazemuls (Actavis UK Ltd)**

  - Diazepam 5 mg per 1 ml (Actavis UK Ltd) 10mg/2ml emulsion for injection ampoules | 10 ampoule (POM) £9.05 (CD4-1)

#### Enema

- **CAUTIONARY AND ADVISORY LABELS** 2, 19

  - **Diazepam (Non-proprietary)**

    - Diazepam 2 mg per 1 ml (Actavis UK Ltd) 5mg RecTubes | 5 tube (POM) £5.85 DT price = £5.85 (CD4-1)

    - Diazepam 2.5mg/1.25ml rectal solution tube | 5 tube (POM) £6.65 (CD4-1)

    - Diazepam 2.5mg RecTubes | 5 tube (POM) £5.65 (CD4-1)

    - Diazepam 5mg/2.5ml rectal solution tube | 5 tube (POM) £6.30 DT price = £5.85 (CD4-1)
Oxazepam

**INDICATIONS AND DOSE**

**Anxiety (short-term use)**
- **By mouth**
  - Adult: 15–30 mg 3–4 times a day, for debilitating patients, use elderly dose
  - Elderly: 10–20 mg 3–4 times a day

**Insomnia associated with anxiety**
- **By mouth**
  - Adult: 15–25 mg once daily (max. per dose 50 mg), dose to be taken at bedtime

**SIDE-EFFECTS**

- Common or very common
  - Amnesia
  - Ataxia (especially in the elderly)
  - Confusion (especially in the elderly)
  - Dependence
  - Drowsiness the next day
  - Lightheadedness
  - Muscle weakness
  - Paradoxical increase in aggression

- Uncommon
  - Changes in libido
  - Dizziness
  - Dysarthria
  - Gastro-intestinal disturbances
  - Gynaecomastia
  - Headache
  - Hypotension
  - Incontinence
  - Salivation changes
  - Slurred speech
  - Tremor
  - Urinary retention
  - Vertigo
  - Visual disturbances

- Rare
  - Apnoea
  - Blood disorders
  - Jaundice
  - Respiratory depression
  - Skin reactions

**BREAST FEEDING**

- Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**HEPATIC IMPAIRMENT**

- Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives are safer.

Avoid in severe impairment.

**RENAI IMPAIRMENT**

- Start with small doses in severe impairment.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**

- May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

**CONTRA-INDICATIONS**

- Chronic psychosis
- Hypokinesia
- Not for use alone to treat depression or anxiety associated with depression
- Obsessional states
- Phobic states
- Respiratory depression

**CAUTIONS**

- Muscle weakness
- Organic brain changes
- Personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

**CAUTIONS, FURTHER INFORMATION**

- Paradoxical effects
  - A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**MEDICINAL FORMS**

- **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 2
  - Oxazepam (Non-proprietary)
  - Oxazepam 10 mg Oxazepam 10 mg tablets | 28 tablet £7.97 DT price = £1.13 (CD4-1)
  - Oxazepam 15 mg Oxazepam 15 mg tablets | 28 tablet £7.97 DT price = £1.17 (CD4-1)

**HYPNOTICS, SEDATIVES AND ANXIOLYRICS**

**NON-BENZODIAZEPINE HYPNOTICS AND SEDATIVES**

**Meprobamate**

**INDICATIONS AND DOSE**

- **Short-term use in anxiety—not recommended**
  - **By mouth**
    - Adult: 400 mg 3–4 times a day
    - Elderly: Up to 200 mg 3–4 times a day

**IMPORTANT SAFETY INFORMATION**

- The European Medicines Agency has recommended (January 2012) the suspension of all marketing authorisations for meprobamate because the risks, particularly of serious CNS side-effects, outweigh the benefits.

**CONTRA-INDICATIONS**

- Acute porphyrias p. 930
- Acute pulmonary insufficiency
- Respiratory depression

**CAUTIONS**

- Abrupt withdrawal (may precipitate convulsions)
- Avoid prolonged use
- Debilitated elderly
- Epilepsy (may induce seizures)
- History of alcohol abuse
- History of drug abuse
- Marked personality disorder
- Muscle weakness
- Respiratory disease

**INTERACTIONS**

- Appendix 1 (anxiolytics and hypnotics).

**SIDE-EFFECTS**

- Common or very common
  - Amnesia
  - Ataxia (especially in the elderly)
  - Confusion (especially in the elderly)
  - Dependence
  - Drowsiness the next day
  - Lightheadedness
  - Muscle weakness
  - Paradoxical increase in aggression

- Uncommon
  - Changes in libido
  - Dizziness
  - Dysarthria
  - Gastro-intestinal disturbances
  - Gynaecomastia
  - Headache
  - Hypotension
  - Incontinence
  - Salivation changes
  - Slurred speech
  - Tremor
  - Urinary retention
  - Vertigo
  - Visual disturbances

- Rare
  - Apnoea
  - Blood disorders
  - Jaundice
  - Respiratory depression
  - Skin reactions

**BREAST FEEDING**

- Avoid. Concentration in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in infant.

**HEPATIC IMPAIRMENT**

- Can precipitate coma.

**RENAI IMPAIRMENT**

- Start with small doses in severe impairment. Increased cerebral sensitivity.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**

- Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

**LESS SUITABLE FOR PRESCRIBING**

- Meprobamate is less suitable for prescribing.
3.2 Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder

**Management**

Central nervous system stimulants include the amphetamines (dexamphetamine sulfate p. 328 and lisdexamphetamine mesilate p. 329) and related drugs (e.g. methylphenidate hydrochloride p. 326). They have very few indications and in particular, should not be used to treat depression, obesity, senility, debility, or for relief of fatigue.

CNS stimulants should be prescribed for children with severe and persistent symptoms of attention deficit hyperactivity disorder (ADHD), when the diagnosis has been confirmed by a specialist; children with moderate symptoms of ADHD can be treated with CNS stimulants when psychological interventions have been unsuccessful or are unavailable. Prescribing of CNS stimulants may be continued by general practitioners, under a shared-care arrangement. Treatment of ADHD often needs to be continued into adolescence, and may need to be continued into adulthood.

Drug treatment of ADHD should be part of a comprehensive treatment programme. The choice of medication should take into consideration co-morbid conditions (such as tic disorders, Tourette syndrome, and epilepsy), the adverse effect profile, potential for drug misuse, tolerance and dependance; and preferences of the patient and carers. Methylphenidate hydrochloride and atomoxetine below are used for the management of ADHD; dexamphetamine sulfate and lisdexamphetamine mesilate are an alternative in children who do not respond to these drugs. Guanfacine p. 329, a non-stimulant alpha-2-adrenoceptor agonist, can be used in children for whom stimulants are not suitable, not tolerated, or ineffective. Therapeutic response to guanfacine should be evaluated every 3 months for the first year and then at least yearly, when prescribed for extended periods.

The need to continue drug treatment for ADHD should be reviewed at least annually. This may involve suspending treatment.

**CNS STIMULANTS** > CENTRALLY ACTING SYMPATHOMIMETICS

**Atomoxetine**

**INDICATIONS AND DOSE**

Attention deficit hyperactivity disorder (initiated by a specialist)

- **BY MOUTH**
  - Child 6–17 years (body-weight up to 70 kg): Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1200 mg per day
  
- Adult (body-weight up to 70 kg): Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 1200 mg per day
  
- Adult (body-weight 70 kg and above): Initially 40 mg daily for 7 days, dose is increased according to response; maintenance 80–100 mg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 1200 mg per day

**UNLICENSED USE** Atomoxetine doses in BNF may differ from those in product literature.

- In children Doses above 100 mg daily not licensed.
- In adults Dose maximum of 120 mg not licensed.

**CONTRA-INDICATIONS** Phaeochromocytoma • severe cardiovascular disease • severe cerebrovascular disease

**CAUTIONS** QT-interval prolongation • aggressive behaviour • cardiovascular disease • cerebrovascular disease • emotional lability • history of seizures • hostility • hypertension • mania • psychosis • structural cardiac abnormalities • susceptibility to angle-closure glaucoma • tachycardia

**INTERACTIONS** → Appendix 1 (atomoxetine). Avoid concomitant use of drugs that prolong QT interval.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain • anorexia • anxiety • chills • constipation • depression • dermatitis • dizziness • drowsiness • dry mouth • dyspepsia • flatulence • flushing • headache • increased blood pressure • irritability • laryngitis • malaise • mydriasis • nausea • palpitation • paraesthesia • prostatitis • rash • sexual dysfunction • sleep disturbances • sweating • tachycardia • taste disturbances • tremor • urinary dysfunction • vomiting

- **Uncommon** Aggression • cold extremities • emotional lability • hostility • hypoaesthesia • menstrual disturbances • muscle spasms • pruritus • psychosis • QT-interval prolongation • suicidal ideation • syncope • tics

- **Rare** Raynaud’s phenomenon • seizures

- **Very rare** Angle-closure glaucoma • hepatic disorders

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Avoid present in milk in animal studies.

**HEPATIC IMPAIRMENT** Halve dose in moderate impairment. Quarter dose in severe impairment.

**MONITORING REQUIREMENTS**

- Monitor for appearance or worsening of anxiety, depression or tics.
- Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Atomoxetine for attention deficit hyperactivity disorder (ADHD) www.medicinesforchildren.org.uk/atomoxetine-attention-deficit-hyperactivity-disorder-adhd
Suicidal ideation Following reports of suicidal thoughts and behaviour, patients and their carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression.

Hepatic impairment Following rare reports of hepatic disorders, patients and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought if in case of abdominal pain, unexplained nausea, malaise, darkening of the urine, or jaundice.

NATIONAL FUNDING/ACCESS DECISIONS

Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) (March 2006) NICE TA98

Atomoxetine is recommended, within its licensed indications, as an option for the management of ADHD in children and adolescents.

www.nice.org.uk/TA98

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (December 2015) that atomoxetine oral solution (Strattera®) is accepted for restricted use, within its licensed indications, for treating patients who are unable to swallow capsules.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Capsule

CAUTIONARY AND ADVISORY LABELS 3

Strattera (Eli Lilly and Company Ltd)

Atomoxetine (as Atomoxetine hydrochloride) 10 mg Strattera 10mg capsules | 7 capsule PPM £13.28 | 28 capsule PPM £53.09 DT price = £53.09

Atomoxetine (as Atomoxetine hydrochloride) 18 mg Strattera 18mg capsules | 7 capsule PPM £13.28 | 28 capsule PPM £53.09 DT price = £53.09

Atomoxetine (as Atomoxetine hydrochloride) 25 mg Strattera 25mg capsules | 7 capsule PPM £13.28 | 28 capsule PPM £53.09 DT price = £53.09

Atomoxetine (as Atomoxetine hydrochloride) 40 mg Strattera 40mg capsules | 7 capsule PPM £13.28 | 28 capsule PPM £53.09 DT price = £53.09

Atomoxetine (as Atomoxetine hydrochloride) 60 mg Strattera 60mg capsules | 28 capsule PPM £53.09 DT price = £53.09

Atomoxetine (as Atomoxetine hydrochloride) 80 mg Strattera 80mg capsules | 28 capsule PPM £70.79 DT price = £70.79

Atomoxetine (as Atomoxetine hydrochloride) 100 mg Strattera 100mg capsules | 28 capsule PPM £70.79 DT price = £70.79

Oral solution

CAUTIONARY AND ADVISORY LABELS 3

Strattera (Eli Lilly and Company Ltd)

Atomoxetine (as Atomoxetine hydrochloride) 4 mg per 1 ml Strattera 4mg/1ml oral solution sugar-free | 300 ml PPM £85.00 DT price = £85.00

Methylphenidate hydrochloride

INDICATIONS AND DOSE

Attention deficit hyperactivity disorder (initiated under specialist supervision)

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 6–17 years: Initially 5 mg 1–2 times a day, increased in steps of 5–10 mg daily if required, at weekly intervals, increased if necessary up to 60 mg daily in 2–3 divided doses, increased if necessary up to 2.1 mg/kg daily in 2–3 divided doses, the licensed maximum dose is 60 mg daily in 2–3 doses, higher dose (up to a maximum of 90 mg daily) under the direction of a specialist, discontinue if no response after 1 month, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation

Adult: Initially 5 mg 2–3 times a day, dose is increased if necessary at weekly intervals according to response, increased if necessary up to 100 mg daily in 2–3 divided doses, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation

Narcolepsy

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: 10–60 mg daily in divided doses; usual dose 20–30 mg daily in divided doses, dose to be taken before meals

CONCERTA® XL

Attention deficit hyperactivity disorder

BY MOUTH

Child 6–17 years: Initially 18 mg once daily, dose to be taken in the morning, increased in steps of 18 mg every week, adjusted according to response; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 54 mg once daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 108 mg per day

Adult: Initially 18 mg once daily, dose to be taken in the morning; adjusted at weekly intervals according to response; maximum 108 mg per day

DOSE EQUIVALENCE AND CONVERSION

Total daily dose of 15 mg of standard-release formulation is considered equivalent to Concerta® XL 18 mg once daily.

EQUASYM® XL

Attention deficit hyperactivity disorder

BY MOUTH

Child 6–17 years: Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day

Adult: Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; maximum 100 mg per day

MEDIKINET® XL

Attention deficit hyperactivity disorder

BY MOUTH

Child 6–17 years: Initially 10 mg once daily, dose to be taken in the morning with breakfast; adjusted at weekly intervals according to response; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day

Adult: Initially 10 mg once daily, dose to be taken in the morning with breakfast; adjusted at weekly intervals according to response; maximum 100 mg per day

UNLICENSED USE

Doses over 60 mg daily not licensed; doses of Concerta XL over 54 mg daily not licensed

in children Not licensed for use in children under 6 years.

in adults Not licensed for use in narcolepsy. Not licensed for use in adults for attention deficit hyperactivity disorder.

CONTRA-INDICATIONS

Anorexia nervosa • arrhythmias • cardiomyopathy • cardiovascular disease • cerebrovascular disorders • heart failure • hyperthyroidism • phaeochromocytoma • psychosis • severe depression •
severe hypertension, structural cardiac abnormalities, suicidal ideation, uncontrolled bipolar disorder, vasculitis

**CAUTIONS**
- Agitation
- Alcohol dependence
- Anxiety
- Drug dependence
- Epilepsy (discontinue if increased seizure frequency)
- Family history of Tourette syndrome
- Susceptibility to angle-closure glaucoma
- Ticss

**CONCERTA® XL**
- Dysphagia (dose form not appropriate)
- Restricted gastro-intestinal lumen (dose form not appropriate)

**INTERACTIONS**
- Appendix 1 (sympathomimetics)

**SIDE-EFFECTS**
- Common or very common
  - Abdominal pain, aggression
  - Alopecia, anorexia, arrhythmias, arthralgia, asthenia
  - Changes in blood pressure, cough, depression, diarrhoea, dizziness, drowsiness, dry mouth, dyspepsia, fever, growth restriction, headache, insomnia, irritability, movement disorders, nasopharyngitis, nausea, nervousness, palpitation, pruritus, rash, reduced weight gain, tachycardia, tics, vomiting

- Uncommon
  - Abnormal dreams, confusion, constipation, dyspnœa, epistaxis, haematuria, muscle cramps, suicidal ideation, urinary frequency

- Rare
  - Angina, sweating, visual disturbances

- Very rare
  - Angle-closure glaucoma, blood disorders, cerebral arteritis, dependence, erythema multiforme, exfoliative dermatitis, hepatic dysfunction, leucopenia, myocardial infarction, neuroleptic malignant syndrome, psychosis, seizures, thrombocytopenia, tolerance

- Unlikely
  - Angina pectoris, atrial fibrillation, cardiovascular disorders, cerebrovascular disorders, convulsions, delirium, dystonia, dyskinesia, emotional lability, enuresis, eosinophilia, fever, gingival hyperplasia, heterochromia iridum, hyperaesthesia, hypertension, irritable bowel syndrome, insomnia, ketoacidosis, leucocytosis, leukocytosis, myopathy, neuropathy, otitis media, paronychia, paresthesia, photosensitivity reaction, psychosis, purpura, rash, Stevens-Johnson syndrome, sweat gland hyperplasia, tachycardia

- Frequency not known
  - Bradyarrhythmia, convulsions, supraventricular tachycardia

**PREGNANCY**
- Limited experience—avoid unless potential benefit outweighs risk.

**BREAST FEEDING**
- Limited information available—avoid.

**MONITORING REQUIREMENTS**
- Monitor for psychiatric disorders

- Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

**TREATMENT CESSION**
- Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION**

**MEDIKINET® XL**
- Contents of capsule can be sprinkled on a tablespoon of apple sauce or yoghurt (then swallowed immediately without chewing).

**EQUASYM® XL**
- Contents of capsule can be sprinkled on a tablespoon of apple sauce (then swallowed immediately without chewing).

**PRESCRIBING AND DISPENSING INFORMATION**
- Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of methylphenidate, prescribers should specify the brand to be dispensed.

**CONCERTA® XL**
- Consists of an immediate-release component (22% of the dose) and a modified-release component (78% of the dose).

**MEDIKINET® XL**
- Consists of an immediate-release component (50% of the dose) and a modified-release component (50% of the dose).

**EQUASYM® XL**
- Consists of an immediate-release component (30% of the dose) and a modified-release component (70% of the dose).

**PATIENT AND CARER ADVICE**

**Drugs and Driving**
- Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g., driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

- 2015 legislation regarding driving whilst taking certain drugs, may also apply to methylphenidate, see Drugs and driving under Guidance on prescribing p. 1.

**CONCERTA® XL**
- Tablet membrane may pass through gastro-intestinal tract unchanged.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (Tas)**
- Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) (March 2006) NICE TA98
- Methylphenidate is recommended, within its licensed indications, as an option for the management of ADHD in children and adolescents. www.nice.org.uk/TA98

**MEDICAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| Methylphenidate hydrochloride (Non-proprietary) | Methylphenidate hydrochloride 5 mg | Methylphenidate 5 mg tablets | 30 tablet | £3.03 DT price = £3.03 (CD2) |
| | Methylphenidate hydrochloride 10 mg | Methylphenidate 10 mg tablets | 30 tablet | £5.49 DT price = £5.49 (CD2) |
| | Methylphenidate hydrochloride 20 mg | Methylphenidate 20 mg tablets | 30 tablet | £10.92 DT price = £10.92 (CD2) |
| | Medikinet (Flynn Pharma Ltd) | Methylphenidate hydrochloride 5 mg | Medikinet 5 mg tablets | 30 tablet | £3.03 DT price = £3.03 (CD2) |
| | Methylphenidate hydrochloride 10 mg | Medikinet 10 mg tablets | 30 tablet | £5.49 DT price = £5.49 (CD2) |
| | Methylphenidate hydrochloride 20 mg | Medikinet 20 mg tablets | 30 tablet | £10.92 DT price = £10.92 (CD2) |
| | Ritalin (Novartis Pharmaceuticals UK Ltd) | Methylphenidate hydrochloride 10 mg | Ritalin 10 mg tablets | 30 tablet | £6.68 DT price = £5.49 (CD2) |
| | Tranquilyn (Genesis Pharmaceuticals Ltd) | Methylphenidate hydrochloride 5 mg | Tranquilyn 5 mg tablets | 30 tablet | £3.03 DT price = £3.03 (CD2) |
| | Methylphenidate hydrochloride 10 mg | Tranquilyn 10 mg tablets | 30 tablet | £5.49 DT price = £5.49 (CD2) |
| | Methylphenidate hydrochloride 20 mg | Tranquilyn 20 mg tablets | 30 tablet | £10.92 DT price = £10.92 (CD2) |

**Modified-release tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 25</th>
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<tbody>
<tr>
<td>Concerta XL (Jansen-Cilag Ltd)</td>
</tr>
<tr>
<td>Methylphenidate hydrochloride 18 mg</td>
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<tr>
<td>Methylphenidate hydrochloride 27 mg</td>
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<tr>
<td>Methylphenidate hydrochloride 36 mg</td>
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<td>Methylphenidate hydrochloride 54 mg</td>
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</table>

**Modified-release capsule**

<table>
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<th>CAUTIONARY AND ADVISORY LABELS 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equasym XL (Shire Pharmaceuticals Ltd)</td>
</tr>
<tr>
<td>Methylphenidate hydrochloride 10 mg</td>
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<tr>
<td>Methylphenidate hydrochloride 20 mg</td>
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<td>Methylphenidate hydrochloride 30 mg</td>
</tr>
<tr>
<td>Medikinet XL (Flynn Pharma Ltd)</td>
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<td>Methylphenidate hydrochloride 5 mg</td>
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<tr>
<td>Methylphenidate hydrochloride 20 mg</td>
</tr>
<tr>
<td>Methylphenidate hydrochloride 30 mg</td>
</tr>
</tbody>
</table>
Dexamfetamine sulfate
(Dexamphetamine sulfate)

- **INDICATIONS AND DOSE**
  - **Narcolepsy**
    - **BY MOUTH**
    - Adult: Initially 10 mg daily in divided doses, increased in steps of 10 mg every week, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day
    - Elderly: Initially 5 mg daily in divided doses, increased in steps of 5 mg every week, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day
  - **Refractory attention deficit hyperactivity disorder (initiated under specialist supervision)**
    - **BY MOUTH**
    - Child 6–17 years: Initially 2.5 mg 2–3 times a day, increased in steps of 5 mg once weekly if required, increased if necessary up to 1 mg/kg daily, maintenance dose to be given in 2–4 divided doses, up to 20 mg daily (40 mg daily has been required in some children)
    - Adult: Initially 5 mg twice daily, dose is increased at weekly intervals according to response, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day

- **UNLICENSED USE**
  Not licensed for use in adults for refractory attention deficit hyperactivity disorder.

- **CONTRA-INDICATIONS**
  Advanced arteriosclerosis (in adults) • agitated states • cardiovascular disease • history of alcohol abuse • history of drug abuse • hypereexcitability • hyperthyroidism • moderate hypertension • severe hypertension • structural cardiac abnormalities

- **CAUTIONS**
  Anorexia • bipolar disorder • history of epilepsy (discontinue if seizures occur) • mild hypertension • psychosis • susceptibility to angle-closure glaucoma • tics • Tourette syndrome

- **CAUTIONS, FURTHER INFORMATION**
  Tics and Tourette syndrome Discontinue use if tics occur.
  Growth restriction in children Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity).

- **INTERACTIONS**
  Appendix 1 (sympathomimetics).

- **SIDE-EFFECTS**
  Common or very common
  Abdominal cramps • acidosis • aggression • alopexia • anhedonia • anorexia • anxiety • ataxia • cardiomyopathy • cardiovascular collapse • cerebral vasculitis • chest pain • confusion • depression • diarrhoea • dizziness • dry mouth • dysphoria • euphoria • growth restriction in children • headache • hyperactivity • hyperpyrexia (in children) • hyperreflexia • hypertension • hypotension • impaired concentration • irritability • ischemic colitis • malaise • mydriasis • myocardial infarction • nausea • nervousness • neuroleptic malignant syndrome • obsessive-compulsive behaviour • palpitations • panic attack • paranoia • psychosis • pyrexia (in adults) • rash • renal impairment • restlessness • rhadomyolysis • seizures • sexual dysfunction • sleep disturbances • stroke • sweating • tachycardia • taste disturbance • Tourette syndrome (in predisposed individuals) • tremor • urticaria • visual disturbances • weight loss
  Very rare
  Angle-closure glaucoma
  Frequency not known
  Choreaathetoid movements (in predisposed individuals) • dyskinesia (in predisposed individuals) • increased appetite • tics (in predisposed individuals)

- **OVERDOSE**
  Amphetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. See Stimulants under Emergency treatment of poisoning p. 1204.

- **PREGNANCY**
  Avoid (retrospective evidence of uncertain significance suggesting possible embryotoxicity).

- **BREAST FEEDING**
  Significant amount in milk—avoid.

- **RENAI IMPAIRMENT**
  Use with caution.

- **MONITORING REQUIREMENTS**
  Monitor growth in children.
  Monitor for aggressive behaviour or hostility during initial treatment.
  Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

- **TREATMENT CESSATION**
  Avoid abrupt withdrawal.

- **DIRECTIONS FOR ADMINISTRATION**
  In children Tablets can be halved.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Data on safety and efficacy of long-term use not complete.

- **PATIENT AND CARER ADVICE**
  Driving and skilled tasks
  Drugs and Driving Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.
  For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including amphetamines, see Drugs and driving under Guidance on prescribing p. 1.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  NICE technology appraisals (TAs)
  Methylenidate, atomoxetine and dexamphetamine for attention deficit hyperactivity disorder (ADHD) (March 2006) NICE TA98
  Dexamphetamine is recommended, within its licensed indications, as an option for the management of ADHD in children and adolescents.
  www.nice.org.uk/TA98

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release capsule, oral suspension, oral solution

  **Tablet**
  - **Dexamphetamine sulfate (Non-proprietary)**
    - **Dexamphetamine sulfate 5 mg** Dexamphetamine 5mg tablets | 28 tablet
      - **Price** £24.75 DT price = £24.75
    - **Amfexa** (Flynn Pharma Ltd)
      - **Dexamphetamine sulfate 5 mg** Amfexa 5mg tablets | 30 tablet
        - **Price** £15.89
      - **Dexamphetamine sulfate 10 mg** Amfexa 10mg tablets | 30 tablet
        - **Price** £38.78
      - **Dexamphetamine sulfate 20 mg** Amfexa 20mg tablets | 30 tablet
        - **Price** £59.67
Lisdexamfetamine mesilate

**INDICATIONS AND DOSE**  
Attention deficit hyperactivity disorder refractory to methylphenidate (initiated by a specialist)

- **BY MOUTH**
  - Child 6–17 years: Initially 30 mg once daily, increased in steps of 20 mg every week if required, dose to be taken in the morning, discontinue if response insufficient after 1 month; maximum 70 mg per day.
  - Adult: Initially 30 mg once daily, increased in steps of 20 mg every week if required, dose to be taken in the morning, discontinue if response insufficient after 1 month; maximum 70 mg per day.

**UNLICENSED USE**  
Not licensed for use in adults for attention deficit hyperactivity disorder.

**CONTRA-INDICATIONS**  
Advanced arteriosclerosis · agitated states · hypereexcitability · hypothyroidism · moderate hypertension · severe hypertension · symptomatic cardiovascular disease

**CAUTIONS**  
Anorexia · bipolar disorder · history of alcohol abuse · history of cardiac abnormalities · history of cardiovascular disease · history of drug abuse · may lower seizure threshold (discontinue if seizures occur) · psychosis · susceptibility to angle-closure glaucoma · tics · Tourette syndrome

**CAUTIONS, FURTHER INFORMATION**

- Tics and Tourette syndrome: Discontinue use if tics occur.
- Growth restriction in children: Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity).

**INTERACTIONS**  
Appendix 1 (sympathomimetics).

**SIDE-EFFECTS**

- Common or very common: Abdominal cramps · aggression · decreased appetite · diarrhoea · dizziness · drowsiness · dry mouth · dysphoria · increase in appetite · increase in weight · insomnia · irritability · libido · mood swings · nausea · pyrexia · sleep disturbances · tics · vomiting · weight loss
- Uncommon: Anorexia · anxiety · depression · dermatillomania · dysphoria · hallucination · hypertension · logorrhoea · mania · palpitation · paranoia · rash · restlessness · sexual dysfunction · sweating · tachycardia · tremor · visual disturbances
- Very rare: Angle-closure glaucoma
- Frequency not known: Cardiomyopathy · choreoathetoid movements (in predisposed individuals) · dyskinesia (in predisposed individuals) · euphoria · seizures · Tourette syndrome (in predisposed individuals)

**OVERDOSE**  
Amphetamines cause wakfulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. See Stimulants under Emergency treatment of poisoning p. 1204.

**PREGNANCY**  
Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**  
Manufacturer advises avoid—present in human milk.

**RENAL IMPAIRMENT**  
Max. dose 50 mg daily in severe impairment.

**MONITORING REQUIREMENTS**

- Monitor for aggressive behaviour or hostility during initial treatment.
- Monitor growth in children.
- Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

**TREATMENT CESSATION**  
Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION**  
Swallow whole or mix contents of capsule in yoghurt or a glass of water or orange juice; contents should be dispersed completely and consumed immediately.

**PATIENT AND CARER ADVICE**  
Patients and carers should be counselled on the administration of capsules.

**Drugs and Driving**  
Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g., driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including amphetamines, see Drugs and driving under Guidance on prescribing p. 1.

**MEDICINAL FORMS**  
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS**  
  - **Elvanse** (Shire Pharmaceuticals Ltd)
    - Lisdexamfetamine dimesylate 20 mg: Elvanse 20 mg capsules | 28 capsule £54.62 DT price = £54.62 (CD)
    - Lisdexamfetamine dimesylate 30 mg: Elvanse Adult 30 mg capsules | 28 capsule £58.24 DT price = £58.24 (CD)
    - Lisdexamfetamine dimesylate 40 mg: Elvanse 40 mg capsules | 28 capsule £62.82 DT price = £62.82 (CD)
    - Lisdexamfetamine dimesylate 50 mg: Elvanse Adult 50 mg capsules | 28 capsule £68.60 DT price = £68.60 (CD)
    - Lisdexamfetamine dimesylate 60 mg: Elvanse 60 mg capsules | 28 capsule £75.18 DT price = £75.18 (CD)
    - Lisdexamfetamine dimesylate 70 mg: Elvanse 70 mg capsules | 28 capsule £83.16 DT price = £83.16 (CD)

**SYMPATHOMIMETICS**  
**α1-ADRENERGIC RECEPTOR AGONISTS**

**Guanfacine**

26-May-2016

**INDICATIONS AND DOSE**  
Attention deficit hyperactivity disorder in children for whom stimulants are not suitable, not tolerated or ineffective (initiated under specialist supervision)

- **BY MOUTH**
  - Child 6–12 years (body-weight 25 kg and above): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 4 mg), for optimal weight-adjusted dose titrations, consult product literature continued →
330  Mental health disorders

Nervous system

• Child 13-17 years (body-weight 34–41.4 kg): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 4 mg), for optimal weight-adjusted dose titrations, consult product literature

• Child 13-17 years (body-weight 41.5–49.4 kg): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 5 mg), for optimal weight-adjusted dose titrations, consult product literature

• Child 13-17 years (body-weight 49.5–58.4 kg): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 6 mg), for optimal weight-adjusted dose titrations, consult product literature

• Child 13-17 years (body-weight 58.5 kg and above): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 7 mg), for optimal weight-adjusted dose titrations, consult product literature

- **CAUTIONS**  Bradycardia (risk of torsade de pointes) • heart block (risk of torsade de pointes) • history of cardiovascular disease • history of QT-interval prolongation • hypokalaemia (risk of torsade de pointes)

- **INTERACTIONS**  → Appendix 1 (guanfacine). Caution with concomitant use of drugs that prolong QT-interval.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain • anxiety • bradycardia • constipation • decreased appetite • depression • diarrhoea • dizziness • dry mouth • enuresis • headache • hypotension • irritability • malaise • mood lability • nausea • rash • sleep disturbance • somnolence • vomiting • weight increase
  - **Uncommon** Agitation • chest pain • convulsion • dyspepsia • first-degree AV block • hallucination • pallor • pollakiuria • pruritus • sinus arrhythmia • syncope • tachycardia
  - **Rare** Hypertension
  - **Frequency not known** Suicidal ideation

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Somnolence and sedation  Somnolence and sedation may occur, predominantly during the first 2–3 weeks of treatment and with dose increases; manufacturer advises to consider dose reduction or discontinuation of treatment if symptoms are clinically significant or persistent.
  - **Overdose** Features may include hypotension, initial hypertension, bradycardia, lethargy, and respiratory depression. Manufacturer advises that patients who develop lethargy should be observed for development of more serious toxicity for up to 24 hours.
  - **CONCEPTION AND CONTRACEPTION**  Manufacturer recommends effective contraception in females of childbearing potential.
  - **PREGNANCY**  Manufacturer advises avoid—toxicity in animal studies.
  - **BREAST FEEDING**  Manufacturer advises avoid—present in milk in animal studies.
  - **HEPATIC IMPAIRMENT**  Manufacturer advises consider dose reduction.
  - **RENAL IMPAIRMENT**  Manufacturer advises consider dose reduction in severe impairment and end-stage renal disease.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises to conduct a baseline evaluation to identify patients at risk of somnolence, sedation, hypotension, bradycardia, QT-prolongation, and arrhythmia; this should include assessment of cardiovascular status. Monitor for signs of these adverse effects weekly during dose titration and then every 3 months during the first year of treatment, and every 6 months thereafter. Monitor BMI prior to treatment and then every 3 months for the first year of treatment, and every 6 months thereafter. More frequent monitoring is advised following dose adjustments.
  - **TREATMENT CESSATION**  Manufacturer advises avoid abrupt withdrawal; consider dose tapering to minimise potential withdrawal effects.
  - **DIRECTIONS FOR ADMINISTRATION**  Manufacturer advises avoid administration with high fat meals (may increase absorption).
  - **PATIENT AND CARER ADVICE**  Patients or carers should be counselled on administration of guanfacine modified-release tablets.
  - **Missed doses** Manufacturer advises that patients and carers should inform their prescriber if more than one dose is missed; consider dose re-titration.
  - **Driving and skilled tasks** Manufacturer advises patients and carers should be counselled about the effects on driving and performance of skilled tasks—increased risk of dizziness and syncope.

### 3.3 Bipolar disorder and mania

**Drugs for mania and hypomania**

Antimanic drugs are used to control acute attacks and to prevent recurrence of episodes of mania or hypomania. Long-term treatment of bipolar disorder should continue for at least two years from the last manic episode and up to five years if the patient has risk factors for relapse.

An antidepressant drug may also be required for the treatment of co-existing depression, but should be avoided in patients with rapid cycling bipolar disorder, a recent history of hypomania, or with rapid mood fluctuations.

**Benzodiazepines**

Use of benzodiazepines (such as lorazepam p. 317) may be helpful in the initial stages of treatment for behavioural disturbance or agitation; they should not be used for long periods because of the risk of dependence.

**Antipsychotic drugs**

Antipsychotic drugs (normally olanzapine p. 373, quetiapine p. 375, or risperidone p. 377) are useful in acute episodes of mania and hypomania; if the response to antipsychotic drugs is inadequate, lithium or valproate may be added. An
antipsychotic drug may be used concomitantly with lithium or valproate in the initial treatment of severe acute mania. Olanzapine can be used for the long-term management of bipolar disorder in patients whose manic episode responded to olanzapine therapy. It can be given either as monotherapy, or in combination with lithium or valproate if the patient has frequent relapses or continuing functional impairment. Asenapine p. 332, a second-generation antipsychotic, is licensed for the treatment of moderate to severe manic episodes associated with bipolar disorder.

When discontinuing antipsychotics, the dose should be reduced gradually over at least 4 weeks if the patient is continuing with other antimanic drugs; if the patient is not continuing with other antimanics or if there is a history of manic relapse, a withdrawal period of up to 3 months should be considered.

**Carbamazepine**
Carbamazepine p. 291 may be used under specialist supervision for the prophylaxis of bipolar disorder (manic-depressive disorder) in patients unresponsive to a combination of other prophylactic drugs; it is used in patients with rapid-cycling manic-depressive illness (4 or more affective episodes per year). The dose of carbamazepine should not normally be increased if an acute episode of mania occurs.

**Valproate**
Valproate (valproic acid below (as the semisodium salt) and sodium valproate p. 306) is used for the treatment of manic episodes associated with bipolar disorder. It must be started and supervised by a specialist experienced in managing bipolar disorder. Valproate (valproic acid and sodium valproate) is also used for the prophylaxis of bipolar disorder. Valproic acid and sodium valproate should not be used in female children, in females of childbearing potential and pregnant females, unless alternative treatments are ineffective or not tolerated, because of its high teratogenic potential; the benefit and risk of valproate therapy should be carefully re-assessed at regular treatment reviews. In patients with frequent relapse or continuing functional impairment, consider switching therapy to lithium or olanzapine, or adding lithium or olanzapine to valproate. If a patient taking valproate experiences an acute episode of mania that is not ameliorated by increasing the valproate dose, consider concomitant therapy with olanzapine, quetiapine, or risperidone.

**Lithium**
Lithium salts are used in the prophylaxis of manic episodes, hypomania and depression in bipolar disorder (manic-depressive disorder), and in the prophylaxis and treatment of recurrent unipolar depression. Lithium is also used as concomitant therapy with antidepressant medication in patients who have had an incomplete response to treatment for acute bipolar depression and to augment other antidepressants in patients with treatment-resistant depression [unlicensed indication]. It is also licensed for the treatment of aggressive or self-harming behaviour.

The decision to give prophylactic lithium requires specialist advice, and must be based on careful consideration of the likelihood of recurrence in the individual patient, and the benefit of treatment weighed against the risks. The full prophylactic effect of lithium may not occur for six to twelve months after the initiation of therapy. Olanzapine or valproate (given alone or as adjunctive therapy with lithium) are alternative prophylactic treatments in patients who experience frequent relapses or continued functional impairment.

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**Other drugs used for Bipolar disorder and mania**

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**ANTIEPILEPTICS**

### Valproic acid

**INDICATIONS AND DOSE**

**Treatment of manic episodes associated with bipolar disorder**

- **BY MOUTH**
  - Adult: Initially 750 mg daily in 2–3 divided doses, then increased to 1–2 g daily, adjusted according to response, doses greater than 45 mg/kg daily require careful monitoring.

**Migraine prophylaxis**

- **BY MOUTH**
  - Adult: Initially 250 mg twice daily, then increased if necessary to 1 g daily in divided doses.

**DOSE EQUIVALENCE AND CONVERSION**

- Semisodium valproate comprises equimolar amounts of sodium valproate and valproic acid.

**CONVULEX®**

**Epilepsy**

- **BY MOUTH**
  - Adult: Initially 600 mg daily in 2–4 divided doses, increased in steps of 150–300 mg every 3 days; usual maintenance 1–2 g daily in 2–4 divided doses, max. 2.5 g daily in 2–4 divided doses.

**DOSE EQUIVALENCE AND CONVERSION**

- Convulex® has a 1:1 dose relationship with products containing sodium valproate, but nevertheless care is needed if switching or making changes.

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**UNLICENSED USE** Not licensed for migraine prophylaxis.

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**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: VALPROATE AND RISK OF ABNORMAL PREGNANCY OUTCOMES**

Infants exposed to valproate in utero are at a high risk of serious developmental disorders (up to 30–40% risk) and congenital malformations (approx. 11% risk). Valproate should not be used in female children, females of childbearing potential or during pregnancy unless alternative treatments are ineffective or not tolerated.

**CONTRA-INDICATIONS** Acute porphyrias p. 374 · known or suspected mitochondrial disorders (higher rate of acute liver failure and liver-related deaths) · personal or family history of severe hepatic dysfunction.

**CAUTIONS** Systemic lupus erythematosus

**CAUTIONS, FURTHER INFORMATION**

Consider vitamin D supplementation in patients that are exposed to valproate in utero and maintained on valproate for long periods, in those with known or suspected mitochondrial disorders, in patients with a history of liver dysfunction.

**Liver toxicity** Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Increased liver enzymes during valproate treatment are usually transient but may persist in a few patients. Consider switching therapy to lithium or other anticonvulsant medication if valproate continues to be a problem.
prothrombin time (particularly in association with other relevant abnormalities).

### INTERACTIONS
- Appendix 1 (valproic acid).

### SIDE-EFFECTS
- **Common or very common** Diarrhoea, gastric irritation, hyperammonaemia, nausea, thrombocytopenia, transient hair loss (regrowth may be curly), weight gain
- **Uncommon** Agitation, ataxia, behavioural disturbances, hyperactivity, increased alertness, tremor, vasculitis
- **Rare** Anaemia, blood disorders, confusion, drowsiness, hallucinations, hearing loss, hepatic dysfunction, lethargy, leucopenia, pancytopenia, rash, stupor
- **Very rare** Acne, coma, dementia, encephalopathy, enuresis, extrapyramidal symptoms, Fanconi’s syndrome, gynaecoatresia, hirsutism, hyponatraemia, increase in bleeding time, pancreatitis, peripheral oedema, reduced bone mineral density, Stevens-Johnson syndrome, suicidal ideation, toxic epidermal necrolysis
- **Frequency not known** Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, hypersensitivity reactions, male infertility, menstrual disturbances, syndrome of inappropriate secretion of antidiuretic hormone

### CONCEPTION AND CONTRACEPTION
Valproate is associated with teratogenic risks and should not be used in females of child-bearing potential unless there is no safer alternative—this should be fully considered and discussed before prescribing for females of child-bearing age. Effective contraception advised in females of child-bearing potential. In females planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception.

### PREGNANCY
Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valproate should not be used during pregnancy unless there is no safer alternative and only after a careful discussion of the risks. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses to avoid peaks in plasma–valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Neonatal bleeding (related to hypofibrininaemia). Neonatal hepatotoxicity also reported.

Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

### BREAST FEEDING
Present in milk—risk of haematological disorders in breast-fed newborns and infants.

### HEPATIC IMPAIRMENT
Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months). Avoid in active liver disease.

### RENAL IMPAIRMENT
Reduce dose.

### MONITORING REQUIREMENTS
- Monitor closely if dose greater than 45 mg/kg daily.
- Monitor liver function before therapy and during first 6 months especially in patients most at risk.
- Measure full blood count and ensure no undue potential for bleeding before starting and before surgery.

### EFFECT ON LABORATORY TESTS
False-positive urine tests for ketones.

### TREATMENT CESSSION
Avoid abrupt withdrawal; if treatment with valproate is stopped, reduce the dose gradually over at least 4 weeks.

### PRESCRIBING AND DISPENSING INFORMATION
**Convulex®** Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic oral valproic acid product.

### PATIENT AND CARER ADVISE
Risk of abnormal pregnancy outcomes. A patient guide and card should be provided to all female patients. Blood or hepatic disorders Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop.

Pancreatitis Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop.

MHRA advice: Valproate and the risk of abnormal pregnancy outcomes
Female patients and their carers should be counselled on the risk of valproate treatment during pregnancy. Ensure female patients are provided with relevant resources, to support their understanding of the risks. In particular the prescriber must ensure the patient understands:
- the risks associated with valproate during pregnancy;
- the need to use effective contraception;
- the need for regular review of treatment;
- the need to rapidly consult if she is planning a pregnancy or becomes pregnant.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, and gastro-resistant tablets.

#### Gastro-resistant tablet

1. **Dekapot (Sanofi)**
   - Valproic acid (as Valproate semisodium) 500 mg gastro-resistant tablets | 90 tablet £17.08 DT price = £17.08
   - Valproic acid (as Valproate semisodium) 500 mg gastro-resistant tablets | 90 tablet £34.11 DT price = £34.11

2. **Depakote (Pfizer Ltd)**
   - Valproic acid (as Valproate semisodium) 250 mg gastro-resistant tablets | 90 tablet £17.08
   - Valproic acid (as Valproate semisodium) 500 mg gastro-resistant tablets | 90 tablet £34.11

#### Gastro-resistant capsule

1. **Dekapot (Sanofi)**
   - Valproic acid (as Valproate semisodium) 125 mg gastro-resistant capsules | 100 capsule £3.68

2. **Convulex (Pfizer Ltd)**
   - Valproic acid 150 mg Convulex 150mg gastro-resistant capsules | 100 capsule £7.35
   - Valproic acid 300 mg Convulex 300mg gastro-resistant capsules | 100 capsule £12.25

3. **Depakote (Pfizer Ltd)**
   - Valproic acid 150 mg Convulex 150mg gastro-resistant capsules | 100 capsule £6.38
   - Valproic acid 300 mg Convulex 300mg gastro-resistant capsules | 100 capsule £12.25

### ANTIPLATFORMS

#### Asenapine

### INDICATIONS AND DOSE

- **Monotherapy for the treatment of moderate to severe manic episodes associated with bipolar disorder**
  - **BY MOUTH**
  - Adult: Initially 10 mg twice daily, reduced to 5 mg twice daily, adjusted according to response

- **Combination therapy for the treatment of moderate to severe manic episodes associated with bipolar disorder**
  - **BY MOUTH**
  - Adult: Initially 5 mg twice daily, increased if necessary to 10 mg twice daily, adjusted according to response

### CAUTIONS
Dementia with Lewy Bodies
Lithium salts

**SIDE-EFFECTS** Anxiety · dysphagia · glossodynia · hypersalivation · rhabdomyolysis · speech disturbance · taste disturbance · tongue swelling · transient oral hypoesthesia · transient paraesthesia

**PREGNANCY** Use only if potential benefit outweighs risk— toxicity in animal studies.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Use with caution in moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT** Use with caution if eGFR less than 15 mL/minute/1.73 m²—no information available.

**PATIENT AND CARER ADVICE** Patient or carer should be given advice on how to administer asenapine sublingual tablet.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

Sublingual tablet

CAUTIONARY AND ADVISORY LABELS 2, 26

- Asenapine (as Asenapine maleate) 5 mg Sycrest 5mg sublingual tablets sugar-free | 60 tablet (Pack) £102.60 DT price = £102.60 
- Asenapine (as Asenapine maleate) 10 mg Sycrest 10mg sublingual tablets sugar-free | 60 tablet (Pack) £102.60 DT price = £102.60

**ANTIPSYCHOTICS**

**LITHIUM SALTS**

**CONTRA-INDICATIONS** Addison’s disease · cardiac insufficiency · dehydration · family history of Brugada syndrome · low sodium diets · personal history of Brugada syndrome · rhythm disorder · untreated hypothyroidism

**CAUTIONS** Avoid abrupt withdrawal · cardiac disease · concurrent ECT (may lower seizure threshold) · diuretic treatment (risk of toxicity) · elderly (reduce dose) · epilepsy (may lower seizure threshold) · myasthenia gravis · psoriasis (risk of exacerbation) · QT interval prolongation · review dose as necessary in diarrhoea · review dose as necessary in intercurrent infection (especially if sweating profusely) · review dose as necessary in vomiting · surgery

**CAUTIONS, FURTHER INFORMATION**

- Long-term use Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with monitoring of thyroid function every 6 months (more often if there is evidence of deterioration).

  The need for continued therapy should be assessed regularly and patients should be maintained on lithium after 3–5 years only if benefit persists.

**INTERACTIONS** → Appendix 1 (lithium).

Caution with concomitant use of drugs and any therapy that may lower seizure threshold.

Caution with concomitant use of drugs that prolong the QT interval.

Lithium toxicity is made worse by sodium depletion, therefore concurrent use of diuretics (particularly thiazides) is hazardous and should be avoided.

**SIDE-EFFECTS**

- **Very rare** Nystagmus

- **Frequency not known** Acneiform eruptions · alopecia · anorexia · arrhythmia · arthralgia · AV block · benign intracranial hypertension · bradycardia · cardiomyopathy · cognitive impairment · dry mouth · dysgeusia · ECG changes · electrolyte imbalance · encephalopathy · euthyroid goitre · extrapyramidal side-effects · fine tremor · gastritis · gastro-intestinal disturbances · hallucinations · hyperparathyroidism · hypersalivation · hyperthyroidism · hypothyroidism · kidney changes · leucocytosis · malaise · memory loss · myalgia · myasthenia gravis · nephrogenic diabetes insipidus · nphrotic syndrome · oedema · other skin disorders · parathyroid adenoma · peripheral neuropathy · polydipsia · psoriasis exacerbation · QT interval prolongation · Raynaud’s phenomena · renal impairment · sexual dysfunction · sinus node dysfunction · speech disorder · thyroid changes · vertigo · weight changes

**Overdose** Signs of intoxication require withdrawal of treatment and include increasing gastro-intestinal disturbances (vomiting, diarrhoea), visual disturbances, polyuria, muscle weakness, fine tremor increasing to coarse tremor, CNS disturbances (confusion and drowsiness increasing to lack of coordination, restlessness, stupor); abnormal reflexes, myoclonus, incontinence, hyperpyrexia. With severe overdosage seizures, cardiac arrhythmias (including sino-atrial block, bradycardia and first-degree heart block), blood pressure changes, circulatory failure, renal failure, coma and sudden death reported.

For details on the management of poisoning, see Lithium, under Emergency treatment of poisoning p. 1204.

**CONCEPTION AND EMERGENCY CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment for women of child bearing potential.

**PREGNANCY** Dose requirements increased during the second and third trimesters (but on delivery return abruptly to normal). Avoid if possible, particularly in the first trimester (risk of teratogenicity, including cardiac abnormalities).

Close monitoring of serum-lithium concentration advised in pregnancy (risk of toxicity in neonate).

**BREAST FEEDING** Present in milk and risk of toxicity in infant—avoid.

**RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment. In renal impairment monitor serum-lithium concentration closely and adjust dose accordingly.

**MONITORING REQUIREMENTS**

- Serum concentrations Lithium salts have a narrow therapeutic/toxic ratio and should therefore not be prescribed unless facilities for monitoring serum-lithium concentrations are available.

Samples should be taken 12 hours after the dose to achieve a serum-lithium concentration of 0.4–1 mmol/litre (lower end of the range for maintenance therapy and elderly patients).

A target serum-lithium concentration of 0.8–1 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms. It is important to determine the optimum range for each individual patient.

Routine serum-lithium monitoring should be performed weekly after initiation and after each dose change until concentrations are stable, then every 3 months thereafter. Additional serum-lithium measurements should be made if a patient develops significant intercurrent disease or if there is a significant change in a patient’s sodium or fluid intake.

- Renal function should be monitored at baseline and every 6 months thereafter (more often if there is evidence of deterioration or if the patient has other risk factors, such as starting ACE inhibitors, NSAIDs, or diuretics).

- Assess cardiac and thyroid function before initiating, and thereafter every 6 months on stabilised regimens.

**TREATMENT CESSATION** While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of at least 4 weeks (preferably over a period of up to 3 months). Patients and their carers should be warned of...
the risk of relapse if lithium is discontinued abruptly. If lithium is stopped or is to be discontinued abruptly, consider changing therapy to an atypical antipsychotic or valproate.

**PATIENT AND CARER ADVICE** Patients should be advised to report signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction (including polyuria and polydipsia), and benign intracranial hypertension (persistent headache and visual disturbance).

- Maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake.
- Driving and skilled tasks May impair performance of skilled tasks (e.g. driving, operating machinery).

Lithium treatment packs A lithium treatment pack should be given to patients on initiation of treatment with lithium. The pack consists of a patient information booklet, lithium alert card, and a record book for tracking serum-lithium concentration. Packs may be purchased from 3M 0845 610 1112 nhsforms@mmm.uk.com

### Lithium carbonate

**INDICATIONS AND DOSE**

- Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

**BY MOUTH**

- **Adult:** Dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**CAMCOLIT® MODIFIED-RELEASE TABLET**

**Treatment of mania | Treatment of bipolar disorder | Treatment of recurrent depression | Treatment of aggressive or self-harming behaviour**

**BY MOUTH**

- **Adult:** Initially 1–1.5 g daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

- **Elderly:** Reduce initial dose, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**Prophylaxis of mania | Prophylaxis of bipolar disorder | Prophylaxis of recurrent depression | Prophylaxis of aggressive or self-harming behaviour**

**BY MOUTH**

- **Adult:** Initially 300–400 mg daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**Elderly:** Reduce initial dose, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
PRIADEL® TABLETS

Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

> BY MOUTH

> Adult (body-weight up to 50 kg): Initially 200–400 mg daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

> Adult (body-weight 50 kg and above): Initially 0.4–1.2 g once daily, alternatively initially 0.4–1.2 g daily in 2 divided doses, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

> Elderly: Initially 200–400 mg daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

DOSE EQUIVALENCE AND CONVERSION

> Preparations vary widely in bioavailability; changing the preparation requires the same precautions as initiation of treatment.

LITHICIT® LIQUID®

Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

> BY MOUTH

> Adult (body-weight up to 50 kg): Initially 509 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

> Adult (body-weight 50 kg and above): Initially 1.018–3.054 g daily in 2 divided doses, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

> Elderly: Initially 509 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

DOSE EQUIVALENCE AND CONVERSION

> For LI-LIQUID®: Lithium citrate tetrahydrate 509 mg is equivalent to lithium carbonate 200 mg.

Preparations vary widely in bioavailability; changing the preparation requires the same precautions as initiation of treatment.

PRIADEL® LIQUID

Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

> BY MOUTH

> Adult (body-weight up to 50 kg): Initially 520 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised...
4.3.4 Depression

Antidepressant drugs

Overview
Antidepressant drugs are effective for treating moderate to severe depression associated with psychomotor and physiological changes such as loss of appetite and sleep disturbance; improvement in sleep is usually the first benefit of therapy. Ideally, patients with moderate to severe depression should be treated with psychological therapy in addition to drug therapy. Antidepressant drugs are also effective for dysthymia (lower grade chronic depression typically of at least 2 years duration).

Antidepressant drugs should not be used routinely in mild depression, and psychological therapy should be considered initially; however, a trial of antidepressant therapy may be considered in cases refractory to psychological treatments or in those associated with psychosocial or medical problems. Drug treatment of mild depression may also be considered in patients with a history of moderate or severe depression.

Choice
The major classes of antidepressant drugs include the tricyclic and related antidepressants, the selective serotonin re-uptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs). A number of antidepressant drugs cannot be accommodated easily into this classification.

There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual patient’s requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy. Since there may be an interval of 2 weeks before the antidepressant action takes place, electroconvulsive treatment may be required in severe depression when delay is hazardous or intolerable. During the first few weeks of treatment, there is an increased potential for agitation, anxiety, and suicidal ideation.

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants and should be considered first-line for treating depression. In patients with unstable angina or who have had a recent myocardial infarction, sertraline p. 344 has been shown to be safe.

Tricyclic antidepressants have similar efficacy to SSRIs but are more likely to be discontinued because of side-effects, toxicity in overdose is also a problem. SSRIs are less sedating and have fewer antimuscarinic and cardiotoxic effects than tricyclic antidepressants.

MAOIs have dangerous interactions with some foods and drugs, and should be reserved for use by specialists. Although anxiety is often present in depressive illness (and may be the presenting symptom), the use of an antipsychotic or an anxiolytic may mask the true diagnosis. Anxiolytics or antipsychotic drugs should therefore be used with caution in depression but they are useful adjuncts in agitated patients. Augmenting antidepressants with antipsychotics under specialist supervision may also be necessary in patients who have depression with psychotic symptoms.

St John’s wort (Hypericum perforatum) is a popular herbal remedy on sale to the public for treating mild depression. It should not be prescribed or recommended for depression because St John’s wort can induce drug metabolising enzymes and a number of important interactions with conventional drugs, including conventional antidepressants, have been identified. Furthermore, the amount of active ingredient varies between different preparations of St John’s wort and switching from one to another can change the degree of enzyme induction. If a patient stops taking St John’s wort, the concentration of interacting drugs may increase, leading to toxicity.

Management
Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy. In cases of partial response, continue for a further 2–4 weeks (elderly patients may take longer to respond).

Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly), or for at least 12 months in patients receiving treatment for generalised anxiety disorder (as the likelihood of relapse is high). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.

Hyponatraemia and antidepressant therapy
Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants; however, it has been reported more frequently with SSRIs than with other antidepressants. Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.
Suicidal behaviour and antidepressant therapy

The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

Serotonin syndrome

Serotonin syndrome or serotonin toxicity is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity. Onset of symptoms, which range from mild to life-threatening, can occur within hours or days following the initiation, dose escalation, or overdose of a serotonergic drug; the addition of a new serotonergic drug; or the replacement of one serotonergic drug by another without allowing a long enough washout period in-between, particularly when the first drug is an irreversible MAOI or a drug with a long half-life. Severe toxicity, which is a medical emergency, usually occurs with a combination of serotonergic drugs, one of which is generally an MAOI.

The characteristic symptoms of serotonin syndrome fall into 3 main areas, although features from each group may not be seen in all patients—neuromuscular hyperactivity (such as tremor, hyperreflexia, clonus, myoclonus, rigidity), autonomic dysfunction (tachycardia, blood pressure changes, hyperthermia, diaphoresis, shivering, diarrhoea), and altered mental state (agitation, confusion, mania). Treatment consists of withdrawal of the serotonergic medication and supportive care; specialist advice should be sought.

Failure to respond

Failure to respond to initial treatment with an SSRI may require an increase in the dose, or switching to a different SSRI or mirtazapine p. 349. Other second-line choices include loperamide p. 354, moclobemide p. 340, and reboxetine p. 340. Other tricyclic antidepressants and venlafaxine p. 345 should be considered for more severe forms of depression; irreversible MAOIs should only be prescribed by specialists. Failure to respond to a second antidepressant may require the addition of another antidepressant of a different class, or use of an augmenting agent (such as lithium, aripiprazole p. 370 [unlicensed], olanzapine p. 373 [unlicensed], quetiapine p. 375, or risperidone p. 377 [unlicensed]), but such adjunctive treatment should be initiated only by doctors with special experience of these combinations. Electroconvulsive therapy may be initiated in severe refractory depression.

Anxiety disorders and obsessive-compulsive disorder

Management of acute anxiety generally involves the use of a benzodiazepine or buspirone hydrochloride p. 320. For chronic anxiety (of longer than 4 weeks’ duration) it may be appropriate to use an antidepressant. Combined therapy with a benzodiazepine may be required until the antidepressant takes effect. Patients with generalised anxiety disorder, a form of chronic anxiety, should be offered psychological treatment before initiating an antidepressant. If drug treatment is needed, an SSRI such as escitalopram p. 342, paroxetine p. 344, or sertraline p. 344 [unlicensed], can be used. Duloxetine p. 345 and venlafaxine p. 345 (serotonin and noradrenaline reuptake inhibitors) are also recommended for the treatment of generalised anxiety disorder; if the patient cannot tolerate SSRIs or serotonin and noradrenaline reuptake inhibitors (or if treatment has failed to control symptoms), pregabalin p. 304 can be considered.

Panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobic states such as social anxiety disorder are treated with SSRIs. Clomipramine hydrochloride p. 351 or imipramine hydrochloride p. 353 can be used second-line in panic disorder [unlicensed]; clomipramine hydrochloride can also be used second-line for obsessive-compulsive disorder. Moclobemide p. 340 is licensed for the treatment of social anxiety disorder.

Tricyclic and related antidepressant drugs

Choice

Tricyclic and related antidepressants block the re-uptake of both serotonin and noradrenaline, although to different extents. For example, clomipramine hydrochloride is more selective for serotonergic transmission, and imipramine hydrochloride is more selective for noradrenergic transmission. Tricyclic and related antidepressant drugs can be roughly divided into those with additional sedative properties and those that are less sedating. Agitated and anxious patients tend to respond best to the sedative compounds, whereas withdrawn and apathetic patients will often obtain most benefit from the less sedating ones. Those with sedative properties include amitriptyline hydrochloride p. 349, clomipramine hydrochloride, dosulepin hydrochloride p. 352, doxepin p. 353, mianserin hydrochloride p. 348, trazodone hydrochloride p. 347, and trimipramine p. 356. Those with less sedative properties include imipramine hydrochloride, lofepramine p. 354, and nortriptyline p. 355.

Some tricyclic antidepressants also have varying degrees of antimuscarinic side-effects and cardiotoxicity in overdose, which may be important in individual patients. Lofepramine has a lower incidence of side-effects and is less dangerous in overdose but is infrequently associated with hepatic toxicity. Imipramine hydrochloride is also well established, but has more marked antimuscarinic side-effects than other tricyclic and related antidepressants. Amitriptyline hydrochloride and dosulepin hydrochloride are effective but they are particularly dangerous in overdose and are not recommended for the treatment of depression; dosulepin hydrochloride should be initiated by a specialist.

Dosage

About 10 to 20% of patients fail to respond to tricyclic and related antidepressant drugs and inadequate dosage may account for some of these failures. It is important to use doses that are sufficiently high for effective treatment but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. In most patients the long half-life of tricyclic antidepressant drugs allows once-daily administration, usually at night; the use of modified-release preparations is therefore unnecessary.

Some tricyclic antidepressants are used in the management of panic and other anxiety disorders. Some tricyclic antidepressants may also have a role in some forms of neuralgia and in nocturnal enuresis in children.

Children and adolescents

Studies have shown that tricyclic antidepressants are not effective for treating depression in children.

Monoamine-oxidase inhibitors

Monoamine-oxidase inhibitors are used much less frequently than tricyclic and related antidepressants, or SSRIs and related antidepressants because of the dangers of dietary and drug interactions and the fact that it is easier to prescribe MAOIs when tricyclic antidepressants have been unsuccessful than vice versa.

Tranylcypromine p. 339 has a greater stimulant action than phenelzine p. 339 or isocarboxazid p. 339 and is more likely to cause a hypertensive crisis. Isocarboxazid and phenelzine are more likely to cause hepatotoxicity than tranylcypromine.

Moclobemide should be reserved as a second line treatment.

Phobic patients and depressed patients with atypical, hypochondriacal, or hysterical features are said to respond best to MAOIs. However, MAOIs should be tried in any
patients who are refractory to treatment with other antidepressants as there is occasionally a dramatic response. Response to treatment may be delayed for 3 weeks or more and may take an additional 1 or 2 weeks to become maximal.

**Other antidepressant drugs**

The thioxanthene flupentixol (Fluanxol®) p. 362 has antidepressant properties when given by mouth in low doses. Flupentixol is also used for the treatment of psychoses.

Vortioxetine p. 357, an antidepressant thought to directly modulate serotonergic receptor activity and inhibit the re-uptake of serotonin, is recommended in patients whose condition has responded inadequately to 2 antidepressants within the current episode.

*Other drugs used for Depression* Lithium carbonate, p. 334
- Lithium citrate, p. 335

**ANTIDEPRESSANTS › MELATONIN RECEPTOR AGONISTS**

*Agomelatine*

- **DRUG ACTION** A melatonin receptor agonist and a selective serotonin-receptor antagonist; it does not affect the uptake of serotonin, noradrenaline, or dopamine.

- **INDICATIONS AND DOSE**
  - **Major depression**
    - **BY MOUTH**
    - Adult: 25 mg daily, dose to be taken at bedtime, dose to be increased if necessary after 2 weeks, increased if necessary to 50 mg daily, dose to be taken at bedtime

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Caution—dose adjustment may be necessary if smoking started or stopped during treatment.

- **CONTRA-INDICATIONS**
  - Dementia - patients over 75 years of age

- **CAUTIONS**
  - Bipolar disorder • diabetes • excessive alcohol consumption • hypomania • mania • non-alcoholic fatty liver disease • obesity

- **INTERACTIONS** → Appendix 1 (agomelatine).
  - Caution with concomitant use of drugs associated with hepatic injury.

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain • agitation • anxiety • back pain • constipation • diarrhoea • dizziness • drowsiness • fatigue • headache • increased serum transaminases • nausea • sleep disturbances • sweating • vomiting

  - Uncommon Blurred vision • eczema • paraesthesia • restless legs syndrome • tinnitus

  - Rare Hepatic failure • hepatic injury • hepatitis • rash • weight changes

  - Frequency not known Pruritus • suicidal behaviour

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Suicidal behaviour The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

- **PREGNANCY**
  - Manufacturer advises avoid.

- **BREAST FEEDING**
  - Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Avoid. Do not start if serum transaminases exceed 3 times the upper limit of reference range.

- **RENAL IMPAIRMENT**
  - Caution in moderate to severe impairment.

- **MONITORING REQUIREMENTS**
  - Test liver function before treatment and after 3, 6, 12 and 24 weeks of treatment, and then regularly thereafter when clinically indicated (restart monitoring schedule if dose increased); discontinue if serum transaminases exceed 3 times the upper limit of reference range or symptoms of liver disorder.

- **PATIENT AND CARER ADVICE**
  - Patients should be given a booklet with more information on the risk of hepatic side-effects.

**MENTS**

Hepatotoxicity Patients should be told how to recognise signs of liver disorder, and advised to seek immediate medical attention if symptoms such as dark urine, light coloured stools, jaundice, bruising, fatigue, abdominal pain, or pruritus develop.

- **MIDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Valdoxan (Servier Laboratories Ltd)
    - Agomelatine 25 mg Valdoxan 25mg tablets | 28 tablet £30.00 DT price + £30.00

**ANTIDEPRESSANTS › MONOAMINE-OXIDASE INHIBITORS**

*Monoamine-oxidase inhibitors*

- **DRUG ACTION** MAOIs inhibit monoamine oxidase, thereby causing an accumulation of amine neurotransmitters.

- **CONTRA-INDICATIONS**
  - Cerebrovascular disease • not indicated in manic phase • phaeochromocytoma

- **CAUTIONS**
  - Acute porphyria • avoid in agitated patients • blood disorders • cardiovascular disease • concurrent electroconvulsive therapy • diabetes mellitus • elderly (great caution) • epilepsy • severe hypertensive reactions to certain drugs and foods • surgery

- **INTERACTIONS** → Appendix 1 (MAOIs).

  - The metabolism of some amine drugs such as indirect-acting sympathomimetics (present in many cough and decongestant preparations) is inhibited and their pressor action may be potentiated; the pressor effect of tyramine (in some foods, such as mature cheese, pickled herring, broad bean pods, and Bovril® , Oxo®, Marmite® or any similar meat or yeast extract or fermented soya bean extract) may also be dangerously potentiated. These interactions may cause a dangerous rise in blood pressure. An early warning symptom may be a throbbing headache. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued.

  - Some psychiatrists use selected tricyclics in conjunction with MAOIs but this is hazardous, indeed potentially lethal, except in experienced hands and there is no evidence that the combination is more effective than when either constituent is used alone.

- **SIDE-EFFECTS**
  - Common or very common Dizziness • postural hypotension (especially in elderly)

  - Uncommon Agitation • arrhythmias • blurred vision • confusion • constipation • convulsions • difficulty in micturition • drowsiness • dry mouth • elevated liver enzymes • euphoria • fatigue • gastro-intestinal disturbances • hallucinations • headache • hypereflexia • insomnia • leucopenia • myoclonic movement disorder • nervousness • nystagmus • oedema • psychotic episodes with hypomanic behaviour • purpura • rashes • sexual disturbances • suicidal behaviour • sweating • tremors • weakness • weight gain with inappropriate appetite
**Isocarboxazid**

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - **Adult:** Initially 30 mg daily until improvement occurs, initial dose may be given in single or divided doses, dose may be increased if necessary after 4 weeks, increased to 60 mg daily for 4–6 weeks, dose to be increased under close supervision only, then reduced to 10–20 mg daily, usual maintenance dose, but up to 40 mg daily may be required
  - **Elderly:** 5–10 mg daily

**BREAST FEEDING** Avoid.

**HEPATIC IMPAIRMENT** Avoid in hepatic impairment.

**RENAI IMPAIRMENT** Use with caution.

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>3, 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocarboxazid (Non-proprietary)</td>
<td></td>
</tr>
<tr>
<td>Isocarboxazid 10 mg</td>
<td>56 tablet</td>
</tr>
</tbody>
</table>

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**Phenelzine**

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - **Adult:** Initially 15 mg 3 times a day, response is usually seen within first week; dose may be increased if necessary after 2 weeks if response is not evident, increased if necessary to 15 mg 4 times a day, doses up to 30 mg three times a day may be used in hospital patients; response may not become apparent for up to 4 weeks; once satisfactory response has been achieved, reduce dose gradually to lowest suitable maintenance dose (15 mg on alternate days may be adequate)

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Avoid in hepatic impairment or if abnormal liver function tests.

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>3, 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nardil (Kyowa Kirin Ltd)</td>
<td></td>
</tr>
<tr>
<td>Phenelzine (as Phenelzine sulfate) 15 mg</td>
<td>100 tablet</td>
</tr>
</tbody>
</table>

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**Tranilcyprromine**

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - **Adult:** Initially 10 mg twice daily, dose to be taken at a time no later than 3 p.m, dose may be increased if necessary after 1 week, increased if necessary to 10 mg daily, dose to be taken in the morning and 20 mg daily, dose to be taken in the afternoon, doses above 30 mg daily, under close supervision only; maintenance 10 mg daily

**CONTRA-INDICATIONS** Congestive heart failure, history of hepatic disease, hyperthyroidism

**INTERACTIONS** The combination of tranilcypromine with clomipramine is particularly dangerous.

**SIDE-EFFECTS**

- **Common or very common** Insomnia
  - **Uncommon** Hyperpyrexia, lupus erythematosus-like syndrome, speech disturbances
  - **Very rare** Angle-closure glaucoma, dysthyroidism, with throbbing headache, liver damage (less frequent than with phenelzine)
  - **Frequency not known** Blood dyscrasias
HEPATIC IMPAIRMENT

BREAST FEEDING

Rare ▶

SIDE-EFFECTS, FURTHER INFORMATION

- Hypertensive crisis
- Hypertensive crisis and throbbing headache requiring discontinuation of treatment is more frequent than with other MAOIs.
- BREAST FEEDING
- Present in milk in animal studies.
- HEPATIC IMPAIRMENT
- Avoid if history of hepatic disease or if abnormal liver function tests.
- LESS SUITABLE FOR PRESCRIBING
- Less suitable for prescribing.

MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 10

- Tranylcypromine (Non-proprietary)
- Tranylcypromine (as Tranylcypromine sulfate)
- 10 mg Tranylcypromine 10mg tablets | 28 tablet \(\text{P}^\text{SM}\) £243.98 DT price = £236.44

ANTIDEPRESSANTS › MONOAMINE-OXIDASE A INHIBITORS, REVERSIBLE

Moclobemide

DRUG ACTION

Moclobemide is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA).

INDICATIONS AND DOSE

Depressive illness

- BY MOUTH
- Adult: Initially 300 mg daily in divided doses, adjusted according to response; usual dose 150–600 mg daily, dose to be taken after food

Social anxiety disorder

- BY MOUTH
- Adult: Initially 300 mg daily for 3 days, then increased to 600 mg daily in 2 divided doses continued for 8–12 weeks to assess efficacy

CONTRA-INDICATIONS

- Acute confusional states
- Phaeochromocytoma

CAUTIONS

- Avoid in agitated or excited patients (or give with sedative for up to 2–3 weeks) • may provoke manic episodes in bipolar disorders • thyrotoxicosis

INTERACTIONS → Appendix 1 (moclobemide).

The risk of drug interactions is claimed to be less than with the traditional (irreversible) MAOIs, but patients still need to avoid sympathomimetics such as ephedrine and pseudoephedrine. In addition, moclobemide should not be given with another antidepressant. Owing to its short duration of action no treatment-free period is required after it has been stopped but it should not be started until at least a week after a tricyclic or related antidepressant or an SSRI or related antidepressant has been stopped (at least 5 weeks in the case of fluoxetine), or for at least a week after an MAOI has been stopped.

SIDE-EFFECTS

- Rare
- Galactorrhoea • hyponatraemia • raised liver enzymes
- Frequency not known
- Agitation • confusional states • dizziness • dry mouth • gastrointestinal disorders • headache • oedema • paraesthesia • restlessness • skin reactions • sleep disturbances • visual disturbances

PREGNANCY

Safety in pregnancy has not been established—manufacturer advises avoid unless there are compelling reasons.

BREAST FEEDING

Amount too small to be harmful, but patient information leaflet advises avoid.

HEPATIC IMPAIRMENT

Reduce dose in severe hepatic disease.

TREATMENT CESSATION

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

PATIENT AND CARER ADVICE

Moclobemide is claimed to cause less potentiation of the pressor effect of tyramine than the traditional (irreversible) MAOIs, but patients should avoid consuming large amounts of tyramine-rich food (such as mature cheese, yeast extracts and fermented soya bean products).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 10, 21

- Moclobemide (Non-proprietary)
- Moclobemide 150 mg Moclobemide 150mg tablets | 30 tablet \(\text{P}^\text{SM}\) £22.12 DT price = £22.07
- Moclobemide 300 mg Moclobemide 300mg tablets | 30 tablet \(\text{P}^\text{SM}\) £15.00 DT price = £13.99
- Manerix (Meda Pharmaceuticals Ltd)
- Moclobemide 150 mg Manerix 150mg tablets | 30 tablet \(\text{P}^\text{SM}\) £9.33 DT price = £9.27
- Moclobemide 300 mg Manerix 300mg tablets | 30 tablet \(\text{P}^\text{SM}\) £13.99 DT price = £13.99

ANTIDEPRESSANTS › NORADRENALINE REUPTAKE INHIBITORS

Reboxetine

DRUG ACTION

Reboxetine is a selective inhibitor of noradrenaline re-uptake.

INDICATIONS AND DOSE

Major depression

- BY MOUTH
- Adult: 4 mg twice daily for 3–4 weeks, then increased if necessary to 10 mg daily in divided doses; maximum 12 mg per day

CAUTIONS

- Bipolar disorder • history of cardiovascular disease • history of epilepsy • prostatic hypertrophy • susceptibility to angle-closure glaucoma • urinary retention

INTERACTIONS → Appendix 1 (reboxetine).

SIDE-EFFECTS

- Common or very common
- Anorexia • chills • constipation • dizziness • dry mouth • headache • impaired visual accommodation • impotence • insomnia • lowering of plasma-potassium concentration on prolonged administration in the elderly • nausea • palpitation • postural hypotension • sweating • tachycardia • urinary retention • vasodilation

- Very rare
- Angle-closure glaucoma

PREGNANCY

Use only if potential benefit outweighs risk—limited information available.

BREAST FEEDING

Small amount present in milk—use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT

Initial dose 2 mg twice daily, increased according to tolerance.
UPTAKE INHIBITORS

Hypersensitivity reactions

▶ Frequency not known
▶ Very rare
▶ Uncommon
▶ Common or very common

SIDE-EFFECTS

INTERACTIONS

CAUTIONS

DRUG ACTION

Selective serotonin re-uptake inhibitors

INDICATIONS AND DOSE

Depressive illness

▶ BY MOUTH USING TABLETS
▶ BY MOUTH USING ORAL DROPS

Panic disorder

▶ BY MOUTH USING TABLETS
▶ BY MOUTH USING ORAL DROPS

PREGNANCY

Manufacturers advise avoid during pregnancy unless the potential benefit outweighs the risk. There is a small increased risk of congenital heart defects when taken during early pregnancy. If used during the third trimester there is a risk of neonatal withdrawal symptoms, and persistent pulmonary hypertension in the newborn has been reported.

TREATMENT CESSATION

Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck, and spine, tinnitus, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; palpitation and visual disturbances can occur less commonly. The dose should be tapered over at least a few weeks to avoid these effects. For some patients, it may be necessary to withdraw treatment over a longer period; consider obtaining specialist advice if symptoms persist. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

PATIENT AND CARER ADVICE

Driving and skilled tasks

Counselling advised.

Driving and skilled tasks

May also impair performance of skilled tasks (e.g. driving, operating machinery).

Citalopram

INDICATIONS AND DOSE

Depressive illness

▶ BY MOUTH USING TABLETS
▶ BY MOUTH USING ORAL DROPS

Panic disorder

▶ BY MOUTH USING TABLETS
▶ BY MOUTH USING ORAL DROPS

PREGNANCY

Manufacturers advise avoid during pregnancy unless the potential benefit outweighs the risk. There is a small increased risk of congenital heart defects when taken during early pregnancy. If used during the third trimester there is a risk of neonatal withdrawal symptoms, and persistent pulmonary hypertension in the newborn has been reported.

CONTRA-INDICATIONS

QT-interval prolongation

CAUTIONS

Susceptibility to QT-interval prolongation

INTERACTIONS

Avoid concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS

Taste disturbance - abnormal dreams - aggression - amnesia - bradycardia - confusion - coughing - euphoria - haemorrhage - hepatitis - hypokalaemia -
impaired concentration • increased salivation • malaise •
micturition disorders • migraine • mydriasis • oedema •
palpitation • paradoxical increased anxiety during initial
treatment of panic disorder (reduce dose) • paraesthesia •
polyuria • postural hypotension • pruritus • QT-interval
prolongation • rhinitis • tachycardia • tinnitus • yawning

● BREAST FEEDING Present in milk—use with caution.

● HEPATIC IMPAIRMENT Use doses at lower end of range; for
tablets up to maximum 20 mg; for oral solution up to
maximum 16 mg.

● RENAL IMPAIRMENT No information available for eGFR
less than 20 mL/minute/1.73 m².

● DIRECTIONS FOR ADMINISTRATION Cipramil® oral drops
should be mixed with water, orange juice, or apple juice
before taking.

● PATIENT AND CARER ADVICE Counselling on
administration of oral drops is advised.

Driving and skilled tasks
Patients should be advised of the effects of citalopram on
driving and skilled tasks.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines
containing the same drug.

Tablet
● Citalopram (Non-proprietary)
Citalopram (as Citalopram hydrobromide) 10 mg Citalopram
tablets | 28 tablet (Ph) £8.90 DT price = £0.79
Citalopram (as Citalopram hydrobromide) 20 mg Citalopram
tablets | 28 tablet (Ph) £15.99 DT price = £0.86
Citalopram (as Citalopram hydrobromide) 40 mg Citalopram
40 mg tablets | 28 tablet (Ph) £27.00 DT price = £0.90
● Cipramil (Lundbeck Ltd)
Citalopram (as Citalopram hydrobromide) 20 mg Cipramil 20 mg
tablets | 28 tablet (Ph) £8.95 DT price = £0.86

Oral drops
EXCIPIENTS: May contain Alcohol
● Citalopram (Non-proprietary)
Citalopram (as Citalopram hydrochloride) 40 mg per
1 ml Citalopram 40 mg/ml oral drops sugar free sugar-free | 15
ml (Ph) £20.16 DT price = £5.04
● Cipramil (Lundbeck Ltd)
Citalopram (as Citalopram hydrochloride) 40 mg per
1 ml Cipramil 40 mg/ml oral drops sugar-free | 15 ml (Ph) £10.08 DT
price = £5.04

Escitalopram
● DRUG ACTION Escitalopram is the active enantiomer of
citalopram.

● INDICATIONS AND DOSE
Depressive illness • Generalised anxiety disorder •
Obsessive-compulsive disorder
► BY MOUTH
Adult: 10 mg once daily; increased if necessary up to
20 mg daily
Elderly: Initially 5 mg once daily; maximum 10 mg per
day

Panic disorder
► BY MOUTH
Adult: Initially 5 mg once daily for 7 days, then
increased to 10 mg daily; maximum 20 mg per day
Elderly: Initially 2.5 mg once daily; maximum 10 mg
per day

Social anxiety disorder
► BY MOUTH
Adult: Initially 10 mg once daily for 2–4 weeks, dose to
be adjusted after 2–4 weeks of treatment; usual dose
5–20 mg daily

● CONTRA-INDICATIONS QT-interval prolongation

● CAUTIONS Susceptibility to QT-interval prolongation

● INTERACTIONS Avoid concomitant administration of drugs
that prolong QT interval.

● SIDE-EFFECTS
► Common or very common Abnormal dreams • fatigue •
paraesthesia • pyrexia • restlessness • sinusitis • yawning
► Uncommon Alopecia • bruxism • confusion • epistaxis •
menstrual disturbances • mydriasis • oedema • pruritus •
syncope • tachycardia • taste disturbance • tinnitus
► Rare Aggression • bradycardia • depersonalisation

● DIRECTIONS FOR ADMINISTRATION Oral drops can be
mixed with water, orange juice, or apple juice before
taking.

● PATIENT AND CARER ADVICE Counselling on
administration of oral drops advised.

Driving and skilled tasks
Patients should be counselled about the effects on driving.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines
containing the same drug.

Tablet
● Escitalopram (Non-proprietary)
Escitalopram (as Escitalopram oxalate) 5 mg Escitalopram
5 mg tablets | 28 tablet (Ph) £8.52 DT price = £1.45
Escitalopram (as Escitalopram oxalate) 10 mg Escitalopram
10 mg tablets | 28 tablet (Ph) £14.55 DT price = £1.47
Escitalopram (as Escitalopram oxalate) 20 mg Escitalopram
20 mg tablets | 28 tablet (Ph) £23.94 DT price = £1.66
● Cipralex (Lundbeck Ltd)
Escitalopram (as Escitalopram oxalate) 5 mg Cipralex 5mg tablets
| 28 tablet (Ph) £8.97 DT price = £1.45
Escitalopram (as Escitalopram oxalate) 10 mg Cipralex 10 mg
tablets | 28 tablet (Ph) £14.91 DT price = £1.47
Escitalopram (as Escitalopram oxalate) 20 mg Cipralex 20 mg
tablets | 28 tablet (Ph) £25.20 DT price = £1.66

Oral drops
● Escitalopram (Non-proprietary)
Escitalopram (as Escitalopram oxalate) 20 mg per
1 ml Escitalopram 20 mg/ml oral drops sugar free sugar-free | 15
ml (Ph) no price available
● Cipralex (Lundbeck Ltd)
Escitalopram (as Escitalopram oxalate) 20 mg per 1 ml Cipralex
20 mg/ml oral drops sugar-free | 15 ml (Ph) £20.16

Fluoxetine
● INDICATIONS AND DOSE
Major depression
► BY MOUTH
Adult: Initially 20 mg daily, dose is increased after
3–4 weeks if necessary, and at appropriate intervals
thereafter, daily dose may be administered as a single
or divided dose; maximum 60 mg per day
Elderly: Initially 20 mg daily, dose is increased after
3–4 weeks if necessary, and at appropriate intervals
thereafter, daily dose may be administered as a single
or divided dose, usual maximum dose is 40 mg daily but
doses up to 60 mg daily can be used
Fluoxetine maleate

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: Initially 50–100 mg daily, dose to be taken in the evening, dose to be increased gradually, increased if necessary up to 300 mg daily, doses over 150 mg daily are given in divided doses; maintenance 100 mg daily

**Obessive-compulsive disorder**

- **BY MOUTH**
  - Adult: Initially 50 mg daily, dose to be taken in the evening, dose is increased gradually if necessary after several weeks, increased if necessary up to 300 mg daily; maintenance 100–300 mg daily, doses over 150 mg daily are given in divided doses, if no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered

**SIDE-EFFECTS**

- Common or very common: Malaise - palpitation - tachycardia
- Uncommon: Ataxia - confusion - postural hypotension
- Rare: Abnormal liver function, usually symptomatic (discontinue treatment)
- Frequency not known: Neuroleptic malignant syndrome-like event - paraesthesia - taste disturbance

**BREAST FEEDING**

Present in milk—avoid.

**HEPATIC IMPAIRMENT**

Start with low dose.

**RENEAL IMPAIRMENT**

Start with low dose.

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks: Patients should be counselled about the effects on driving and skilled tasks.

**MEDICAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution.

**Dispersible tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 20 mg</td>
<td>Olena 20mg dispersible tablets sugar-free</td>
</tr>
</tbody>
</table>

**Capsule**

<table>
<thead>
<tr>
<th>Fluoxetine (Non-proprietary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 10 mg</td>
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<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 20 mg</td>
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<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 30 mg</td>
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<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 40 mg</td>
</tr>
<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 60 mg</td>
</tr>
<tr>
<td>Oxactin (Discovery Pharmaceuticals)</td>
</tr>
<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 20 mg</td>
</tr>
<tr>
<td>Prozac (Eli Lilly and Company Ltd)</td>
</tr>
<tr>
<td>Fluoxetine (as Fluoxetine hydrochloride) 20 mg</td>
</tr>
</tbody>
</table>
Paroxetine

**INDICATIONS AND DOSE**

**Major depression** | **Social anxiety disorder** | **Post-traumatic stress disorder** | **Generalised anxiety disorder**
--- | --- | --- | ---
**BY MOUTH**
- Adult: 20 mg daily, dose to be taken in the morning, no evidence of greater efficacy at higher doses; maximum 50 mg per day
- Elderly: 20 mg daily, dose to be taken in the morning, no evidence of greater efficacy at higher doses; maximum 40 mg per day

**Obsessive-compulsive disorder**
- **BY MOUTH**
  - Adult: Initially 20 mg daily, dose to be increased in steps of 10 mg, dose to be increased gradually, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day
  - Elderly: Initially 20 mg daily, dose to be increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day

**Panic disorder**
- **BY MOUTH**
  - Adult: Initially 10 mg daily, dose to be increased gradually, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day
  - Elderly: Initially 10 mg daily, dose to be increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day

**Caution**
- Achlorhydria or high gastric pH
- Causes reduced absorption of the oral suspension.

**Side-effects**
- Common or very common: Abnormal dreams, raised cholesterol, yawning
- Uncommon: Arrhythmias, confusion, urinary incontinence
- Rare: Depersonalisation, neuroleptic malignant syndrome-like event, panic attacks, paradoxical increased anxiety during initial treatment of panic disorder (reduce dose), restless legs syndrome
- Very rare: Acute glaucoma, hepatic disorders, hepatitis, peripheral oedema, priapism
- Frequency not known: Extrapyramidal reactions, orofacial dystonias, tinnitus, withdrawal reactions
- Pregnancy: Increased risk of congenital malformations, especially if used in the first trimester.
- Breastfeeding: Present in milk but amount too small to be harmful.
- Hepatic impairment: Reduce dose.
- Renal impairment: Reduce dose if eGFR less than 30 mL/minute/1.73 m².
- Treatment cessation: Associated with a higher risk of withdrawal reactions.
- Patient and carer advice
  - Driving and skilled tasks
  - Patients should be counselled about the effect on driving.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**Cautionary and advisory labels 21**
- **Paroxetine (Non-proprietary)**
  - Paroxetine (as Paroxetine hydrochloride) 10 mg Paroxetine 10 mg tablets 28 tablet [Porn] £18.12 DT price = £16.65
  - Paroxetine (as Paroxetine hydrochloride) 20 mg Paroxetine 20 mg tablets 30 tablet [Porn] £3.00 DT price = £1.64
  - Paroxetine (as Paroxetine hydrochloride) 30 mg Paroxetine 30 mg tablets 30 tablet [Porn] £4.04 DT price = £1.67
  - Paroxetine (as Paroxetine hydrochloride) 40 mg Paroxetine 40 mg tablets 28 tablet [Porn] £17.03 | 30 tablet [Porn] £25.07

**Seroxat** (GlaxoSmithKline UK Ltd)
- Paroxetine (as Paroxetine hydrochloride) 10 mg Seroxat 10 mg tablets 28 tablet [Porn] £14.21 DT price = £16.65
- Paroxetine (as Paroxetine hydrochloride) 20 mg Seroxat 20 mg tablets 30 tablet [Porn] £15.23 DT price = £1.64
- Paroxetine (as Paroxetine hydrochloride) 30 mg Seroxat 30 mg tablets 30 tablet [Porn] £26.74 DT price = £1.67

**Oral suspension**

**Cautionary and advisory labels 5, 21**
- Seroxat (GlaxoSmithKline UK Ltd)
  - Paroxetine (as Paroxetine hydrochloride) 2 mg per 1 ml Seroxat 20 mg/10 ml liquid sugar-free 150 ml [Porn] £9.12 DT price = £9.12

Sertraline

**INDICATIONS AND DOSE**

**Depressive illness**
- **BY MOUTH**
  - Adult: Initially 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maintenance 50 mg daily; maximum 200 mg per day

**Obsessive-compulsive disorder**
- **BY MOUTH**
  - Adult: Initially 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maximum 200 mg per day

**Panic disorder**
- **Post-traumatic stress disorder**
- **Social anxiety disorder**

**Side-effects**
- Aggression, amnesia, bronchospasm, hepatitis, hypercholesterolaemia, hyperprolactinaemia, hypertension, hypoglycaemia, hypothyroidism, jaundice, leucopenia, liver failure, menstrual irregularities, palpitation, pancreatitis, paraesthesia, postural hypotension, stomatitis, tachycardia, tinnitus, urinary incontinence

**Breastfeeding**
- Not known to be harmful but consider discontinuing breast-feeding.

**Hepatic impairment**
- Reduce dose or increase dose interval in mild or moderate impairment. Avoid in severe impairment.

**Renal impairment**
- Use with caution.

**Patient and carer advice**
- Driving and skilled tasks
  - Patients should be counselled on the effects on driving and skilled tasks.
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- Duloxetine (Non-proprietary)
  - Duloxetine (as Duloxetine hydrochloride) 20 mg
  - Duloxetine (as Duloxetine hydrochloride) 30 mg
  - Duloxetine (as Duloxetine hydrochloride) 60 mg
  - Duloxetine (as Duloxetine hydrochloride) 90 mg
- Lustral
  - Lustral (as Sertraline hydrochloride) 50 mg
  - Lustral (as Sertraline hydrochloride) 100 mg

**SIDE-EFFECTS**

- Angle-closure glaucoma
- Syncope
- Hypothyroidism
- Gastritis
- Pruritus
- Insomnia
- Susceptibility to angle-closure glaucoma
- History of mania
- Bleeding disorders
- Appetite disorders
- Diarrhoea
- Dreaming disorders
- Fatigue
- Headache
- Nervousness
- Abdominal pain
- Abnormal dreams
- Anorexia
- Anxiety
- Constipation
- Decreased appetite
- Diarrhoea
- Dizziness
- Drowsiness
- Dry mouth
- Dyspepsia
- Fatigue
- Flatulence
- Headache
- Hot flush
- Insomnia
- Nausea
- Nervousness
- Palpitation
- Paraesthesia
- Pruritus
- Sexual dysfunction
- Sweating
- Tremor
- Visual disturbances
- Vomiting
- Weakness
- Weight changes
- Uncommon
  - Angina
  - Chest pain
  - Hallucinations
  - Hypersensitivity reactions
  - Hypotension
  - Impaired attention
  - Impaired temperature regulation
  - Movement disorders
  - Muscle twitching
  - Musculoskeletal pain
  - Photosensitivity
  - Postural hypotension
  - Raised cholesterol
  - Stomatitis
  - Syncope
  - Tachycardia
  - Taste disturbance
  - Thirst
  - Urinary disorders

**INTERACTIONS**

- Antidepressants

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant capsule**

**CAUTIONARY AND ADVISORY LABELS**

- Duloxetine (Non-proprietary)

  - **Duloxetine (as Duloxetine hydrochloride) 20 mg**
    - Duloxetine 20mg gastro-resistant capsules | 28 capsule | £18.48 DT price = £3.99
  - **Duloxetine (as Duloxetine hydrochloride) 30 mg**
    - Duloxetine 30mg gastro-resistant capsules | 28 capsule | £22.40 DT price = £3.99
  - **Duloxetine (as Duloxetine hydrochloride) 40 mg**
    - Duloxetine 40mg gastro-resistant capsules | 56 capsule | £36.96 DT price = £6.61
  - **Duloxetine (as Duloxetine hydrochloride) 60 mg**
    - Duloxetine 60mg gastro-resistant capsules | 28 capsule | £27.72 DT price = £3.34
  - **Duloxetine (as Duloxetine hydrochloride) 90 mg**
    - Duloxetine 90mg gastro-resistant capsules | 28 capsule | £40.25 DT price = £3.50
  - **Cymbalta**
    - Cymbalta 30mg gastro-resistant capsules | 28 capsule | £22.40 DT price = £2.90
  - **Cymbalta 60mg gastro-resistant capsules**
    - Cymbalta 60mg gastro-resistant capsules | 28 capsule | £27.72 DT price = £3.34
  - **Duloxetine (as Duloxetine hydrochloride) 30 mg**
    - Duloxetine 30mg gastro-resistant capsules | 28 capsule | £22.40 DT price = £2.90
  - **Duloxetine (as Duloxetine hydrochloride) 60 mg**
    - Duloxetine 60mg gastro-resistant capsules | 28 capsule | £27.72 DT price = £3.34
  - **Venlafaxine**
    - Venlafaxine Hydrochloride 20 mg
      - Venlafaxine 20mg gastro-resistant capsules | 28 capsule | £18.48 DT price = £3.99
    - **Venlafaxine Hydrochloride 40 mg**
      - Venlafaxine 40mg gastro-resistant capsules | 56 capsule | £36.96 DT price = £6.61

**DRUG ACTION**

Inhibits the re-uptake of serotonin and noradrenaline.

**INDICATIONS AND DOSE**

- **Major depressive disorder**
  - **By mouth**
  - Adult: 60 mg once daily

- **Generalised anxiety disorder**
  - **By mouth**
  - Adult: Initially 30 mg once daily, increased if necessary to 60 mg once daily; maximum 120 mg per day

- **Diabetic neuropathy**
  - **By mouth**
  - Adult: 60 mg once daily, discontinue if inadequate response after 2–4 months; review treatment at least every 3 months, maximum dose to be given in divided doses; maximum 120 mg per day

- **Moderate to severe stress urinary incontinence**
  - **By mouth**
  - Adult (female): 40 mg twice daily, patient should be assessed for benefit and tolerability after 2–4 weeks, alternatively initially 20 mg twice daily for 2 weeks, this can minimise side effects, then increased to 40 mg twice daily, the patient should be assessed for benefit and tolerability after 2–4 weeks.

**CAUTIONS**

- Bleeding disorders
- Cardiac disease
- Elderly
- History of mania
- History of seizures
- Hypertension (avoid if uncontrolled)
- Increased intra-ocular pressure
- Susceptibility to angle-closure glaucoma

**INTERACTIONS**

- Appendix 1 (duloxetine).

**SIDE-EFFECTS**

- **Common or very common**
  - Abdominal pain
  - Abnormal dreams
  - Anorexia
  - Anxiety
  - Constipation
  - Decreased appetite
  - Diarrhoea
  - Dizziness
  - Drowsiness
  - Dry mouth
  - Dyspepsia
  - Fatigue
  - Flatulence
  - Headache
  - Hot flush
  - Insomnia
  - Nausea
  - Nervousness
  - Palpitation
  - Paraesthesia
  - Pruritus
  - Sexual dysfunction
  - Sweating
  - Tremor
  - Visual disturbances
  - Vomiting
  - Weakness
  - Weight changes
- **Uncommon**
  - Angina
  - Chest pain
  - Hallucinations
  - Hypersensitivity reactions
  - Hypotension
  - Impaired attention
  - Impaired temperature regulation
  - Movement disorders
  - Muscle twitching
  - Musculoskeletal pain
  - Photosensitivity
  - Postural hypotension
  - Raised cholesterol
  - Stomatitis
  - Syncope
  - Tachycardia
  - Taste disturbance
  - Thirst
  - Urinary disorders

**VENLAFAXINE**

**DRUG ACTION**

A serotonin and noradrenaline re-uptake inhibitor.

**INDICATIONS AND DOSE**

- **Major depression**
  - **By mouth using immediate-release medicines**
  - Adult: Initially 75 mg daily in 2 divided doses, then increased if necessary up to 200 mg daily, dose to be increased if necessary at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 75 mg per day; continued →
**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Adult:** Initially 75 mg once daily, increased if necessary up to 375 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 375 mg per day

**Generalised anxiety disorder**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- **Adult:** 75 mg once daily, increased if necessary up to 225 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks; maximum 225 mg per day

**Social anxiety disorder**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- **Adult:** 75 mg once daily, there is no evidence of greater efficacy at higher doses, increased if necessary up to 225 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks; maximum 225 mg per day

**CONTRA-INDICATIONS**  Conditions associated with high risk of cardiac arrhythmia - uncontrolled hypertension

**CAUTIONS**  Diabetes - heart disease (monitor blood pressure) - history of bleeding disorders - history of epilepsy - history or family history of mania - susceptibility to angle-closure glaucoma

**INTERACTIONS**  → Appendix 1 (venlafaxine).

**SIDE-EFFECTS**

- **Common or very common**  Abnormal dreams - anorexia - anxiety (on withdrawal) - asthenia - changes in serum cholesterol - chills - confusion - constipation - difficulty with micturition - dizziness - dizziness (on withdrawal) - drowsiness - dry mouth - gastro-intestinal disturbances (on withdrawal) - headache - headache (on withdrawal) - hypertension - hypotension - insomnia - menstrual disturbances - mydriasis - nausea - nervousness - palpitation - paraesthesia (on withdrawal) - sensory disturbances - sexual dysfunction - sleep disturbances (on withdrawal) - sweating - sweating (on withdrawal) - tremor - tremor (on withdrawal) - vasodilatation - visual disturbances - vomiting - weight changes - yawning


- **Rare**  Akathisia - extrapyramidal symptoms - hypomania - mania - seizures - urinary incontinence

- **Very rare**  Angle-closure glaucoma

- **Frequency not known**  Aggression - blood dyscrasias - delirium - hepatitis - hyperprolactinaemia - hypotension - neuroleptic malignant syndrome - pancreatitis - pruritus - QT interval prolongation - rhabdomyolysis - Stevens-Johnson syndrome - suicidal behaviour - syndrome of inappropriate anti-diuretic hormone secretion - urticaria - vertigo

**PREGNANCY**  Avoid unless potential benefit outweighs risk—tOXICITY in animal studies. Risk of withdrawal effects in neonate.

**BREAST FEEDING**  Present in milk—avoid.

**HEPATIC IMPAIRMENT**  Consider reducing dose by 50% in mild or moderate impairment; use with caution and reduce dose by at least 50% in severe impairment.

**RENAL IMPAIRMENT**  Use with caution. Use half normal dose (immediate-release tablets may be given once daily) if eGFR less than 30 mL/minute/1.73 m².

**TREATMENT CESSATION**  Associated with a higher risk of withdrawal effects compared with other antidepressants.

Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, tremor, sleep disturbances, and sweating are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

May affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 3**

- **Venlafaxine (Non-proprietary)**
  - Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 225 mg

- **ViePax (Dexcel-Pharma Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 225 mg

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 3, 21, 25**

- **Sunveniz XL (Sun Pharmaceuticals UK Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **Venlalic XL (Dexcel-Pharma Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **Venlalic XL (Ethylpharm UK Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **ViePax XL (Dexcel-Pharma Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

**Modified-release capsule**

**CAUTIONARY AND ADVISORY LABELS 3, 21, 25**

- **Venlafaxine (Non-proprietary)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **Alventa XL (Consilient Health Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **Depefex XL (Chiesi Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **Efexor XL (Pfizer Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg

- **Politid XL (Actavis UK Ltd)**
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg
Venlafaxine (as Venlafaxine hydrochloride) 150 mg  Politid XL
150mg capsules  |  28 capsule  |  £39.03 DT price  |  £36.81

- **Rodemel XL** (Teva UK Ltd)

Venlafaxine (as Venlafaxine hydrochloride) 75 mg  Rodemel XL
75mg capsules  |  28 capsule  |  £17.91 DT price  |  £22.08

Venlafaxine (as Venlafaxine hydrochloride) 150 mg  Rodemel XL
150mg capsules  |  28 capsule  |  £29.85 DT price  |  £36.81

- **Tonpular XL** (Wockhardt UK Ltd)

Venlafaxine (as Venlafaxine hydrochloride) 75 mg  Tonpular XL
75mg capsules  |  28 capsule  |  £7.00 DT price  |  £22.08

Venlafaxine (as Venlafaxine hydrochloride) 150 mg  Tonpular XL
150mg capsules  |  28 capsule  |  £12.00 DT price  |  £36.81

- **Venax XL** (AMCo)

Venlafaxine (as Venlafaxine hydrochloride) 75 mg  Venax XL
75mg capsules  |  28 capsule  |  £10.40 DT price  |  £22.08

Venlafaxine (as Venlafaxine hydrochloride) 150 mg  Venax XL
150mg capsules  |  28 capsule  |  £17.40 DT price  |  £36.81

- **Venlablue XL** (Bluefish Pharmaceuticals AB)

Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg  Venlablue XL
37.5mg capsules  |  28 capsule  |  £5.25

Venlafaxine (as Venlafaxine hydrochloride) 75 mg  Venlablue XL
75mg capsules  |  28 capsule  |  £6.95 DT price  |  £22.08

Venlafaxine (as Venlafaxine hydrochloride) 150 mg  Venlablue XL
150mg capsules  |  28 capsule  |  £9.95 DT price  |  £36.81

- **Vensir XL** (Morningside Healthcare Ltd)

Venlafaxine (as Venlafaxine hydrochloride) 75 mg  Vensir XL
75mg capsules  |  28 capsule  |  £2.60 DT price  |  £22.08

Venlafaxine (as Venlafaxine hydrochloride) 150 mg  Vensir XL
150mg capsules  |  28 capsule  |  £3.90 DT price  |  £36.81

Venlafaxine (as Venlafaxine hydrochloride) 225 mg  Vensir XL
225mg capsules  |  28 capsule  |  £21.90

**ANTIDEPRESSANTS > SEROTONIN UPTAKE INHIBITORS**

**INDICATIONS AND DOSE**
Depressive illness (particularly where sedation is required)

- **BY MOUTH**

  - **Adult:** Initially 150 mg daily in divided doses, dose to be taken after food, alternatively initially 150 mg once daily, dose to be taken at bedtime, increased if necessary to 300 mg daily; increased if necessary to 600 mg daily in divided doses, higher dose for use in hospital patients only

  - **Elderly:** Initially 100 mg daily in divided doses, dose to be taken after food, alternatively initially 100 mg once daily, dose to be taken at bedtime, increased if necessary to 300 mg daily; increased if necessary to 600 mg daily in divided doses, higher dose for use in hospital patients only

**Anxiety**

- **BY MOUTH**

  - **Adult:** 75 mg daily, increased if necessary to 300 mg daily

**CONTRA-INDICATIONS**  Acute porphyrias p. 930 · arrhythmias · during the manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction

**CAUTIONS**  Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intracranial pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS**  Antidepressants, tricyclic (related).

**SIDE-EFFECTS**

- **Rare** Extrapyramidal symptoms · paralytic ileus

- **Very rare** Precipitation of angle-closure glaucoma

**Frequency not known**  Changes in blood sugar · dry mouth · postural hypotension · agitation · alopecia · anorexia · anxiety · arrhythmia · arthralgia · blurred vision · breast enlargement · chills (on withdrawal) · confusion · constipation · convulsions · delusions · dizziness · drowsiness · dysarthria · dyspepsia · dyspnoea · ECG changes · galactorrhoea · gynaecomastia · haematological reactions · hallucinations · headache (on withdrawal) · heart block · hepatic reactions · hypersalivation · hypertension · hypomania · hypotension · increased appetite · influenza-like symptoms (on withdrawal) · insomnia (on withdrawal) · irritability · mania · movement disorders (on withdrawal) · myalgia · myalgia (on withdrawal) · nausea · nauscea (on withdrawal) · palpitation · paraesthesia · photosensitivity · priapism (discontinue immediately) · pruritus · rash · sexual dysfunction · sleep disturbances · sudden death of patients with cardiac disease · sweating · sweating (on withdrawal) · tachycardia · taste disturbance · tinnitus · tremor · urinary retention · urticaria · vivid dreams (on withdrawal) · vomiting · weight gain · weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**

The tricyclic-related antidepressant drugs may be associated with a lower risk of cardiotoxicity in overdosage.

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

- **PREGNANCY**  Avoid during first trimester—limited information available. Monitor infant for signs of withdrawal if used until delivery.

- **BREAST FEEDING**  The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT**  Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

- **RENAL IMPAIRMENT**  Use with caution in severe impairment.

**TREATMENT CESSION**  Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 4 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION**  Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and
epileptogenic effects are dangerous in overdose.

● **PATIENT AND CARER ADVICE**

Driving and skilled tasks
Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

● **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

CAUTIONARY AND ADVISORY LABELS 2, 21

▶ **Trazodone hydrochloride (Non-proprietary)**

- Trazodone hydrochloride 150 mg Trazodone 150mg tablets | 28 tablet (PO) £45.33 DT price = £26.34
- Molipaxin (Zentiva) Trazodone hydrochloride 150 mg Molipaxin 150mg tablets | 28 tablet (PO) £16.08 DT price = £26.34

### Capsule

CAUTIONARY AND ADVISORY LABELS 2, 21

▶ **Trazodone hydrochloride (Non-proprietary)**

- Trazodone hydrochloride 50 mg Trazodone 50mg capsules | 84 capsule (PO) £36.20 DT price = £29.85
- Trazodone hydrochloride 100 mg Trazodone 100mg capsules | 56 capsule (PO) £52.10 DT price = £38.63
- Molipaxin (Zentiva) Molipaxin hydrochloride 50 mg Molipaxin 50mg capsules | 84 capsule (PO) £23.92 DT price = £29.85
- Trazodone hydrochloride 100 mg Molipaxin 100mg capsules | 56 capsule (PO) £52.10 DT price = £38.63

### Oral solution

CAUTIONARY AND ADVISORY LABELS 2, 21

▶ **Trazodone hydrochloride (Non-proprietary)**

- Trazodone hydrochloride 10 mg per 1 ml Trazodone 50mg/5ml oral solution sugar free sugar-free | 120 ml (PO) £180.00 DT price = £162.85

## ANTIDEPRESSANTS > TETRACYCLIC ANTIDEPRESSANTS

### Mianserin hydrochloride

- **INDICATIONS AND DOSE**

Depressive illness (particularly where sedation is required)

▶ **BY MOUTH**

- Adult: Initially 30–40 mg daily in divided doses, alternatively initially 30–40 mg once daily, dose to be taken at bedtime, increase dose gradually as necessary; usual dose 30–90 mg
- Elderly: Initially 30 mg daily in divided doses, alternatively initially 30 mg once daily, dose to be taken at bedtime, increase dose gradually as necessary; usual dose 30–90 mg

- **CONTRA-INDICATIONS**

Acute porphyrias p. 930 · arrhythmias · during the manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction

- **CAUTIONS**

Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intra-ocular pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention

- **CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS**

Antidepressants, tricyclic (related).

- **SIDE-EFFECTS**

▶ **Common or very common**

- Agitation · anxiety · arrhythmia · blurred vision · confusion · dizziness · dry mouth · ECG changes · heart block · irritability · paraesthesia · postural hypotension · sleep disturbances · sudden death of patients with cardiac disease · tachycardia

▶ **Rare**

- Dysarthria · extrapyramidal symptoms · paralytic ileus · tremor · urinary retention

▶ **Very rare**

- Constipation · neuroleptic malignant syndrome · precipitation of angle-closure glaucoma

- **Frequency not known**

- Alopecia · anorexia · arthralgia · arthritides · blood dyscrasias · breast enlargement · changes in blood sugar · chills (on withdrawal) · convulsions · delusions · galactorrhoea · gynaecomastia · haemato logical reactions · hallucinations · headache (on withdrawal) · hepatic reactions · hypomania · hyponatraemia · increased appetite · influenza-like symptoms (on withdrawal) · Insomnia (on withdrawal) · jaundice · mania · movement disorders (on withdrawal) · myalgia (on withdrawal) · nausea · nausea (on withdrawal) · oedema · photosensitivity · pruritus · rash · sexual dysfunction · suicidal behaviour · sweating · sweating (on withdrawal) · taste disturbance · tinnitus · urticaria · vivid dreams (on withdrawal) · vomiting · weight gain · weight loss

### SIDE-EFFECTS, FURTHER INFORMATION

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**

The tricyclic-related antidepressant drugs may be associated with a lower risk of cardiotoxicity in overdose.

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hyperthermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

- **PREGNANCY** Avoid.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Caution in renal impairment.

- **MONITORING REQUIREMENTS** A full blood count is recommended every 4 weeks during the first 3 months of treatment; clinical monitoring should continue subsequently and treatment should be stopped and a full blood count obtained if fever, sore throat, stomatitis, or other signs of infection develop.

- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.
Mirtazapine

**DRUG ACTION** Mirtazapine is a presynaptic α2-adrenoreceptor antagonist which increases central noradrenergic and serotonergic neurotransmission.

**INDICATIONS AND DOSE**

**Major depression**

▷ **BY MOUTH**

▷ Adult: Initially 15–30 mg daily for 2–4 weeks, dose to be taken at bedtime, then adjusted according to response to up to 45 mg once daily, alternatively up to 45 mg daily in 2 divided doses

**CAUTIONS**

Cardiac disorders · diabetes mellitus · elderly · history of bipolar depression · history of seizures · history of urinary retention · hypotension · psychoses (may aggravate psychotic symptoms) · susceptibility to angle-closure glaucoma

**INTERACTIONS** → Appendix 1 (mirtazapine).

**SIDE-EFFECTS**

▷ Common or very common Abnormal dreams · agitation (on withdrawal) · anxiety · anxiety (on withdrawal) · arthralgia · confusion · dizziness · dizziness (on withdrawal) · drowsiness · dry mouth · fatigue · headache (on withdrawal) · increased appetite · insomnia · myalgia · nausea (on withdrawal) · oedema · postural hypotension · tremor · vomiting (on withdrawal) · weight gain

▷ Uncommon Hallucinations · mania · movement disorders · syncope

▷ Rare Aggression · myoclonus · pancreatitis

▷ Frequency not known Angle-closure glaucoma · blood disorders · convulsions · dysarthria · hypersalivation · hyponatraemia · inappropriate secretion of antidiuretic hormone · sedation during initial treatment · Stevens-Johnson syndrome · suicidal behaviour · toxic epidermal necrolysis

**PREGNANCY** Use with caution—limited experience; monitor neonate for withdrawal effects.

**BREAST FEEDING** Present in milk; use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT** Use with caution. Discontinue if jaundice occurs.

**RENAL IMPAIRMENT** Clearance reduced by 30% if eGFR less than 40 mL/minute/1.73 m²; clearance reduced by 50% if eGFR less than 10 mL/minute/1.73 m².

**TREATMENT CESSATION** Nausea, vomiting, dizziness, agitation, anxiety, and headache are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks.

**DIRECTIONS FOR ADMINISTRATION** Orodispersible tablet (Zispin SolTab®) should be placed on the tongue, allowed to disperse and swallowed.

**MEDICINAL FORMS**

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2, 25**

▷ Mianserin hydrochloride (Non-proprietary)

  Mianserin hydrochloride 10 mg Mianserin 10 mg tablets | 28 tablet (Po) £8.37 DT price = £8.34

  Mianserin hydrochloride 30 mg Mianserin 30 mg tablets | 28 tablet (Po) £18.34 DT price = £18.34

**INDICATIONS AND DOSE**

**Adult:**

▷ **Mianserin hydrochloride 30 mg orodispersible tablets (Merck Sharp & Dohme Ltd)**

  Mianserin 30 mg tablets | 30 tablet (Po) £19.19 DT price = £1.46

  Mianserin 45 mg tablets | 30 tablet (Po) £19.19 DT price = £2.00

▷ **Zispin SolTab (Merck Sharp & Dohme Ltd)**

  Mianserin 15 mg Zispin SolTab 15 mg tablets | 30 tablet (Po) £15.06 DT price = £1.45

  Mianserin 30 mg Zispin SolTab 30 mg tablets | 30 tablet (Po) £15.06 DT price = £1.46

  Mianserin 45 mg Zispin SolTab 45 mg tablets | 30 tablet (Po) £15.06 DT price = £2.00

**Orodispersible tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

**Excipients:** May contain Aspartame

▷ **Mianserin (Non-proprietary)**

  Mianserin 15 mg Mianserin 15 mg tablets | 30 tablet (Po) £19.19 DT price = £1.45

  Mianserin 30 mg Mianserin 30 mg tablets | 30 tablet (Po) £19.19 DT price = £1.46

  Mianserin 45 mg Mianserin 45 mg tablets | 30 tablet (Po) £19.19 DT price = £2.00

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 2**

**Excipients:** May contain Aspartame

▷ **Mianserin (Non-proprietary)**

  Mianserin 15 mg per 1 ml Mianserin 15 mg/ml oral solution | 66 ml (Po) £51.05 DT price = £50.28

**ANTIDEPRESSANTS**

**TRICYCLIC ANTIDEPRESSANTS**

 Amitriptyline hydrochloride

**INDICATIONS AND DOSE**

Abdominal pain or discomfort (in patients who have not responded to laxatives, loperamide, or antispasmodics)

▷ **BY MOUTH**

▷ Adult: Initially 5–10 mg daily, to be taken at night; increased in steps of 10 mg at least every 2 weeks as required; maximum 30 mg per day

**Depressive illness (not recommended—increased risk of fatality in overdose)**

▷ **BY MOUTH**

▷ Adult: Initially 75 mg daily in divided doses, alternatively initially 75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–200 mg daily, dose to be increased gradually

▷ Elderly: Initially 30–75 mg daily in divided doses, alternatively initially 30–75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–200 mg daily, dose to be increased gradually

**Neuropathic pain**

▷ **BY MOUTH**

▷ Adult: Initially 10 mg once daily, increased if necessary to 75 mg once daily, dose to be taken at night, dose to be increased gradually, higher doses to be given on specialist advice

**PATIENT AND CARER ADVICE**

Counselling on administration of orodispersible tablet advised.

Blood Disorders Patients should be advised to report any fever, sore throat, stomatitis or other signs of infection during treatment. Blood count should be performed and the drug stopped immediately if blood dyscrasia suspected.
Migraine prophylaxis

- **BY MOUTH**
- **Adult:** Initially 10 mg once daily, then increased if necessary to 50–75 mg once daily (max. per dose 150 mg), dose to be taken at night

- **UNLICENSED USE** Not licensed for use in neuropathic pain. Not licensed for use in migraine prophylaxis. Not licensed for use in abdominal pain or discomfort in patients who have not responded to laxatives, loperamide, or antispasmodics.

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 - arrhythmias during manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

- **CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS** → Appendix 1 (Antidepressants, tricyclic).

**SIDE-EFFECTS**

- Common or very common Abdominal pain - fatigue - hypertension - mydriasis - oedema - palpitation - restlessness - stomatitis
- Rare Dysarthria - extrapyramidal symptoms - paralytic ileus - tremor
- Very rare Neuroleptic malignant syndrome - precipitation of angle-closure glaucoma
- Frequency not known Agitation - alopecia - anorexia - anxiety - arrhythmia - blurred vision - breast enlargement - changes in blood sugar - chills (on withdrawal) - confusion - constipation - convulsions - delusions - dizziness - drowsiness - dry mouth - ECG changes - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache (on withdrawal) - heart block - hepatic reactions - hyponatraemia - increased appetite - increased intra-ocular pressure - influenza-like symptoms (on withdrawal) - Insomnia (on withdrawal) - irritability - mania - movement disorders (on withdrawal) - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - paraesthesia - photosensitivity - postural hypotension - pruritus - rash - sexual dysfunction - sleep disturbances - sudden death of patients with cardiac disease - suicidal behaviour - sweating - sweating (on withdrawal) - tachycardia - taste disturbance - tinnitus - urinary retention - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**

Overdosage with amitriptyline is associated with a relatively high rate of fatality. Symptoms of overdosage may include dry mouth, coma of varying degree, hypotension, hyperthermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning, see Tricyclic and related antidepressants, under Emergency treatment of poisoning p. 1204.

**PREGNANCY** Use only if potential benefit outweighs risk.

**BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**LESS SUITABLE FOR PRESCRIBING** Amitriptyline hydrochloride is less suitable for prescribing; see Tricyclic and related antidepressant drugs in Antidepressant drugs p. 336.

**MEDITICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 2 |
| Amitriptyline hydrochloride (Non-proprietary) |
| Amitriptyline hydrochloride 10 mg | 28 tablet (Psd) £1.20 DT price = £1.20 |
| Amitriptyline hydrochloride 25 mg | 28 tablet (Psd) £2.10 DT price = £0.79 |
| Amitriptyline hydrochloride 50 mg | 28 tablet (Psd) £5.99 DT price = £1.15 |

**Oral solution**

| CAUTIONARY AND ADVISORY LABELS | 2 |
| Amitriptyline hydrochloride (Non-proprietary) |
| Amitriptyline hydrochloride 2 mg per 1 ml | 150 ml (Psd) £15.12 |
| Amitriptyline hydrochloride 5 mg per 1 ml | 150 ml (Psd) £18.00 DT price = £18.00 |
| Amitriptyline hydrochloride 10 mg per 1 ml | 150 ml (Psd) £19.20 DT price = £19.20 |

**Amitriptyline with perphenazine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, amitriptyline hydrochloride p. 349, perphenazine p. 364.

**INDICATIONS AND DOSE**

**Depression with anxiety**

- **BY MOUTH**
- **Adult:** 1 tablet 3 times a day, an additional tablet may be taken at bedtime when required

**LESS SUITABLE FOR PRESCRIBING** Amitriptyline with perphenazine is less suitable for prescribing.
Clomipramine hydrochloride

**INDICATIONS AND DOSE**

**Depressive illness**
- **BY MOUTH**
  - Adult: Initially 10 mg daily, then increased if necessary to 30–150 mg daily in divided doses, dose to be increased gradually, alternatively increased if necessary to 30–150 mg once daily, dose to be taken at bedtime; maximum 250 mg per day
  - Elderly: Initially 10 mg daily, then increased to 30–75 mg daily, dose to be increased carefully over approximately 10 days

**Phobic and obsessional states**
- **BY MOUTH**
  - Adult: Initially 25 mg daily, then increased to 100–150 mg daily, dose to be increased gradually over 2 weeks; maximum 250 mg per day
  - Elderly: Initially 10 mg daily, then increased to 100–150 mg daily, dose to be increased gradually over 2 weeks; maximum 250 mg per day

**Adjunctive treatment of cataplexy associated with narcolepsy**
- **BY MOUTH**
  - Adult: Initially 10 mg daily, dose to be gradually increased until satisfactory response; increased if necessary to 10–75 mg daily

**CONTRA-INDICATIONS**
Acute porphyrias p. 930.
- arrhythmias – during the manic phase of bipolar disorder
- heart block – immediate recovery period after myocardial infarction

**CAUTIONS**
Cardiovascular disease – chronic constipation
- diabetes – epilepsy – history of bipolar disorder – history of psychosis – hyperthyroidism (risk of arrhythmias)
- increased intra-ocular pressure – patients with a significant risk of suicide – phaeochromocytoma (risk of arrhythmias) – prostatic hypertrophy – susceptibility to angle-closure glaucoma – urinary retention

**CAUTIONS, FURTHER INFORMATION**
Treatment should be stopped if the patient enters a manic phase.
Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS**
- Appendix 1 (antidepressants, tricyclic)

**SIDE-EFFECTS**
- **Common or very common**
  - ECG changes – gynaecomastia – headache
  - Heart block – hypertension – increased appetite – neurological symptoms
  - Insomnia (on withdrawal) – irritability – mania – movement disorders (on withdrawal)
  - Myalgia (on withdrawal) – nausea – seizures (on withdrawal)

- **Rare**
  - ECG changes – galactorrhoea – gynaecomastia – haematological reactions – hallucinations – headache

**PRESCRIBING AND DISPENSING INFORMATION**

**SIDE-EFFECTS, FURTHER INFORMATION**
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**
Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

**PREGNANCY**
Neonatal withdrawal symptoms reported if used during third trimester.

**BREAST FEEDING**
The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT**
Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**TREATMENT CESSION**
Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION**
Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**
Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**
- **Clomipramine hydrochloride (Non-proprietary)**
  - Clomipramine hydrochloride 10 mg | 28 capsule | £1.34
  - Clomipramine hydrochloride 25 mg | 28 capsule | £1.59
  - Clomipramine hydrochloride 50 mg | 28 capsule | £1.88

- **Clomipramine hydrochloride 1 mg Perphenazine 2 mg, Amitriptyline hydrochloride 25 mg Triptafen tablets | 100 tablet | £3.13**
Dosulepin hydrochloride
(Dothiepin hydrochloride)

- **INDICATIONS AND DOSE**
  - **Depressive illness, particularly where sedation is required (not recommended—increased risk of fatality in overdose) (Initiated by a specialist)**
    - **BY MOUTH**
    - Adult: Initially 75 mg daily in divided doses, alternatively initially 75 mg once daily, dose to be taken at bedtime, increased if necessary to 150 mg daily, doses to be increased gradually; up to 225 mg daily in some circumstances (e.g. hospital use)
    - Elderly: Initially 50–75 mg daily in divided doses, alternatively initially 50–75 mg once daily, dose to be taken at bedtime, increased if necessary to 75–150 mg daily, doses to be increased gradually; up to 225 mg daily in some circumstances (e.g. hospital use)
  - **SIDE-EFFECTS**
    - **CONTRA-INDICATIONS** Acute porphyrias p. 930 · arrhythmias · during the manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction
  - **CAUTIONS** Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intraocular pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention
  - **INTERACTIONS** → Appendix 1 (antidepressants, tricyclic).
  - **SIDE-EFFECTS**
    - **Rare** Dysarthria · extrapyramidal symptoms · paralytic ileus · tremor
    - **Very rare** Neuroleptic malignant syndrome · precipitation of angle-closure glaucoma
    - **Frequency not known** Agitation · alopecia · anorexia · anxiety · arrhythmias · blurred vision · breast enlargement · changes in blood sugar · chills (on withdrawal) · confusion · constipation · convulsions · delusions · dizziness · dry mouth · ECG changes · galactorrhea · gynaecomastia · haematological reactions · hallucinations · headache (on withdrawal) · heart block · hepatic reactions · hypomania · hypoglycaemia · increased appetite · increased intraocular pressure · influenza-like symptoms (on withdrawal) · insomnia (on withdrawal) · irritability · mania · movement disorders (on withdrawal) · myalgia (on withdrawal) · nausea · nausea (on withdrawal) · paraesthesia · photosensitivity · postural hypotension · pruritus · rash · sexual dysfunction · sleep disturbances · sudden death of patients with cardiac disease · suicidal behaviour · sweating · sweating (on withdrawal) · tachycardia · taste disturbance · tinnitus · urinary retention · urticaria · vivid dreams (on withdrawal) · vomiting · weight gain · weight loss
  - **PATIENT AND CARER ADVICE**
    - **Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.
    - **LESS SUITABLE FOR PRESCRIBING** Dosulepin hydrochloride is less suitable for prescribing, see Tricyclic and related antidepressant drugs in Antidepressant drugs p. 336.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 2
  - **Dosulepin hydrochloride (Non-proprietary)**
    - Dosulepin hydrochloride 75 mg Dosulepin 75mg tablets | 28 tablet £1.70 DT price = £1.56
    - Prothiaden (Teofarma)
      - Dosulepin hydrochloride 75 mg Prothiaden 75mg tablets | 28 tablet £2.97 DT price = £1.56

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 2
  - **Dosulepin hydrochloride (Non-proprietary)**
    - Dosulepin hydrochloride 25 mg Dosulepin 25mg capsules | 28 capsule £3.00 DT price = £1.40
    - Prothiaden (Teofarma)
      - Dosulepin hydrochloride 25 mg Prothiaden 25mg capsules | 28 capsule £1.70 DT price = £1.40

**Overdose**

Overdosage with dosulepin is associated with a relatively high rate of fatality.

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

- **PREGNANCY** Use only if potential benefit outweighs risk.
- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.
- **HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.
- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge. (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

A maximum prescription equivalent to 2 weeks’ supply of 75 mg daily should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dose adjustment, and until improvement occurs.
Doxepin

**INDICATIONS AND DOSE**

**Depressive illness (particularly where sedation is required)**

- **BY MOUTH**
  - Adult: Initially 75 mg daily in divided doses, alternatively 75 mg once daily, adjusted according to response, dose to be increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.
  - Elderly: Start with lower doses and adjust according to response.

**CONTRA-INDICATIONS** Acute porphyrias p. 930 · arrhythmias · during manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction

**CAUTIONS** Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intra-ocular pressure · patients with significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention.

**INTERACTIONS** → Appendix 1 (antidepressants, tricyclic).

**SIDE-EFFECTS**

- Common or very common: Agitation · anxiety · confusion · dizziness · drowsiness · irritability · paraesthesia · sleep disturbances.
- Rare: Dysarthria · extrapyramidal symptoms · paralytic ileus · tremor.
- Very rare: Neuroleptic malignant syndrome · precipitation of angle-closure glaucoma.

**Frequency not known** Abdominal pain · alopecia · anorexia · arrhythmia · blurred vision · breast enlargement · changes in blood sugar · chills (on withdrawal) · constipation · convulsions · delusions · diarrhoea · dry mouth · ECG changes · flushing · galactorrhoea · gynaecomastia · haematological reactions · hallucinations · headache (on withdrawal) · heart block · hepatic reactions · hypomania · hynoponatremia · increased appetite · influenza-like symptoms (on withdrawal) · insomnia (on withdrawal) · mania · movement disorders (on withdrawal) · myalgia (on withdrawal) · nausea · nausea (on withdrawal) · oedema · photosensitivity · postural hypotension · pruritus · rash · sexual dysfunction · stomatitis · sudden death of patients with cardiac disease · suicidal behaviour · sweating · sweating (on withdrawal) · tachycardia · taste disturbance · tinnitus · urinary retention · urticaria · vivid dreams (on withdrawal) · vomiting · weight gain · weight loss.

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

**PREGNANCY** Use with caution—limited information available.

**BREAST FEEDING** The amount secreted into breast milk is too small to be harmful. Accumulation of metabolite may cause sedation and respiratory depression in neonate.

**HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**RENAL IMPAIRMENT** Use with caution.

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks. Drowsiness may affect performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>DT price = £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin (Non-proprietary)</td>
<td>28 capsule</td>
</tr>
<tr>
<td>Doxepin (as Doxepin hydrochloride) 50 mg</td>
<td>28 capsule</td>
</tr>
</tbody>
</table>

Imipramine hydrochloride

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: Initially up to 75 mg daily in divided doses, then increased to 150–200 mg daily, up to 150 mg may be given as a single dose at bedtime, dose to be increased gradually.
  - Elderly: Initially 10 mg daily, increased to 30–50 mg daily, dose to be increased gradually.

**Depressive illness in hospital patients**

- **BY MOUTH**
  - Adult: Initially up to 75 mg daily in divided doses, dose to be increased gradually, increased to up to 300 mg daily in divided doses.

**Nocturnal enuresis**

- **BY MOUTH**
  - Child 6–7 years: 25 mg once daily, to be taken at bedtime, initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course.
  - Child 8–10 years: 25–50 mg once daily, to be taken at bedtime, initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course.
• Child 11-17 years: 50–75 mg once daily, to be taken at bedtime, initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course

**CONTRA-INDICATIONS** Immediate recovery period after myocardial infarction (in adults). Acute porphyrias p. 930. arrhythmia. during the manic phase of bipolar disorder. heart block

**CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias). increased intra-ocular pressure (in adults). patients with a significant risk of suicide. phaeochromocytoma (risk of arrhythmias). prostatic hypertrophy (in adults). susceptibility to angle-closure glaucoma. urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase. Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**SIDE-EFFECTS**

- **Common or very common** Fatigue. flushing. headache. palpitation. restlessness
- **Rare** Extrapyramidal symptoms. paralytic ileus
- **Very rare** Abdominal pain. aggression. allergic alveolitis. cardiac decompensation. diarrhoea (in children). hyperpyrexia. mydriasis. myoclonus. neuroleptic malignant syndrome. oedema. peripheral vasospasm. precipitation of angle-closure glaucoma. stomatitis
- **Frequency not known** Agitation. alopecia. anorexia. anxiety. arrhythmia. blured vision. breast enlargement. changes in blood sugar. chills (on withdrawal). confusion. constipation. convulsions. delusions. dizziness. drowsiness. dry mouth. dysarthria. ECG changes. galactorrhoea. gynaecomastia. haematological reactions. hallucinations. headache (on withdrawal). heart block. hepatic reactions. hypomania. hypotension. nausea. nervousness (on withdrawal). paraesthesia. photosensitivity. postural hypotension. pruritus. rash. sexual dysfunction. sleep disturbances. sudden death of patients with cardiac disease. suicidal behaviour. sweating. vomiting. weight gain. weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**

- In adults The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**

Tricyclic and related antidepressants cause dry mouth, coma of varying degree. hypotension. hypothermia. hyperreflexia. extensor plantar responses. convulsions. respiratory failure. cardiac conduction defects. and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

**PREGNANCY** Colic. tachycardia. dyspnoea. irritability. muscle spasms. respiratory depression and withdrawal symptoms reported in neonates when used in the third trimester.

**BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**RENAL IMPAIRMENT** Use with caution in severe impairment.

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Imipramine

www.medicinesforchildren.org.uk/imipramine

Driving and skilled tasks

Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 2 |
| Imipramine hydrochloride (Non-proprietary) | 2 |
| Imipramine hydrochloride 10 mg | 28 |
| tablet | £1.02 DT price = £1.02 |
| Imipramine hydrochloride 25 mg | 28 |
| tablet | £1.01 DT price = £0.99 |

**Oral solution**

| CAUTIONARY AND ADVISORY LABELS | 2 |
| Imipramine hydrochloride (Non-proprietary) | 2 |
| Imipramine hydrochloride 5 mg per 1 ml | 150 ml |
| oral solution sugar free | £43.00 DT price = £41.50 |

**Loferane**

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: 140–210 mg daily in divided doses
  - Elderly: May respond to lower doses

**CONTRA-INDICATIONS**

- Acute porphyrias p. 930.
- arrhythmias. during the manic phase of bipolar disorder.
- heart block.
- immediate recovery period after myocardial infarction

**CAUTIONS**

- Cardiovascular disease.
- chronic constipation.
- diabetes.
- epilepsy.
- history of bipolar disorder.
- history of psychosis.
- hyperthyroidism (risk of arrhythmias). increased intra-ocular pressure. patients with a significant risk of suicide. phaeochromocytoma (risk of arrhythmias). prostatic hypertrophy. susceptibility to angle-closure glaucoma.

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase.
Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

### INTERACTIONS
- Appendix 1 (antidepressants, tricyclic).

### SIDE-EFFECTS

- **Common or very common**
  - Agitation
  - Anxiety
  - Confusion
  - Dizziness
  - Irritability
  - Paraesthesia
  - Postural hypotension
  - Sleep disturbances

- **Rare**
  - Extrapyramidal symptoms, paralytic ileus

- **Very rare**
  - Neuroleptic malignant syndrome, precipitation of angle-closure glaucoma

- **Frequency not known**
  - Alopecia
  - Anorexia
  - Arrhythmias
  - Blurred vision
  - Breast enlargement
  - Constipation
  - Convulsions
  - Delusions
  - Diarrhoea
  - Drowsiness
  - Dry mouth
  - Dysarthria
  - ECG changes
  - Galactorrhoea
  - Gynaecomastia
  - Haematological reactions
  - Hallucinations
  - Headache (on withdrawal)
  - Heart block
  - Hepatic reactions
  - Hypomania
  - Hypotension
  - Increased appetite
  - Influenza-like symptoms (on withdrawal)
  - Insomnia (on withdrawal)
  - Mania
  - Movement disorders (on withdrawal)
  - Myalgia (on withdrawal)
  - Nausea
  - Nausea (on withdrawal)
  - Oedema
  - Photosensitivity
  - Pruritus
  - Rash
  - Sexual dysfunction
  - Sudden death of patients with cardiac disease
  - Suicidal behaviour
  - Sweating (on withdrawal)
  - Tachycardia
  - Taste disturbance
  - Tinnitus
  - Tremor
  - Urinary retention
  - Urticaria
  - Vivid dreams (on withdrawal)
  - Vomiting
  - Weight gain
  - Weight loss

### SIDE-EFFECTS, FURTHER INFORMATION

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

### Overdose

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Lofepramine is associated with the lowest risk of fatality in overdose, in comparison with other tricyclic antidepressant drugs. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

### PREGNANCY

Neonatal withdrawal symptoms and respiratory depression reported if used during third trimester.

### BREAST FEEDING

The amount secreted into breast milk is too small to be harmful.

### HEPATIC IMPAIRMENT

Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

### RENAL IMPAIRMENT

Avoid in severe impairment.

### TREATMENT CESSATION

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

### PRESCRIBING AND DISPENSING INFORMATION

Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

### PATIENT AND CARER ADVICE

**Driving and skilled tasks**

Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 2**
  - Lofepramine (Non-proprietary)
    - Lofepramine (as Lofepramine hydrochloride) 70 mg
  - Lofepramine 70mg tablets | 56 tablet | £59.97 DT price | + £13.12

**Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS 2**
  - Lofepramine (Non-proprietary)
    - Lofepramine (as Lofepramine hydrochloride) 14 mg per 1 ml
  - Lofepramine 70mg/5ml oral suspension sugar free sugar-free | 150 ml | £25.22 DT price + £25.22

### Nortriptyline

#### INDICATIONS AND DOSE

**Depressive illness**

- **BY MOUTH**
  - Adult: To be initiated at a low dose, then increased if necessary to 75–100 mg daily in divided doses, alternatively increased if necessary to 75–100 mg once daily; maximum 150 mg per day
  - Elderly: To be initiated at a low dose, then increased if necessary to 30–50 mg daily in divided doses

**Neuropathic pain**

- **BY MOUTH**
  - Adult: Initially 10 mg once daily, to be taken at night, increased if necessary to 75 mg daily, dose to be increased gradually; higher doses to be given under specialist supervision

### UNLICENSED USE

Not licensed for use in neuropathic pain.

### CONTRA-INDICATIONS

- Acute porphyrias
- Diabetes
- Hypersensitivity to tricyclic antidepressants
- Cardiac disease
- Recent myocardial infarction
- Intractable vomiting
- Pregnancy (first trimester)
- Breastfeeding

### CAUTIONS

- Cardiovascular disease
- Chronic constipation
- Diabetes
- Epilepsy
- History of bipolar disorder
- History of psychosis
- Hypothyroidism (risk of arrhythmias)
- Increased intraocular pressure
- Prostate hypertrophy
- Susceptibility to angle-closure glaucoma
- Urinary retention

### CAUTIONS, FURTHER INFORMATION

Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

### INTERACTIONS
- Appendix 1 (antidepressants, tricyclic).

### SIDE-EFFECTS

- **Common or very common**
  - Fatigue
  - Hypertension
  - Mydriasis
  - Restlessness

- **Rare**
  - Extrapyramidal symptoms, paralytic ileus

- **Very rare**
  - Neuroleptic malignant syndrome, precipitation of angle-closure glaucoma

- **Frequency not known**
  - Abdominal pain
  - Agitation
  - Alopecia
  - Anorexia
  - Anxiety
  - Arrhythmia
  - Blurred vision
  - Breast enlargement
  - Changes in blood sugar
  - Chills (on withdrawal)
  - Confusion
  - Constipation
  - Convulsions
  - Delusions
  - Diarrhoea
  - Dizziness
  - Drowsiness
  - Dry mouth
  - Dysarthria
  - ECG changes
  - Flushing
  - Galactorrhoea
  - Hallucinations
  - Headache
  - Hypertension
  - Mydriasis
  - Restlessness
  - Urinary retention
  - Urticaria
  - Vivid dreams
  - Weight gain
gynaecomastia • haematological reactions • hallucinations • headache (on withdrawal) • heart block • hepatic reactions • hypomania • hyponatraemia • increased appetite • influenza-like symptoms (on withdrawal) • insomnia (on withdrawal) • irritability • mania • movement disorders (on withdrawal) • myalgia (on withdrawal) • nausea • nausea (on withdrawal) • oedema • paraesthesia • photosensitivity • postural hypotension • pruritus • rash • sexual dysfunction • sleep disturbances • stomatitis • sudden death of patients with cardiac disease • suicidal behaviour • sweating • sweating (on withdrawal) • tachycardia • taste disturbance • tinnitus • tremor • urinary retention • urticaria • vivid dreams (on withdrawal) • vomiting • weight gain • weight loss

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

Overdose
Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1204.

PATIENT AND CARER ADVICE
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

OVERDOSE MONITORING REQUIREMENTS
In hepatic impairment. Avoid in severe liver disease.

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

SIDE-EFFECTS, FURTHER INFORMATION
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SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

INTERATIONS
Use only if potential benefit outweighs risk.

BREAST FEEDING
The amount secreted into breast milk is too small to be harmful.

HEPATIC IMPAIRMENT
Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

MANUFACTURER ADVISONES
Manufacturer advises plasma-nortriptyline concentration monitoring if dose above 100 mg daily, but evidence of practical value uncertain.

TREATMENT CESSATION
Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

PRESCRIBING AND DISPENSING INFORMATION
Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

PATIENT AND CARER ADVICE
Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

<table>
<thead>
<tr>
<th>TABLET</th>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline (Non-proprietary)</td>
<td>Nortriptyline (as Nortriptyline hydrochloride) 10 mg</td>
<td>100 tablet</td>
</tr>
<tr>
<td>Nortriptyline (as Nortriptyline hydrochloride) 25 mg</td>
<td>100 tablet</td>
<td>PO</td>
</tr>
</tbody>
</table>

INDICATIONS AND DOSE

Depressive illness (particularly where sedation required)

BY MOUTH

Adult: Initially 50–75 mg daily in divided doses, alternatively initially 50–75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–300 mg daily

Elderly: Initially 10–25 mg 3 times a day, maintenance 75–150 mg daily

CONTRA-INDICATIONS
Acute porphyrias p. 930 • arrhythmias • during the manic phase of bipolar disorder • heart block • immediate recovery period after myocardial infarction

CAUTIONS
Cardiovascular disease • chronic constipation • diabetes • epilepsy • history of bipolar disorder • history of psychosis • hyperthyroidism (risk of arrhythmias) • increased intra-ocular pressure • patients with a significant risk of suicide • phaeochromcytoma (risk of arrhythmias) • prostatic hypertrophy • susceptibility to angle-closure glaucoma • urinary retention

CAUTIONS, FURTHER INFORMATION
Treatment should be stopped if the patient enters a manic phase.

SIDE-EFFECTS
Use only if potential benefit outweighs risk.

Nortriptyline (as Nortriptyline hydrochloride) 25 mg

Tablet manufacturers include: oral suspension, oral solution

Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

INTERATIONS
Use only if potential benefit outweighs risk.
**INTERACTIONS**

- **Seizures**: Discontinue treatment in patients who develop seizures or if there is an increase in seizure frequency. Manufacturer advises caution when treating elderly patients with doses over 10 mg daily—limited information.

- **OTHER ANTIDEPRESSANTS**

  **Vortioxetine**

  - **DRUG ACTION**: Vortioxetine inhibits the re-uptake of serotonin (5-HT) and is an antagonist at 5-HT3 and an agonist at 5-HT1A receptors. This multimodal activity appears to be associated with antidepressant and anxiolytic-like effects.

  - **INDICATIONS AND DOSE**
    - **Major depression**
      - **BY MOUTH**
        - Adult: Initially 10 mg once daily; adjusted according to response to 5–20 mg once daily
        - Elderly: Initially 5 mg once daily; increased if necessary up to 20 mg once daily

  - **CAUTIONS**: Bleeding disorders - cirrhosis of the liver (risk of hyponatraemia) - elderly (risk of hyponatraemia) - history of mania (discontinue if patient entering manic phase) - history of seizures - unstable epilepsy

  - **CAUTIONS, FURTHER INFORMATION**
    - **Seizures** Discontinue treatment in patients who develop seizures or if there is an increase in seizure frequency. Elderly: manufacturer advises caution when treating elderly patients with doses over 10 mg daily—limited information.

  - **INTERACTIONS** → Appendix 1 (vortioxetine).

- **SIDE-EFFECTS**
  - **Common or very common**: Abnormal dreams · constipation · diarrhoea · dizziness · nausea · prisuritus · vomiting
  - **Uncommon**: Flushing · night sweats
  - **Rare**: Bleeding disorders
  - **Frequency not known**: Neuroleptic malignant syndrome—discontinue (potentially fatal) · serotonin syndrome · sexual dysfunction (with 20 mg dose only)

- **PREGNANCY**: Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. If used during the later stages of pregnancy, there is a risk of neonatal withdrawal symptoms and persistent pulmonary hypertension in the newborn.

- **BREAST FEEDING**: Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**: Manufacturer advises caution in severe impairment—no information available.

- **RENAL IMPAIRMENT**: Manufacturer advises caution in severe impairment—limited information available.

- **TREATMENT CESSATION**: Manufacturer advises treatment can be stopped abruptly, without need for gradual dose reduction.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.
  - Sedative effects are increased in patients who have been on long-term maintenance treatment or longer if withdrawal symptoms emerge (within 5 days of stopping treatment with antidepressant). Discontinue treatment in patients who develop severe impairment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
  - **BY MOUTH**
    - **Tablet**
      - **CAUTIONARY AND ADVISORY LABELS 2**
        - **Trimipramine (Non-proprietary)**
          - Trimipramine (as Trimipramine maleate) 10 mg: Trimipramine 10mg tablets | 28 tablet [PO] £197.18 DT price = £179.63 | 84 tablet [PO] no price available
          - Trimipramine (as Trimipramine maleate) 25 mg: Trimipramine 25mg tablets | 28 tablet [PO] £205.44 DT price = £200.50 | 84 tablet [PO] no price available
    - **Capsule**
      - **CAUTIONARY AND ADVISORY LABELS 2**
        - **Trimipramine (Non-proprietary)**
          - Trimipramine (as Trimipramine maleate) 50 mg: Trimipramine 50mg capsules | 28 capsule [PO] £190.00 DT price = £190.00

- **OTHER ANTIDEPRESSANTS**

  - **Vortioxetine**

  - **SIDE-EFFECTS**
    - **Common or very common**: Abnormal dreams · constipation · diarrhoea · dizziness · nausea · prisuritus · vomiting
    - **Uncommon**: Flushing · night sweats
    - **Rare**: Bleeding disorders
    - **Frequency not known**: Neuroleptic malignant syndrome—discontinue (potentially fatal) · serotonin syndrome · sexual dysfunction (with 20 mg dose only)

  - **PREGNANCY**: Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. If used during the later stages of pregnancy, there is a risk of neonatal withdrawal symptoms and persistent pulmonary hypertension in the newborn.

  - **BREAST FEEDING**: Manufacturer advises avoid—present in milk in animal studies.

  - **HEPATIC IMPAIRMENT**: Manufacturer advises caution in severe impairment—no information available.

  - **RENAL IMPAIRMENT**: Manufacturer advises caution in severe impairment—limited information available.

  - **TREATMENT CESSATION**: Manufacturer advises treatment can be stopped abruptly, without need for gradual dose reduction.

  - **PATIENT AND CARER ADVICE**
    - Driving and skilled tasks
      - Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
    - **BY MOUTH**
      - **Tablet**
        - **CAUTIONARY AND ADVISORY LABELS 2**
          - **Trimipramine (Non-proprietary)**
            - Trimipramine (as Trimipramine maleate) 10 mg: Trimipramine 10mg tablets | 28 tablet [PO] £197.18 DT price = £179.63 | 84 tablet [PO] no price available
            - Trimipramine (as Trimipramine maleate) 25 mg: Trimipramine 25mg tablets | 28 tablet [PO] £205.44 DT price = £200.50 | 84 tablet [PO] no price available
      - **Capsule**
        - **CAUTIONARY AND ADVISORY LABELS 2**
          - **Trimipramine (Non-proprietary)**
            - Trimipramine (as Trimipramine maleate) 50 mg: Trimipramine 50mg capsules | 28 capsule [PO] £190.00 DT price = £190.00

  - **OTHER ANTIDEPRESSANTS**

    - **Vortioxetine**

      - **DRUG ACTION**: Vortioxetine inhibits the re-uptake of serotonin (5-HT) and is an antagonist at 5-HT3 and an agonist at 5-HT1A receptors. This multimodal activity appears to be associated with antidepressant and anxiolytic-like effects.

      - **INDICATIONS AND DOSE**
        - **Major depression**
          - **BY MOUTH**
            - Adult: Initially 10 mg once daily; adjusted according to response to 5–20 mg once daily
            - Elderly: Initially 5 mg once daily; increased if necessary up to 20 mg once daily

      - **CAUTIONS**: Bleeding disorders - cirrhosis of the liver (risk of hyponatraemia) - elderly (risk of hyponatraemia) - history of mania (discontinue if patient entering manic phase) - history of seizures - unstable epilepsy

      - **CAUTIONS, FURTHER INFORMATION**
        - **Seizures** Discontinue treatment in patients who develop seizures or if there is an increase in seizure frequency. Elderly: manufacturer advises caution when treating elderly patients with doses over 10 mg daily—limited information.

      - **INTERACTIONS** → Appendix 1 (vortioxetine).
3.6 Psychoses and schizophrenia

Psychoses and related disorders

Advice of Royal College of Psychiatrists on doses of antipsychotic drugs above BNF upper limit

Unless otherwise stated, doses in the BNF are licensed doses—any higher dose is therefore unlicensed

- Consider alternative approaches including adjuvant therapy and newer or second-generation antipsychotic drugs such as clozapine.
- Bear in mind risk factors, including obesity; particular caution is indicated in older patients, especially those over 70.
- Consider potential for drug interactions—see interactions: Appendix 1 (antipsychotics).
- Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically and reduce dose if prolonged QT interval or other adverse cardiac abnormality develops.
- Increase dose slowly and not more often than once weekly.
- Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.
- Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important: When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be lower than the corresponding oral dose (owing to absence of first-pass effect), particularly if the patient is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for each route and should not imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least daily.

Antipsychotic drugs

Antipsychotic drugs are also known as ‘neuroleptics’ and (misleadingly) as ‘major tranquillisers’. In the short term they are used to calm disturbed patients whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitation. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

Schizophrenia

The aim of treatment is to alleviate the suffering of the patient (and carer) and to improve social and cognitive functioning. Many patients require life-long treatment with antipsychotic medication. Antipsychotic drugs relieve positive psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse; they are usually less effective on negative symptoms such as apathy and social withdrawal. In many patients, negative symptoms persist between episodes of treated positive symptoms, but earlier treatment of psychotic illness may protect against the development of negative symptoms over time. Patients with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a patient with a definitive diagnosis of schizophrenia is usually required after the first episode of illness in order to prevent relapses. Doses that are effective in acute episodes should generally be continued as prophylaxis.

First-generation antipsychotic drugs

The first-generation antipsychotic drugs act predominantly by blocking dopamine D₂ receptors in the brain. First-generation antipsychotic drugs are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin. The phenothiazine derivatives can be divided into 3 main groups:

- **Group 1**: chlorpromazine hydrochloride p. 361, levomepromazine p. 411, and promazine hydrochloride p. 379, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.
- **Group 2**: pericyazine p. 364, generally characterised by moderate sedative effects, but fewer extrapyramidal side-effects than groups 1 or 3.
- **Group 3**: fluphenazine decanoate p. 368, perphenazine p. 364, prochlorperazine p. 365, and trifluoperazine p. 366, generally characterised by fewer sedative and antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

**Butyrophenones** (benperidol p. 357 and haloperidol p. 363) resemble the group 3 phenothiazines in their clinical properties. **Thioxanthenes** (flupentixol p. 362 and zuclopenthixol p. 367) have moderate sedative, antimuscarinic effects, and extrapyramidal effects.

**Diphenylbutylpiperidines** (pimozide p. 364) and the **substituted benzamides** (sulpride p. 366) have reduced sedative, antimuscarinic, and extrapyramidal effects.

Second-generation antipsychotic drugs

The second-generation antipsychotic drugs (sometimes referred to as atypical antipsychotic drugs) act on a range of...
receptors in comparison to first-generation antipsychotic drugs and have more distinct clinical profiles, particularly with regard to side-effects.

**Prescribing for the elderly**

The balance of risks and benefit should be considered before prescribing antipsychotic drugs for elderly patients. In elderly patients with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack. Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper- and hypothermia in hot or cold weather.

It is recommended that:

- Antipsychotic drugs should not be used in elderly patients to treat mild to moderate psychotic symptoms.
- Initial doses of antipsychotic drugs in elderly patients should be reduced (to half the adult dose or less), taking into account factors such as the patient’s weight, comorbidity, and concomitant medication.
- Treatment should be reviewed regularly.

**Side effects of antipsychotic drugs**

Side-effects caused by antipsychotic drugs are common and contribute significantly to non-adherence to therapy.

Extrapyramidal symptoms occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (benperidol and haloperidol), and the first-generation depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.

Extrapyramidal symptoms consist of:

- **Parkinsonian symptoms** (including tremor), which may occur more commonly in adults or the elderly and may appear gradually;
- **Dystonia** (abnormal face and body movements) and **dyskinesia**, which occur more commonly in children or young adults and appear after only a few doses;
- **Akathisia** (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated;
- **Tardive dyskinesia** (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

**Parkinsonian symptoms** remit if the drug is withdrawn and may be suppressed by the administration of antimuscarinic drugs. However, routine administration of such drugs is not justified because not all patients are affected and they may unmask or worsen tardive dyskinesia.

**Tardive dyskinesia** is the most serious manifestation of extrapyramidal symptoms; it is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. In children, tardive dyskinesia is more likely to occur when the antipsychotic drug is withdrawn. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermicular movements of the tongue) may halt its full development. Tardive dyskinesia occurs fairly frequently, especially in the elderly, and treatment must be carefully and regularly reviewed.

**Hyperprolactinaemia**

Most antipsychotic drugs, both first- and second-generation, increase prolactin concentration to some extent because dopamine inhibits prolactin release. Aripiprazole reduces prolactin because it is a dopamine-receptor partial agonist. Risperidone, amisulpride, and first-generation antipsychotic drugs are most likely to cause symptomatic hyperprolactinaemia. The clinical symptoms of hyperprolactinaemia include sexual dysfunction, reduced bone mineral density, menstrual disturbances, breast enlargement, and galactorrhoea.

**Sexual dysfunction**

Sexual dysfunction is one of the main causes of non-adherence to antipsychotic medication; physical illness, psychiatric illness, and substance misuse are contributing factors. Antipsychotic-induced sexual dysfunction is caused by more than one mechanism. Reduced dopamine transmission and hyperprolactinaemia decrease libido; antimuscarinic effects can cause disorders of arousal; and alpha2-adrenoceptor antagonists are associated with erection and ejaculation problems in men. Risperidone and haloperidol commonly cause sexual dysfunction. If sexual dysfunction is thought to be antipsychotic-induced, dose reduction or switching medication should be considered.

**Cardiovascular side-effects**

Antipsychotic drugs have been associated with cardiovascular side-effects such as tachycardia, arrhythmias, and hypotension. QT-interval prolongation is a particular concern with pimozide and haloperidol. There is also a higher probability of QT-interval prolongation in patients using any intravenous antipsychotic drug, or any antipsychotic drug or combination of antipsychotic drugs with doses exceeding the recommended maximum. Cases of sudden death have occurred.

**Hyperglycaemia**

Hyperglycaemia and sometimes diabetes can occur with antipsychotic drugs, particularly clozapine, olanzapine, quetiapine, and risperidone. All antipsychotic drugs may cause weight gain, but the risk and extent varies. Clozapine and olanzapine commonly cause weight gain.

**Hypotension and interference with temperature regulation**

Hypotension and interference with temperature regulation are dose-related side-effects that are liable to cause dangerous falls and hypothermia or hyperthermia in the elderly. Clozapine, chlorpromazine, lurasidone, and quetiapine can cause postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some patients.

**Neuroleptic malignant syndrome**

Neuroleptic malignant syndrome (hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of all antipsychotic drugs. Discontinuation of the antipsychotic drug is essential because there is no proven effective treatment, but bromocriptine and dantrolene have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used.

**Blood dyscrasias**

Perform blood counts if unexplained infection or fever develops.

**Choice**

There is little meaningful difference in efficacy between each of the antipsychotic drugs (other than clozapine p. 371), and response and tolerability to each antipsychotic drug varies. There is no first-line antipsychotic drug which is suitable for all patients. Choice of antipsychotic medication is influenced by the patient’s medication history, the degree of sedation required (although tolerance to this usually develops), and consideration of individual patient factors such as risk of extrapyramidal side-effects, weight gain, impaired glucose tolerance, QT-interval prolongation, or the presence of negative symptoms.

**Negative symptoms**

Second generation antipsychotic drugs may be better at treating the negative symptoms of schizophrenia.
Extrapyramidal side-effects

Second-generation antipsychotic drugs should be prescribed if extrapyramidal side-effects are a particular concern. Of these, aripiprazole p. 370, clozapine, olanzapine p. 373, and quetiapine p. 375 are least likely to cause extrapyramidal side-effects. Although amisulpride p. 370 is a dopamine-receptor antagonist, extrapyramidal side-effects are less common than with the first-generation antipsychotic drugs because amisulpride selectively blocks mesolimbic dopamine receptors, and extrapyramidal symptoms are caused by blockade of the striatal dopamine pathway.

QT interval


Diabetes

Schizophrenia is associated with insulin resistance and diabetes; the risk of diabetes is increased in patients with schizophrenia who take antipsychotic drugs. First-generation antipsychotic drugs are less likely to cause diabetes than second-generation antipsychotic drugs, and of the first-generation antipsychotic drugs, fluphenazine decanoate and haloperidol p. 363 are lowest risk. Amisulpride and aripiprazole have the lowest risk of diabetes of the second-generation antipsychotic drugs. amisulpride, aripiprazole, haloperidol, sulpiride, and trifluoperazine p. 366 are least likely to cause weight gain.

Sexual dysfunction and prolactin

The antipsychotic drugs with the lowest risk of sexual dysfunction are aripiprazole and quetiapine. Olanzapine may be considered if sexual dysfunction is judged to be secondary to hyperprolactinaemia. Hyperprolactinaemia is usually not clinically significant with aripiprazole, clozapine, olanzapine, and quetiapine treatment. When changing from other antipsychotic drugs, a reduction in prolactin concentration may increase fertility.

Patients should receive an antipsychotic drug for 4–6 weeks before it is deemed ineffective. Prescribing more than one antipsychotic drug at a time should be avoided except in exceptional circumstances (e.g. clozapine augmentation or when changing medication during titration) because of the increased risk of adverse effects such as extrapyramidal symptoms, QT-interval prolongation, and sudden cardiac death.

Clozapine is licensed for the treatment of schizophrenia in patients unresponsive to, or intolerant of, other antipsychotic drugs. Clozapine should be introduced if schizophrenia is not controlled despite the sequential use of two or more antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for at least 6–8 weeks. If symptoms do not respond adequately to an optimised dose of clozapine, plasma-clozapine concentration should be checked before adding a second antipsychotic drug to augment clozapine; allow 8–10 weeks’ treatment to assess response. Patients must be registered with a clozapine patient monitoring service.

Monitoring

Full blood count, urea and electrolytes, and liver function test monitoring is required at the start of therapy with antipsychotic drugs, and then annually thereafter.

Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly.

Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly.

Before initiating antipsychotic drugs, an ECG may be required, particularly if physical examination identifies cardiovascular risk factors, if there is a personal history of cardiovascular disease, or if the patient is being admitted as an inpatient.

Blood pressure monitoring is advised before starting therapy and frequently during dose titration of antipsychotic drugs.

Other uses

Some antipsychotic drugs can be used for the treatment of nausea and vomiting, choreas, and motor tics. Chlorpromazine hydrochloride p. 361 and haloperidol can be used for intractable hiccup. Benperidol p. 357 is used in deviant antisocial sexual behaviour but its value is not established.

Psychomotor agitation should be investigated for an underlying cause; it can be managed with low doses of chlorpromazine hydrochloride p. 361 or haloperidol p. 363 used for short periods. Antipsychotic drugs can be used with caution for the short-term treatment of severe agitation and restlessness in the elderly.

Equivalent doses of oral antipsychotics

These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication. Equivalent daily dose of antipsychotic drug:

- Chlorpromazine 100 mg
- Clozapine 50 mg
- Haloperidol 2–3 mg
- Pimozide 2 mg
- Risperidone 0.5–1 mg
- Sulpiride 200 mg
- Trifluoperazine 5 mg

Important: These equivalences must not be extrapolated beyond the maximum dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate.

Dosage

After an initial period of stabilisation, in most patients, the total daily oral dose can be given as a single dose. The Royal College of Psychiatrists has published advice on doses of antipsychotic drugs above BNF upper limit.

Antipsychotic depot injections

Long-acting depot injections are used for maintenance therapy especially when compliance with oral treatment is unreliable. However, depot injections of conventional antipsychotics may give rise to a higher incidence of extrapyramidal reactions than oral preparations; extrapyramidal reactions occur less frequently with second-generation antipsychotic depot preparations, such as risperidone p. 377 and olanzapine embonate p. 378.

Choice

There is no clear-cut division in the use of the conventional antipsychotics, but zuclopenthixol p. 367 may be suitable for the treatment of agitated or aggressive patients whereas flupenthixol decanoate p. 367 can cause over-excitement in such patients. Zuclopenthixol decanoate p. 369 may be more effective in preventing relapses than other conventional antipsychotic depot preparations. The incidence of extrapyramidal reactions is similar for the conventional antipsychotics.
**SIDE-EFFECTS**

- **Very rare** Precipitation of angle-closure glaucoma
- **Frequency not known** Agitation, agranulocytosis, akathisia, antimuscarinic symptoms, apathy, blood dyscrasias, blurred vision, cardiovascular side-effects, confusion, constipation, contact sensitisation, convulsions, corneal and lens opacities, diabetes, difficulty with micturition, dizziness, drowsiness, dry mouth, dystonia, excitement, extrapyramidal symptoms, gastrointestinal disturbances, headache, hyperglycaemia, hyperprolactinaemia, hypotension (dose related), insomnia, interference with temperature regulation (dose related), jaundice (including cholestatic), leucopenia, nasal congestion, parkinsonian symptoms, photosensitisation, purpura, pigmentation of the conjunctiva, purpura, pigmentation of the cornea, purpura, pigmentation of the retina, purpura, pigmentation of the skin, rashes, sexual dysfunction, tardive dyskinesia, venous thromboembolism, weight gain

**Chlorpromazine hydrochloride**

**INDICATIONS AND DOSE**

- **Schizophrenia and other psychoses**
- **Mania**
- **Short-term adjunctive management of severe anxiety**
- **Psychomotor agitation, excitement, and violent or dangerously impulsive behaviour**
  - **By mouth**
    - **Adult:** Initially 25 mg 3 times a day, adjusted according to response, alternatively initially 75 mg once daily, adjusted according to response, dose to be taken at night; maintenance 75–300 mg daily, increased if necessary up to 1 g daily, this dose may be required in psychoses; use a third to half adult dose in the elderly or debilitated patients
  - **By rectum**
    - **Adult:** 100 mg every 6–8 hours, dose expressed as chlorpromazine base

**Intractable hiccup**

- **By mouth**
- **Adult:** 25–50 mg 3–4 times a day

**MONITORING REQUIREMENTS**

- **It is advisable to monitor prolactin concentration at the start of therapy, at 6 months, and then yearly. Patients taking antipsychotic drugs not normally associated with symptomatic hyperprolactinaemia should be considered for prolactin monitoring if they show symptoms of hyperprolactinaemia (such as breast enlargement and galactorrhea).**

**PATIENT AND CARER ADVICE**

- **As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.**

**Driving and skilled tasks**

Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

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**ANTIPSYCHOTICS**

**Antipsychotic drugs**

- **CAUTIONS** Blood dyscrasias, cardiovascular disease, conditions predisposing to seizures, depression, epilepsy, history of jaundice, myasthenia gravis, Parkinson’s disease (may be exacerbated in adults), photosensitisation (may occur with higher dosages), prostatic hypertrophy (in adults), severe respiratory disease, susceptibility to angle-closure glaucoma

**CAUTIONS, FURTHER INFORMATION**

- **Cardiovascular disease** An ECG may be required, particularly if physical examination identifies cardiovascular risk factors, personal history of cardiovascular disease, or if the patient is being admitted as an inpatient.

**INTERACTIONS**

- **Appendix 1 (antipsychotics).** Increased risk of toxicity with myelosuppressive drugs.

**INDICATIONS AND DOSE**

- **Schizophrenia and other psychoses; use a third to half adult dose in the elderly**
- **Night; maintenance adjusted according to response, dose to be taken at night**
- **Attention; effects of alcohol are enhanced**
- **BREAST FEEDING** There is limited information available on the short- and long-term effects of antipsychotic drugs on the breast-fed infant. Animal studies indicate possible adverse effects of antipsychotic medicines on the developing nervous system. Chronic treatment with antipsychotic drugs whilst breast-feeding should be avoided unless absolutely necessary. Phenothiazine derivatives are sometimes used in breast-feeding women for short-term treatment of nausea and vomiting.

**MONITORING REQUIREMENTS**

- **It is advisable to monitor prolactin concentration at the start of therapy, at 6 months, and then yearly. Patients taking antipsychotic drugs not normally associated with symptomatic hyperprolactinaemia should be considered for prolactin monitoring if they show symptoms of hyperprolactinaemia (such as breast enlargement and galactorrhea).**

**PATIENT AND CARER ADVICE**

- **As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.**

**Driving and skilled tasks**

Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

**ANTIPSYCHOTICS**

**FIRST-GENERATION**
Relief of acute symptoms of psychoses (under expert supervision)
  ▶ BY DEEP INTRAMUSCULAR INJECTION
    ▶ Adult: 25–50 mg every 6–8 hours

Nausea and vomiting of terminal illness (where other drugs have failed or are not available)
  ▶ BY MOUTH
    ▶ Child 1–5 years: 500 micrograms/kg every 4–6 hours; maximum 40 mg per day
    ▶ Child 6–11 years: 500 micrograms/kg every 4–6 hours; maximum 75 mg per day
    ▶ Child 12–17 years: 10–25 mg every 4–6 hours
    ▶ Adult: 10–25 mg every 4–6 hours
  ▶ BY DEEP INTRAMUSCULAR INJECTION
    ▶ Child 1–5 years: 500 micrograms/kg every 6–8 hours; maximum 40 mg per day
    ▶ Child 6–11 years: 500 micrograms/kg every 6–8 hours; maximum 75 mg per day
    ▶ Child 12–17 years: Initially 25 mg, then 25–50 mg every 3–4 hours until vomiting stops
    ▶ Adult: Initially 25 mg, then 25–50 mg every 3–4 hours until vomiting stops
  ▶ BY RECTUM
    ▶ Adult: 100 mg every 6–8 hours

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Dose adjustment may be necessary if smoking started or stopped during treatment.

DOSE EQUIVALENCE AND CONVERSION
  ▶ For equivalent therapeutic effect 100 mg chlorpromazine base given rectally as a suppository = 20–25 mg chlorpromazine hydrochloride by intramuscular injection = 40–50 mg of chlorpromazine base or hydrochloride given by mouth.

UNLICENSED USE
  ▶ With rectal use in adults Rectal route is not licensed.

CONTRA-INDICATIONS
  CNS depression · comatose states · hypothyroidism · phaeochromocytoma

CAUTIONS
  Diabetes

SIDE-EFFECTS
SIDE-EFFECTS, FURTHER INFORMATION
  ▶ Acute dystonic reactions Phenothiazines can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.

HEPATIC IMPAIRMENT
Can precipitate coma; phenothiazines are hepatotoxic.

RENAL IMPAIRMENT
Start with small doses in severe renal impairment because of increased cerebral sensitivity.

MONITORING REQUIREMENTS
  ▶ With intramuscular use Patients should remain supine, with blood pressure monitoring for 30 minutes after intramuscular injection.

HANDLING AND STORAGE
Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, suppository

Tablet
CAUTIONARY AND ADVISORY LABELS  2, 11
  ▶ Chlorpromazine hydrochloride (Non-proprietary)
  Chlorpromazine hydrochloride 25 mg
  Chlorpromazine 25 mg tablets
  28 tablet [PO] £4.92 DT price = £1.92

Chlorpromazine hydrochloride 50 mg
  Chlorpromazine 50 mg tablets
  28 tablet [PO] £5.28 DT price = £1.76

Chlorpromazine hydrochloride 100 mg
  Chlorpromazine 100 mg tablets
  28 tablet [PO] £5.70 DT price = £1.81

Oral solution
CAUTIONARY AND ADVISORY LABELS  2, 11
  ▶ Chlorpromazine hydrochloride (Non-proprietary)
  Chlorpromazine hydrochloride 5 mg per 1 ml
  Chlorpromazine 25mg/5ml
  150 ml [PO] £2.35 DT price = £2.35
  Chlorpromazine 25mg/5ml oral solution
  150 ml [PO] £2.35 DT price = £2.35
  Chlorpromazine hydrochloride 20 mg per 1 ml
  Chlorpromazine 100mg/5ml
  150 ml [PO] £5.50 DT price = £5.50

Solution for injection
  ▶ Largactil (Sanofi)
  Chlorpromazine hydrochloride 25 mg per 1 ml
  Largactil 50mg/2ml
  solution for injection ampoules
  10 ampoule [PO] £7.51

Flupentixol
(Flupenthixol)
  ▶ INDICATIONS AND DOSE
  Schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity
  ▶ BY MOUTH
    ▶ Adult: Initially 3–9 mg twice daily, adjusted according to response, for debilitated patients, use elderly dose; maximum 18 mg per day
    ▶ Elderly: Initially 0.75–4.5 mg twice daily, adjusted according to response

Depressive illness
  ▶ BY MOUTH
    ▶ Adult: Initially 1 mg once daily, dose to be taken in the morning, increased if necessary to 2 mg after 1 week, doses above 2 mg to be given in divided doses, last dose to be taken before 4 pm; discontinue if no response after 1 week at maximum dosage; maximum 3 mg per day
    ▶ Elderly: Initially 500 micrograms daily, dose to be taken in the morning, then increased if necessary to 1 mg after 1 week, doses above 1 mg to be given in divided doses, last dose to be taken before 4 pm; discontinue if no response after 1 week at maximum dosage; maximum 1.5 mg per day

CONTRA-INDICATIONS
  Circulatory collapse · CNS depression · comatose states · excitable patients · impaired consciousness · overactive patients · phaeochromocytoma

CAUTIONS
  Acute porphyrias p. 930 · cardiac disorders · cardiovascular disease · cerebral arteriosclerosis · diabetes · elderly · parkinsonism · QT-interval prolongation · senile confusional states

INTERACTIONS
  Avoid concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS
  Asthenia · dysphoria · hypersalivation · myalgia · sudden death · tordes de pointes

SIDE-EFFECTS, FURTHER INFORMATION
  Less sedating but extrapyramidal symptoms frequent.

PREGNANCY
  Avoid unless potential benefit outweighs risk.

BREAST FEEDING
  Present in breast milk—avoid.

HEPATIC IMPAIRMENT
Can precipitate coma. Consider serum-flupentixol concentration monitoring in hepatic impairment.

RENAL IMPAIRMENT
  Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity. Manufacturer advises caution in renal failure.
Haloperidol

**INDICATIONS AND DOSE**

**Nausea and vomiting**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 1–2 mg

**Nausea and vomiting in palliative care**
- **BY MOUTH**
  - Adult: Initially 1.5 mg 1–2 times a day, increased if necessary to 5–10 mg daily in divided doses
  - **BY CONTINUOUS SUBCUTANEOUS INFUSION**
  - Adult: 5–15 mg, to be administered over 24 hours
  - **BY SUBCUTANEOUS INFUSION**
  - Adult: 2.5–10 mg/24 hours

**Schizophrenia** | **Psychoses** | **Mania and hypomania** | **Organic brain damage (depending on symptoms)**

- **BY MOUTH**
  - Adult: Initially 2–20 mg once daily, alternatively initially 2–20 mg daily in divided doses; maintenance 1–3 mg 3 times a day, adjusted according to response, daily maximum to be given in divided doses, for debilitated patients, use elderly dose; maximum 20 mg per day
  - Elderly: Initially 1–10 mg once daily, alternatively initially 1–10 mg daily in divided doses; maintenance 1–3 mg 3 times a day, adjusted according to response, daily maximum to be given in divided doses; maximum 20 mg per day
  - **BY INTRAMUSCULAR INJECTION**
  - Adult: 2–5 mg, repeated if necessary, repeated dose given according to response and tolerability, for debilitated patients, use elderly dose; maximum 12 mg per day
  - Elderly: Initially 1–2.5 mg, repeated if necessary, repeated dose given according to response and tolerability; maximum 12 mg per day

**Agitation and restlessness in the elderly**
- **BY MOUTH**
  - Elderly: Initially 0.75–1.5 mg 2–3 times a day, adjusted according to response, if necessary

**Management of mental or behavioural problems such as aggression, hyperactivity and self-mutilation in patients with intellectual disabilities and in patients with organic brain damage (depending on symptoms)**
- Gilles de la Tourette syndrome
- Severe tics
- Intractable hiccup
- Adjunct to short-term management of moderate to severe psychomotor agitation, excitement and, violent or dangerously impulsive behaviour

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose adjustment may be necessary if smoking started or stopped during treatment.

**CONTRA-INDICATIONS**
- Bradycardia
- CNS depression
- Comatose states
- Lesions of the basal ganglia
- Parkinson’s disease
- Phaeochromocytoma
- QT-interval prolongation

**CAUTIONS**
- Arteriosclerosis
- Hypocalcaemia
- Hypokalaemia
- Hypomagnesaemia
- Metabolic disturbances
- Subarachnoid haemorrhage
- Thyrotoxicosis

**INTERACTIONS**
- Avoid concomitant administration of drugs that prolong QT interval.

**SIDE-EFFECTS**
- Common or very common: Depressions - weight loss
- Uncommon: Dystonia - oedema
- Rare: Bronchospasm - hypoglycaemia - inappropriate antidiuretic hormone secretion - photosensitivity reactions - pigmentation

**Frequency not known**
- Hypertension
- Stevens-Johnson syndrome
- Sweating
- Toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

Less sedating and fewer antimuscarinic or hypotensive symptoms.

**PREGNANCY**
- Avoid unless benefits outweigh risks.

**HEPATIC IMPAIRMENT**
- Can precipitate coma.

**RENAI IMPAIRMENT**
- Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**MONITORING REQUIREMENTS**
- Baseline ECG required before treatment—assess need for further ECGs during treatment on an individual basis.

**PRESCRIBING AND DISPENSING INFORMATION**

For further information on the use of haloperidol in palliative care, see <http://www.palliativedrugs.com/formulary/en/haloperidol.html>.
**Pericyazine**

**Pericyazine** (Percidazine)

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet** CAUTIONARY AND ADVISORY LABELS 2
- **Haloperidol (Non-proprietary)**
  - Haloperidol 500 microgram Haloperidol 500microgram tablets | 28 tablet [POM] £1.10–£20.05
  - Haloperidol 1.5 mg Haloperidol 1.5mg tablets | 28 tablet [POM] £5.99 DT price = £1.96
  - Haloperidol 5 mg Haloperidol 5mg tablets | 28 tablet [POM] £3.80 DT price = £2.35
  - Haloperidol 10 mg Haloperidol 10mg tablets | 28 tablet [POM] £12.99 DT price = £12.93

**Capsule** CAUTIONARY AND ADVISORY LABELS 2
- **Serence** (Teva UK Ltd)
  - Haloperidol 500 microgram Serence 500microgram capsules | 30 capsule [POM] £1.18 DT price = £1.18

**Oral solution** CAUTIONARY AND ADVISORY LABELS 2
- **Haloperidol (Non-proprietary)**
  - Haloperidol 1 mg per 1 ml Haloperidol 5mg/5ml oral solution sugar free sugar-free | 100 ml [POM] £5.99 DT price = £5.47 sugar-free | 500 ml [POM] £32.35
  - Haloperidol 2 mg per 1 ml Haloperidol 10mg/5ml oral solution sugar free sugar-free | 100 ml [POM] £46.75 DT price = £7.10 sugar-free | 500 ml [POM] £35.50
  - **Haldol** (Janssen-Cilag Ltd)
    - Haloperidol 2 mg per 1 ml Haldol 2mg/ml oral solution sugar-free | 100 ml [POM] £4.45 DT price = £7.10

**Solution for injection**
- **Haloperidol (Non-proprietary)**
  - Haloperidol 5 mg per 1 ml Haloperidol 5mg/1ml solution for injection ampoules | 10 ampoule [POM] £35.00

### INDICATIONS AND DOSE
Schizophrenia | Psychoses

- **BY MOUTH**
  - Adult: Initially 75 mg daily in divided doses, then increased in steps of 25 mg every week, adjusted according to response; maximum 300 mg per day
  - Elderly: Initially 15–30 mg daily in divided doses, then increased in steps of 25 mg every week, adjusted according to response; maximum 300 mg per day

Short-term adjunctive management of severe anxiety, psychomotor agitation, and violent or dangerously impulsive behaviour

- **BY MOUTH**
  - Adult: Initially 15–30 mg daily in 2 divided doses, adjusted according to response, larger dose to be taken at bedtime
  - Elderly: Initially 5–10 mg daily in 2 divided doses, adjusted according to response, larger dose to be taken at bedtime

### CONTRA-INDICATIONS
CNS depression · comatose states · phaeochromocytoma

### SIDE-EFFECTS
- **Common or very common** Hypotension (when treatment initiated)
- **Frequency not known** Respiratory depression

SIDE-EFFECTS, FURTHER INFORMATION
More sedating.

### HEPATIC IMPAIRMENT
Can precipitate coma; phenothiazines are hepatotoxic.

### RENAL IMPAIRMENT
Avoid in renal impairment.

**Perphenazine**

### INDICATIONS AND DOSE
Schizophrenia and other psychoses | Mania | Short-term adjunctive management of anxiety | Severe psychomotor agitation, excitement, and violent or dangerously impulsive behaviour | Severe nausea and vomiting unresponsive to other anti-emetics

- **BY MOUTH**
  - Adult: Initially 4 mg 3 times a day, adjusted according to response; maximum 24 mg per day
  - Elderly: Initially 1–2 mg 3 times a day; maximum 12 mg per day

### CONTRA-INDICATIONS
Agitation in the elderly · CNS depression · comatose states · phaeochromocytoma · restlessness in the elderly

### CAUTIONS
Hypothyroidism

### SIDE-EFFECTS
- **Rare** Systemic lupus erythematosus
- **Frequency not known** Dystonic reactions

SIDE-EFFECTS, FURTHER INFORMATION
Less sedating.

Acute dystonic reactions
Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.

### HEPATIC IMPAIRMENT
Can precipitate coma; phenothiazines are hepatotoxic.

### RENAL IMPAIRMENT
Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**Pimozide**

### INDICATIONS AND DOSE
Schizophrenia

- **BY MOUTH**
  - Adult: Initially 2 mg daily, adjusted according to response, then increased in steps of 2–4 mg at intervals of not less than 1 week; usual dose 2–20 mg daily
  - Elderly: Initially 1 mg daily, adjusted according to response, increased in steps of 2–4 mg at intervals of not less than 1 week; usual dose 2–20 mg daily
Prochlorperazine

**INDICATIONS AND DOSE**

**Schizophrenia and other psychoses | Mania**
- **BY MOUTH**
  - Adult: 12.5 mg twice daily for 7 days, dose to be adjusted at intervals of 4–7 days according to response; usual dose 75–100 mg daily
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 12.5–25 mg 2–3 times a day

**Short-term adjunctive management of severe anxiety**
- **BY MOUTH**
  - Adult: 15–20 mg daily in divided doses; maximum 40 mg per day

**Nausea and vomiting, acute attack**
- **BY MOUTH**
  - Adult: Initially 20 mg, then 10 mg after 2 hours
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 12.5 mg as required, to be followed if necessary after 6 hours by an oral dose

**SIDE-EFFECTS**
- Rare
- Hypoanatraemia
- Frequency not known Glycosuria • serious arrhythmias

**CONTRA-INDICATIONS**
- CNS depression • comatose states • history of arrhythmias • history or family history of congenital QT prolongation • phaeochromocytoma

**DOSE EQUIVALENCE AND CONVERSION**

**UNLICENSED USE**

**CONTRA-INDICATIONS**
- Avoid oral route in child under 10 kg • children (in psychotic disorders) • CNS depression • comatose states • phaeochromocytoma

**CAUTIONS**
- Elderly • hypotension (more likely after intramuscular injection)

**SIDE-EFFECTS, FURTHER INFORMATION**
- Dystonic reactions • respiratory depression may occur in susceptible patients

**SIDE-EFFECTS**
- Acute dystonic reactions Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.

**HEPATIC IMPAIRMENT**
- Can precipitate coma; phenothiazines are hepatotoxic.

**RENAL IMPAIRMENT**
- Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**DOSE EQUILIBRIUM AND CONVERSION**
- Doses are expressed as prochlorperazine maleate or mesilate; 1 mg prochlorperazine maleate = 1 mg prochlorperazine mesilate.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

CAUTIONARY AND ADVISORY LABELS 2
- Pimozide (Non-proprietary) Pimozide 4 mg Pimozide 4mg tablets | 100 tablet £31.36 no price available DT price = £40.31
- OraP (Eumedica Pharmaceuticals) Pimozide 4 mg OraP 4mg tablets | 100 tablet £40.31 DT price = £40.31

**Prochlorperazine**

**Hyponatraemia**
Can precipitate coma.

**Caution**
SID-EFFECTS, FURTHER INFORMATION

**Prevention and treatment of nausea and vomiting**
- **BY MOUTH**
  - Adult: 5–10 mg 2–3 times a day
  - Adult: 12.5 mg as required, to be followed if necessary after 6 hours by an oral dose

**Nausea and vomiting, prevention**
- **BY MOUTH**
  - Adult: 5–10 mg 2–3 times a day
  - **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 12.5 mg as required, to be followed if necessary after 6 hours by an oral dose

**SIDE-EFFECTS**
- Rare
- Hypoanatraemia
- Frequency not known Glycosuria • serious arrhythmias

**SIDE-EFFECTS, FURTHER INFORMATION**
- Less sedating.

**HEPATIC IMPAIRMENT**
- Can precipitate coma.

**RENAL IMPAIRMENT**
- Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**MONITORING REQUIREMENTS**
- ECG monitoring Following reports of sudden unexplained death, an ECG is recommended before treatment. It is also recommended that patients taking pimozide should have an annual ECG (if the QT interval is prolonged, treatment should be reviewed and either withdrawn or dose reduced under close supervision) and that pimozide should not be given with other antipsychotic drugs (including depot preparations), tricyclic antidepressants or other drugs which prolong the QT interval, such as certain antimalarials, antiarrhythmic drugs and certain antihistamines and should not be given with drugs which cause electrolyte disturbances (especially diuretics).
Sulpiride

**INDICATIONS AND DOSE**

**Schizophrenia with predominantly negative symptoms**
- **BY MOUTH**
  - Adult: 200–400 mg twice daily; maximum 800 mg per day
  - Elderly: Lower initial dose to be given, increased gradually according to response

**Schizophrenia with mainly positive symptoms**
- **BY MOUTH**
  - Adult: 200–400 mg twice daily; maximum 2.4 g per day
  - Elderly: Lower initial dose to be given, increased gradually according to response

**CONTRA-INDICATIONS** CNS depression · comatose states · phaeochromocytoma

**CAUTIONS** Aggressive patients (even low doses may aggravate symptoms) · agitated patients (even low doses may aggravate symptoms) · excited patients (even low doses may aggravate symptoms)

**SIDE-EFFECTS** Hepatitis

**HEPATIC IMPAIRMENT** Can precipitate coma.

**RENAL IMPAIRMENT** Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**MONITORING REQUIREMENTS** Sulpiride does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include lemon and aniseed.

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Trifluoperazine

**INDICATIONS AND DOSE**

Schizophrenia and other psychoses · Short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour
- **BY MOUTH**
  - Adult: Initially 5 mg twice daily, increased by 5 mg daily after 1 week, then at intervals of 3 days, according to response
  - Elderly: Initially up to 2.5 mg twice daily, increased by 5 mg daily after 1 week, then at intervals of 3 days, according to response

**Short-term adjunctive management of severe anxiety**
- **BY MOUTH**
  - Adult: 2–4 mg daily in divided doses, increased if necessary to 6 mg daily
  - Elderly: Up to 2 mg daily in divided doses, increased if necessary to 6 mg daily

**Severe nausea and vomiting**
- **BY MOUTH**
  - Adult: 2–4 mg daily in divided doses; maximum 6 mg per day

**CONTRA-INDICATIONS** CNS depression · comatose states · phaeochromocytoma

**SIDE-EFFECTS** Anorexia · dystonic reactions · muscle weakness

**SIDE-EFFECTS, FURTHER INFORMATION**

Extrapyramidal symptoms are more frequent, especially at doses exceeding 6 mg daily.

Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises.

**HEPATIC IMPAIRMENT** Can precipitate coma; phenothiazines are hepatotoxic.

**RENAL IMPAIRMENT** Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**MONITORING REQUIREMENTS** Trifluoperazine does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.
Zuclopenthixol

- **INDICATIONS AND DOSE**
  - **Schizophrenia and other psychoses**
    - **BY MOUTH**
      - **Adult:** Initially 20–30 mg daily in divided doses, increased if necessary up to 150 mg daily; usual maintenance 20–50 mg daily (max. per dose 40 mg), for debilitated patients, use elderly dose
      - **Elderly:** Initially 5–15 mg daily in divided doses, increased if necessary up to 150 mg daily; usual maintenance 20–50 mg daily (max. per dose 40 mg)

- **CONTRA-INDICATIONS**
  - Apathetic states • CNS depression • comatose states • phaeochromocytoma • withdrawn states

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **SIDE-EFFECTS**
  - Urinary frequency • urinary incontinence • weight loss (less common than weight gain)

- **HEPATIC IMPAIRMENT**

- **RENAL IMPAIRMENT**
  - Halve dose in renal failure; smaller starting doses used in severe renal impairment because of increased cerebral sensitivity.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  
  **Tablet**
  
  CAUTIONARY AND ADVISORY LABELS 2
  - Zuclopenthixol (as Zuclopenthixol dihydrochloride) 1 mg Triluoperazine 1mg tablets | 112 tablet (PO) £54.00 DT price = £54.00
  - Zuclopenthixol (as Zuclopenthixol dihydrochloride) 5 mg Triluoperazine 5mg tablets | 112 tablet (PO) £123.20 DT price = £123.20

  **Oral solution**
  
  CAUTIONARY AND ADVISORY LABELS 2
  - Zuclopenthixol (as Zuclopenthixol dihydrochloride) 1 mg per 1 ml Triluoperazine 1mg/5ml oral solution sugar free 150 ml | (PO) £25.50 DT price = £25.50

- **Zuclopenthixol acetate**
  
  - **INDICATIONS AND DOSE**
    - **Short-term management of acute psychosis** | **Short-term management of exacerbation of chronic psychosis**
      - **BY DEEP INTRAMUSCULAR INJECTION**
        - **Adult:** 50–150 mg, then 50–150 mg after 2–3 days if required, (1 additional dose may be needed 1–2 days after the first injection); maximum cumulative dose 400 mg in 2 weeks and maximum 4 injections; maximum duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; to be administered into the gluteal muscle or lateral thigh
        - **Elderly:** 50–100 mg, then 50–100 mg after 2–3 days if required, (1 additional dose may be needed 1–2 days after the first injection); maximum cumulative dose 400 mg in 2 weeks and maximum 4 injections; maximum duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; to be administered into the gluteal muscle or lateral thigh

- **IMPORTANT SAFETY INFORMATION**
  - When prescribing, dispensing, or administering, check that this is the correct preparation—this preparation is usually used in hospital for an acute episode and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

- **CONTRA-INDICATIONS**
  - CNS depression • comatose states • phaeochromocytoma

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **HEPATIC IMPAIRMENT**
  - Can precipitate coma.

- **RENAL IMPAIRMENT**
  - Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  
  | Clopixol Acuphase (Lundbeck Ltd) | Zuclopenthixol acetate 50 mg per 1 ml | Clopixol Acuphase 50mg/1ml solution for injection ampoules | 5 ampoule (PO) | £24.21 DT price = £24.21

- **Flupentixol decanoate**
  
  (Flupentixol Decanoate)

  - **INDICATIONS AND DOSE**
    - **Maintenance in schizophrenia and other psychoses**
      - **BY DEEP INTRAMUSCULAR INJECTION**
        - **Adult:** Test dose 20 mg, dose to be injected into the upper outer buttock or lateral thigh, then 20–40 mg after at least 7 days, then 20–40 mg every 2–4 weeks, adjusted according to response, usual maintenance dose 50 mg every 4 weeks to 300 mg every 2 weeks; maximum 400 mg per week
        - **Elderly:** Dose is initially quarter to half adult dose
CONTRA-INDICATIONS  Children · CNS depression · comatose states · excitable patients · overactive patients · phaeochromocytoma

CAUTIONS  An alternative antipsychotic may be necessary if symptoms such as aggression or agitation appear · avoid in Acute porphyrias p. 950 · diabetes · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

SIDE-EFFECTS  Erythema · hyperglycaemia · mood elevating effect · nodules · pain at injection site · swelling

SIDE-EFFECTS, FURTHER INFORMATION
If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

Less sedating but extrapyramidal symptoms frequent.

CAUTIONS

MONITORING REQUIREMENTS

RENAL IMPAIRMENT

START with small doses in severe renal impairment because of increased cerebral sensitivity.

SIDE-EFFECTS

SIDE-EFFECTS, FURTHER INFORMATION
Less sedating and fewer antimuscarinic or hypotensive effects are prolonged.

SIDE-EFFECTS

SIDE-EFFECTS, FURTHER INFORMATION
Less sedating but extrapyramidal symptoms frequent.

SIDE-EFFECTS

SIDE-EFFECTS, FURTHER INFORMATION

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Dose adjustment may be necessary if smoking started or stopped during treatment.

CONTRA-INDICATIONS  Children · CNS depression · comatose states · marked cerebral atherosclerosis · phaeochromocytoma

CAUTIONS  QT-interval prolongation · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

INTERACTIONS  Avoid concomitant drugs that prolong QT interval.

SIDE-EFFECTS

SIDE-EFFECTS, FURTHER INFORMATION
Less sedating and fewer antimuscarinic or hypotensive symptoms, but extrapyramidal symptoms, particularly dystonic reactions and akathisia, more frequent.

Extraapyramidal symptoms usually appear a few hours after injection and continue for about 2 days but may be delayed.

If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

HEPATIC IMPAIRMENT  Avoid in hepatic failure. Can precipitate coma; phenothiazines are hepatotoxic.

RENAI IMPAIRMENT  Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity. Manufacturer advises caution. Avoid in renal failure.

HEPATIC IMPAIRMENT  Avoid in hepatic failure. Can precipitate coma; phenothiazines are hepatotoxic.

RENAI IMPAIRMENT  Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity. Manufacturer advises caution. Avoid in renal failure.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Flupentixol decanoate (Non-proprietary)
  - Flupentixol decanoate 100 mg per 1 ml Flupentixol 100mg/1ml solution for injection ampoules | 10 ampoule (PoM) no price available
  - Flupentixol decanoate 200 mg per 1 ml Flupentixol 200mg/1ml solution for injection ampoules | 5 ampoule (PoM) no price available
- Depixol (Flupentixol decanoate) (Lundbeck Ltd)
  -Depixol (Flupentixol decanoate) 40mg/2ml solution for injection ampoules | 10 ampoule (PoM) £25.39
  -Depixol 40mg/2ml solution for injection ampoules | 10 ampoule (PoM) £15.17
- Flupentixol decanoate 100 mg per 1 ml Depixol Conc 100mg/1ml solution for injection ampoules | 10 ampoule (PoM) £62.51
- Flupentixol decanoate 200 mg per 1 ml Depixol Low Volume 200mg/1ml solution for injection ampoules | 5 ampoule (PoM) £97.59
- Psytxol (Mylan Ltd)
  - Psytxol 20mg/1ml solution for injection ampoules | 10 ampoule (PoM) £25.38
  - Psytxol 50mg/0.5ml solution for injection ampoules | 10 ampoule (PoM) £34.12
- Psytxol 100mg/1ml solution for injection ampoules | 10 ampoule (PoM) £62.50
- Psytxol 200mg/1ml solution for injection ampoules | 5 ampoule (PoM) £97.58

Fluphenazine decanoate

INDICATIONS AND DOSE

Maintenance in schizophrenia and other psychoses

- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: Test dose 12.5 mg, dose to be administered into the gluteal muscle, then 12.5–100 mg after 4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response
  - Elderly: Test dose 6.25 mg, dose to be administered into the gluteal muscle, then 12.5–100 mg after 4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response

4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Dose adjustment may be necessary if smoking started or stopped during treatment.

- Fluphenazine decanoate 25 mg per 1 ml Modcate 50mg/2ml solution for injection ampoules | 5 ampoule (PoM) £22.22
- Modcate (Sanofi) 25mg/1ml solution for injection ampoules | 10 ampoule (PoM) £22.55 DT price = £22.55
- Modcate Concentrate 12.5mg/0.5ml solution for injection ampoules | 5 ampoule (PoM) £6.51
- Modcate Concentrate 50mg/0.5ml solution for injection ampoules | 10 ampoule (PoM) £44.73

- Fluphenazine decanoate 100 mg per 1 ml Modcate Concentrate 100mg/1ml solution for injection ampoules | 5 ampoule (PoM) £43.73 DT price = £43.73
- Modcate Concentrate 50mg/0.5ml solution for injection ampoules | 10 ampoule (PoM) £44.73

- Fluphenazine decanoate 200 mg per 1 ml Modcate Concentrate 200mg/1ml solution for injection ampoules | 5 ampoule (PoM) £43.73 DT price = £43.73
- Modcate Concentrate 50mg/0.5ml solution for injection ampoules | 10 ampoule (PoM) £44.73

- Fluphenazine decanoate 50 mg per 1 ml Modcate Concentrate 50mg/1ml solution for injection ampoules | 5 ampoule (PoM) £22.22
- Modcate Concentrate 50mg/0.5ml solution for injection ampoules | 10 ampoule (PoM) £44.73

- Fluphenazine decanoate 100 mg per 1 ml Modcate Concentrate 100mg/1ml solution for injection ampoules | 5 ampoule (PoM) £43.73 DT price = £43.73
- Modcate Concentrate 50mg/0.5ml solution for injection ampoules | 10 ampoule (PoM) £44.73

If symptoms such as aggression or agitation appear · avoid in Acute porphyrias p. 950 · diabetes · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

- Fluphenazine decanoate 100 mg per 1 ml Fluphenazine decanoate 100 mg/1 ml solution for injection ampoules | 10 ampoule (PoM) £38.73
- Fluphenazine decanoate 200 mg per 1 ml Fluphenazine decanoate 200 mg/1 ml solution for injection ampoules | 5 ampoule (PoM) £50.16
- Fluphenazine decanoate 50 mg per 1 ml Fluphenazine decanoate 50 mg/1 ml solution for injection ampoules | 10 ampoule (PoM) £22.22
- Fluphenazine decanoate 100 mg per 1 ml Fluphenazine decanoate 100 mg/1 ml solution for injection ampoules | 10 ampoule (PoM) £43.73 DT price = £43.73

Haloperidol decanoate

INDICATIONS AND DOSE

Maintenance in schizophrenia and other psychoses

BY DEEP INTRAMUSCULAR INJECTION

Adult: Initially 50 mg every 4 weeks, increased in steps of 50 mg if required, increased if necessary up to 300 mg every 4 weeks, higher doses may be needed in some patients, dose to be administered into gluteal muscle, if 2-weekly administration preferred, doses should be halved

Elderly: Initially 12.5–25 mg every 4 weeks, if 2-weekly administration preferred, doses should be halved

DOSE ADJUSTMENTS DUE TO INTERACTIONS

Dose adjustment may be necessary if smoking started or stopped during treatment.

IMPORTANT SAFETY INFORMATION

When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be used for the rapid control of an acute episode.

CONTRA-INDICATIONS

Bradycardia, children, CNS depression, comatose states, lesions of the basal ganglia, Parkinson’s disease, phaeochromocytoma, QT-interval prolongation

CAUTIONS

Arteriosclerosis, hypocalcaemia, hypokalaemia, hypomagnesaemia, metabolic disturbances, subarachnoid haemorrhage, thyrotoxicosis—when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

INTERACTIONS

Avoid concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS

Common or very common Depressions, weight loss

Uncommon Dyspnœa, oedema

Rare Bronchospasm, hypoglycaemia, inappropriate antidiuretic hormone secretion, photosensitivity reactions, pigmentation

Frequency not known Erythema, hypertension, nodules, pain may occur at injection site, Stevens-Johnson syndrome, sweating, swelling, toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

Less sedating and fewer antimuscarinic or hypotensive symptoms.

PREGNANCY

Avoid unless benefits outweigh risk.

HEPATIC IMPAIRMENT

Can precipitate coma.

RENAL IMPAIRMENT

Start with small doses in severe renal impairment because of increased cerebral sensitivity.

MONITORING REQUIREMENTS

Treatment requires careful monitoring for optimum effect.

Baseline ECG required before treatment—assess need for further ECGs during treatment on an individual basis.

DIRECTIONS FOR ADMINISTRATION

In general not more than 2–3 mL of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Clopixol (Zuclopenthixol decanoate) (Lundbeck Ltd)

Zuclopenthixol decanoate 200 mg per 1 ml Clopixol 200mg/1ml solution for injection ampoules | 5 ampoule £31.51 DT price = £31.51

Zuclopenthixol decanoate 500 mg per 1 ml Clopixol Conc 500mg/1ml solution for injection ampoules | 5 ampoule £37.18 DT price = £37.18

Zuclopenthixol decanoate

INDICATIONS AND DOSE

Maintenance in schizophrenia and paranoid psychoses

BY DEEP INTRAMUSCULAR INJECTION

Adult: Test dose 100 mg, dose to be administered into the upper outer buttock or lateral thigh, followed by 200–500 mg after at least 7 days, then 200–500 mg every 1–4 weeks, adjusted according to response, higher doses of more than 500 mg can be used; do not exceed 600 mg weekly

Elderly: A quarter to half usual starting dose to be used

IMPORTANT SAFETY INFORMATION

When prescribing, dispensing, or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be used for the short-term management of an acute episode.

CONTRA-INDICATIONS

Children, CNS depression, comatose states, phaeochromocytoma

CAUTIONS

Avoid in acute porphyrias p. 930. QT interval prolongation when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

INTERACTIONS

Avoid concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS

Erythema, nodules, pain at injection site, swelling

SIDE-EFFECTS, FURTHER INFORMATION

If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

HEPATIC IMPAIRMENT

Can precipitate coma.

RENAL IMPAIRMENT

Start with small doses in severe renal impairment because of increased cerebral sensitivity.

MONITORING REQUIREMENTS

Treatment requires careful monitoring for optimum effect.

DIRECTIONS FOR ADMINISTRATION

In general not more than 2–3 mL of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Clopixol (Zuclopenthixol decanoate) (Janssen-Cilag Ltd)

Haloperidol (as Haloperidol decanoate) 50 mg per 1 ml Haldol decanoate 50mg/1ml solution for injection ampoules | 5 ampoule £19.06

Haloperidol (as Haloperidol decanoate) 100 mg per 1 ml Haldol decanoate 100mg/1ml solution for injection ampoules | 5 ampoule £25.26
Antipsychotics

Amisulpride

**Drug Action**
Amisulpride is a selective dopamine receptor antagonist with high affinity for mesolimbic D₂ and D₃ receptors.

**Indications and Dose**

### Acute Psychotic Episode in Schizophrenia

- **By Mouth**
  - Adult: 400–800 mg daily in 2 divided doses, adjusted according to response; maximum 1.2 g per day

### Schizophrenia with Predominantly Negative Symptoms

- **By Mouth**
  - Adult: 50–300 mg daily

**Contra-Indications**
CNS depression • comatose states • phaeochromocytoma • prolactin-dependent tumours

**Side-Effects**

- **Common or very common** Anxiety
- **Uncommon** Bradycardia

**Pregnancy**
Avoid.

**Renal Impairment**
Halve dose if eGFR 30–60 mL/minute/1.73 m². Use one-third dose if eGFR 10–30 mL/minute/1.73 m². No information available if eGFR less than 10 mL/minute/1.73 m².

**Monitoring Requirements**
Amisulpride does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

**Prescribing and Dispensing Information**
Flavours of oral liquid formulations may include caramel.

**Medicinal Forms**
There can be variations in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

**Cautionary and Advisory Labels**

- **Amisulpride (Non-proprietary)**
  - Amisulpride 50 mg • Amisulpride 100 mg • Amisulpride 200 mg • Amisulpride 400 mg
  - Solian (Sanofi)

**Oral Solution**

- **Amisulpride (Non-proprietary)**
  - Amisulpride 100 mg per 1 mL • Solian (Sanofi)
  - Solian (Sanofi)

### Important Safety Information
When prescribing, dispensing, or administering, check that the correct preparation is used—the preparation usually used in hospital for the rapid control of an acute episode (solution for injection containing amisulpride 7.5 mg/mL) should not be confused with depot preparations (amisulpride 400 mg vial with solvent), which are usually used in the community or clinics for maintenance treatment.

**Contra-Indications**
CNS depression • comatose state • phaeochromocytoma

**Cautions**

**General Cautions**
Cerebrovascular disease • elderly (reduce initial dose)

**Specific Cautions**
With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

**Side-Effects**

- **Common or very common** Anxiety • hypersalivation • malaise
- **Uncommon** Depression • dry mouth
- **Frequency Not Known** Alopecia • anorexia • bradycardia • hepatitis • hyponatraemia • infection • laryngospasm • myalgia • oedema • oropharyngeal spasm • pancreatitis • pathological gambling • respiratory disorders • rhabdomyolysis • suicidal ideation • sweating • urinary disorders

Aripiprazole

**Drug Action**
Aripiprazole is a dopamine D₂ partial agonist with weak 5-HT₁₅ partial agonism and 5-HT₂A receptor antagonism.

**Indications and Dose**

### Maintenance in Schizophrenia in Patients Stabilised with Oral Aripiprazole

- **Initially by Intramuscular Injection**
  - Adult: 400 mg every month, to be injected into the gluteal muscle, minimum of 26 days between injections, for dose adjustment due to side effects or concomitant use of interacting drugs, consult product literature and (by mouth) 10–20 mg daily continued for 14 consecutive days after the first injection, for missed depot doses consult product literature

### Schizophrenia

- **By Mouth**
  - Adult: 10–15 mg once daily; usual dose 15 mg once daily (max. per dose 30 mg once daily), for dose adjustments due to concomitant use of interacting drugs—consult product literature

### Treatment and Recurrence Prevention of Mania

- **By Mouth**
  - Adult: 15 mg once daily, increased if necessary up to 30 mg once daily, for dose adjustments due to concomitant use of interacting drugs—consult product literature

### Control of Agitation and Disturbed Behaviour in Schizophrenia

- **By Intramuscular Injection**
  - Adult: Initially 5.25–15 mg for 1 dose, alternatively usual dose 9.75 mg for 1 dose, followed by 5.25–15 mg after 2 hours if required, maximum 3 injections daily; maximum daily combined oral and parenteral dose 30 mg, for dose adjustments due to concomitant use of interacting drugs—consult product literature

**Contra-Indications**
CNS depression • comatose state • phaeochromocytoma

**Cautions**

**General Cautions**
Cerebrovascular disease • elderly (reduce initial dose)

**Specific Cautions**
With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

**Side-Effects**

- **Common or very common** Anxiety • hypersalivation • malaise
- **Uncommon** Depression • dry mouth
- **Frequency Not Known** Alopecia • anorexia • bradycardia • hepatitis • hyponatraemia • infection • laryngospasm • myalgia • oedema • oropharyngeal spasm • pancreatitis • pathological gambling • respiratory disorders • rhabdomyolysis • suicidal ideation • sweating • urinary disorders
SPECIFIC SIDE-EFFECTS
- With intramuscular use:ERYTHEMA • nodules • pain at injection site • swelling

SIDE-EFFECTS, FURTHER INFORMATION
- With intramuscular use: If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma–drug concentration may not fall for some time after reducing the dose of the depot injection, therefore it may be a month or longer before side-effects subside.

PREGNANCY
Use only if potential benefit outweighs risk.

BREAST FEEDING
Manufacturer advises avoid—present in milk.

HEPATIC IMPAIRMENT
Use with caution in severe impairment (oral treatment preferred to intramuscular administration).

MONITORING REQUIREMENTS
- Aripiprazole does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.
- With intramuscular use: Treatment requires careful monitoring for optimum effect.

DIRECTIONS FOR ADMINISTRATION
- With oral use: Orodispersible tablets should be placed on the tongue and allowed to dissolve, or be dispersed in water and swallowed.
- With intramuscular use: Correct injection technique (including the use of x-track technique) and rotation of injection sites are essential.

PATIENT AND CARER ADVICE
- With oral use: Patients or carers should be given advice on how to administer aripiprazole orodispersible tablets.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS

Aripiprazole 5 mg Aripiprazole 5mg tablets | 28 tablet £96.04 DT price = £1.72
Aripiprazole 10 mg Aripiprazole 10mg tablets | 28 tablet £96.04 DT price = £1.70
Aripiprazole 15 mg Aripiprazole 15mg tablets | 28 tablet £96.04 DT price = £1.72
Aripiprazole 30 mg Aripiprazole 30mg tablets | 28 tablet £192.08 DT price = £34.38

Abilify (Otsuka Pharmaceuticals (U.K.) Ltd)

Aripiprazole 5 mg Abilify 5mg tablets | 28 tablet £96.04 DT price = £1.72
Aripiprazole 10 mg Abilify 10mg tablets | 28 tablet £96.04 DT price = £1.70
Aripiprazole 15 mg Abilify 15mg tablets | 28 tablet £96.04 DT price = £1.72
Aripiprazole 30 mg Abilify 30mg tablets | 28 tablet £192.08 DT price = £34.38

Orodispersible tablet

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Aspartame

Aripiprazole 10 mg Aripiprazole 10mg orodispersible tablets sugar free-sugar-free | 28 tablet £91.24 DT price = £80.36
Aripiprazole 15 mg Aripiprazole 15mg orodispersible tablets sugar free-sugar-free | 28 tablet £91.24 DT price = £80.36

Abilify (Otsuka Pharmaceuticals (U.K.) Ltd)

Aripiprazole 10 mg Abilify 10mg orodispersible tablets sugar-free | 28 tablet £96.04 DT price = £80.36
Aripiprazole 15 mg Abilify 15mg orodispersible tablets sugar-free | 28 tablet £96.04 DT price = £80.36

Oral solution

CAUTIONARY AND ADVISORY LABELS

Aripiprazole 1 mg per 1 ml Aripiprazole 1mg/ml oral solution | 150 ml £102.90 DT price = £102.90

Abilify (Otsuka Pharmaceuticals (U.K.) Ltd)

Aripiprazole 1 mg per 1 ml Abilify 1mg/ml oral solution | 150 ml £102.90 DT price = £102.90

Solution for injection

Abilify (Otsuka Pharmaceuticals (U.K.) Ltd)

Aripiprazole 7.5 mg per 1 ml Abilify 9.75mg/1.3ml solution for injection vials | 1 vial £3.43

Powder and solvent for suspension for injection

Abilify Maintena (Otsuka Pharmaceuticals (U.K.) Ltd)

Aripiprazole 400 mg Abilify Maintena 400mg powder and solvent for prolonged-release suspension for injection pre-filled syringes | 1 pre-filled disposable injection £220.41
Abilify Maintena 400mg powder and solvent for prolonged-release suspension for injection vials | 1 vial £220.41

Clozapine

DRUG ACTION
Clozapine is a dopamine D2, dopamine D3, 5-HT2A, alpha1-adrenoceptor, and muscarinic-receptor antagonist.

INDICATIONS AND DOSE

Schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs

BY MOUTH

Adult: 12.5 mg once daily, dose to be taken at bedtime, then increased in steps of 12.5 mg up to twice weekly, adjusted according to response; usual dose 25–37.5 mg once daily, dose to be increased gradually over 14–21 days, increased to up to 300 mg daily in divided doses, larger dose to be taken at night, up to 200 mg daily may be taken as a single dose at bedtime; increased in steps of 50–100 mg 1–2 times a week if required, it is preferable to increase once a week; usual dosedose 200–450 mg daily, max. 900 mg per day, if restarting after interval of more than 48 hours, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing

Adult 60 years and over: 12.5 mg once daily for day 1, then increased to 25–37.5 mg for day 2, then increased, if tolerated, in steps of up to 25 mg daily, dose to be increased gradually over 14–21 days, increased to up to 300 mg daily in divided doses, larger dose at to be taken at night, up to 200 mg daily may be taken as a single dose at bedtime; increased in steps of 50–100 mg 1–2 times a week if required, it is preferable to increase once a week; usual dose 200–450 mg daily, max. 900 mg per day, if restarting after interval of more than 48 hours, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing

Psychosis in Parkinson’s disease

BY MOUTH

Adult: 12.5 mg once daily, dose to be taken at bedtime, then increased in steps of 12.5 mg up to twice weekly, adjusted according to response; usual dose 25–37.5 mg once daily, dose to be taken at bedtime; increased in steps of 12.5 mg once weekly, this applies only in exceptional cases, increased if necessary up to 100 mg daily in 1–2 divided doses; Usual maximum 50 mg/24 hours

DOSE ADJUSTMENTS DUE TO INTERACTIONS

Dose adjustment may be necessary if smoking started or stopped during treatment.

CONTRA-INDICATIONS
Alcoholic and toxic psychoses - bone-marrow disorders - coma - drug intoxication - history of agranulocytosis - history of circulatory collapse - history of neutropenia - paralytic ileus - severe cardiac disorders (e.g. myocarditis) - severe CNS depression - uncontrolled epilepsy
CAUTIONS  Age over 60 years; prostatic hypertrophy; susceptibility to angle-closure glaucoma; taper off other antipsychotics before starting

CAUTIONS, FURTHER INFORMATION

- Agranulocytosis  Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if clozarine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm³ or if absolute neutrophil count below 1500/mm³ discontinue permanently and refer to haematologist. Patients who have a low white blood cell count because of benign ethnic neutropenia may be started on clozapine with the agreement of a haematologist. Avoid drugs which depress leucopoiesis; patients should report immediately symptoms of infection, especially influenza-like illness.

- Myocarditis and cardiomyopathy  Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported.
- Perform physical examination and take full medical history before starting
- Specialist examination required if cardiac abnormalities or history of heart disease found—clozapine initiated only in absence of severe heart disease and if benefit outweighs risk
- Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy
- If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient evaluated urgently by cardiologist
- Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy
- Intestinal obstruction  Impairment of intestinal peristalsis, including constipation, intestinal obstruction, faecal impaction, and paralytic ileus, (including fatal cases) reported. Clozapine should be used with caution in patients receiving drugs that may cause constipation (e.g., antimuscarinic drugs) or in those with a history of colonic disease or lower abdominal surgery. It is essential that constipation is recognised and actively treated.

INTERACTIONS  Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis.

SIDE-EFFECTS

- Common or very common  Anorexia; constipation; hypersalivation; malaise; speech disorders; urinary incontinence
- Uncommon  Agranulocytosis
- Rare  Circulatory collapse; dysphagia; hepatitis; myocarditis; pancreatitis; pericarditis; pneumonia; pulmonary aspiration
- Very rare  Cardiomyopathy; hypercholesterolaemia; hypertriglyceridaemia; interstitial nephritis; intestinal obstruction (including fatal cases); myocardial infarction; obsessive compulsive disorder; parotid gland enlargement; respiratory depression
- Frequency not known  Hepatic disorders; hepatic failure; muscle disorders; renal failure

SIDE-EFFECTS, FURTHER INFORMATION

- Hypersalivation  Hypersalivation associated with clozapine therapy can be treated with hyoscine hydrobromide [unlicensed indication], provided that the patient is not at particular risk from the additive antimuscarinic side-effects of hyoscine and clozapine.

PREGNANCY  Use with caution.

BREAST FEEDING  Avoid.


RENAL IMPAIRMENT  Avoid in severe impairment.

MONITORING REQUIREMENTS  

- Monitor leucocyte and differential blood counts. Clozapine requires differential white blood cell monitoring weekly for 18 weeks, then fortnightly for up to one year, and then monthly as part of the clozapine patient monitoring service.
- Close medical supervision during initiation (risk of collapse because of hypotension and convulsions).
- Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotics. Patients taking clozapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.
- Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking clozapine should have fasting blood glucose tested at baseline, after one months’ treatment, then every 4–6 months.
- Patient, prescriber, and supplying pharmacist must be registered with the appropriate Patient Monitoring Service—it takes several days to do this.

TREATMENT CESSATION  On planned withdrawal reduce dose over 1–2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe patient carefully.

DIRECTIONS FOR ADMINISTRATION  Shake oral suspension well for 90 seconds when dispensing or if visibly settled and stand for 24 hours before use; otherwise shake well for 10 seconds before use. May be diluted with water.

PRESCRIBING AND DISPENSING INFORMATION  Clozapine has been used for psychosis in Parkinson’s disease in children aged 16 years and over.

PATIENT AND CARER ADVICE  Patients or carers should be given advice on how to administer clozapine oral suspension.

MEDICINAL FORMS  

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

| CAUTIONARY AND ADVISORY LABELS | 2, 10 |
| Clozaril (Novartis Pharmaceuticals UK Ltd) |
| Clozapine 25 mg | 28 tablet | £2.95 |
| Clozapine 50 mg | 100 tablet | £7.50 |
| (Hospital only) |
| Clozapine 100 mg | 28 tablet | £11.76 |
| (Hospital only) |
| (Hospital only) |
| Denzapine (Britannia Pharmaceuticals Ltd) |
| Clozapine 25 mg | 100 tablet | £16.64 |
| (Hospital only) |
| (Hospital only) |
| Denzapine 100 mg | 100 tablet | £79.20 |

Oral suspension

| CAUTIONARY AND ADVISORY LABELS | 2, 10 |
| Denzapine (Britannia Pharmaceuticals Ltd) |
| Clozapine 50 mg per 1 ml | 100 ml | £39.60 |
Lurasidone hydrochloride

**DRUG ACTION** Lurasidone is a dopamine D₂, 5-HT₂A, 5-HT₇, alpha₂A- and alpha₂C-adrenoceptor antagonist, and is a partial agonist at 5-HT₁A receptors.

**INDICATIONS AND DOSE**

- **Schizophrenia**
  - **BY MOUTH**
  - **Adult:** Initially 37 mg once daily, increased if necessary up to 148 mg once daily

- **Schizophrenia when given with concomitant moderate CYP3A4 inhibitors (e.g. diltiazem, erythromycin, fluconazole, and verapamil)**
  - **BY MOUTH**
  - **Adult:** Initially 18.5 mg once daily (max. per dose 74 mg once daily)

**CAUTIONS** High doses in elderly. Susceptibility to QT-interval prolongation

**INTERACTIONS** Contra-indicated with concomitant use of potent CYP3A4 inhibitors and potent CYP3A4 inducers. Caution with concomitant use of drugs that prolong the QT interval.

**SIDE-EFFECTS**

- **Common or very common** Anxiety, musculoskeletal stiffness
- **Uncommon** Catatonia, decreased appetite, dysarthria, dysuria, hot flush, myalgia, nightmares
- **Frequency not known** Angina, AV block, bradycardia, dysphagia, panic attacks, pruritus, suicidal behaviour, vertigo

**PREGNANCY** Use only if potential benefit outweighs risk—limited information available.

**HEPATIC IMPAIRMENT** Initially 18.5 mg once daily, up to max. 74 mg once daily in moderate impairment. Use with caution in severe impairment—initially 18.5 mg once daily, up to max. 37 mg once daily.

**RENAL IMPAIRMENT** Initially 18.5 mg once daily, up to max. 74 mg once daily if eGFR less than 50 mL/minute/1.73 m². Manufacturer advises use only if potential benefit outweighs risk if eGFR less than 15 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** Patients on doses higher than 111 mg once daily whose treatment is interrupted for longer than 3 days should restart on 111 mg once daily and titrate to usual dose; for all other doses, restart on usual dose.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 2, 21, 25
  - **Latuda** (Sunovion Pharmaceuticals Europe Ltd)
    - Lurasidone (as Lurasidone hydrochloride) 18.5 mg Latuda 18.5mg tablets | 28 tablet | £90.72
    - Lurasidone (as Lurasidone hydrochloride) 37 mg Latuda 37mg tablets | 28 tablet | £90.72
    - Lurasidone (as Lurasidone hydrochloride) 74 mg Latuda 74mg tablets | 28 tablet | £90.72

Olanzapine

**DRUG ACTION** Olanzapine is a dopamine D₁, D₂, D₄, 5-HT₂, histamine-1, and muscarinic-receptor antagonist.

**INDICATIONS AND DOSE**

- **Schizophrenia | Combination therapy for mania**
  - **BY MOUTH**
  - **Adult:** 10 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 10 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day

**Preventing recurrence in bipolar disorder**

- **BY MOUTH**
  - **Adult:** 10 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 10 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day

**Monotherapy for mania**

- **BY MOUTH**
  - **Adult:** 15 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 15 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day

**Control of agitation and disturbed behaviour in schizophrenia or mania**

- **BY INTRAMUSCULAR INJECTION**
  - **Adult:** Initially 5–10 mg for 1 dose; usual dose 10 mg for 1 dose, followed by 5–10 mg after 2 hours if required, maximum 3 injections daily for 3 days; maximum daily combined oral and parenteral dose 20 mg, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase
  - **Elderly:** Initially 2.5–5 mg, followed by 2.5–5 mg after 2 hours if required, maximum 3 injections daily for 3 days; maximum daily combined oral and parenteral dose 20 mg, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose adjustment may be necessary if smoking started or stopped during treatment.

- **CONTRA-INDICATIONS**
  - With intramuscular use Acute myocardial infarction, bradycardia, recent heart surgery, severe hypotension, sick sinus syndrome, unstable angina

**CAUTIONS**

- Bone-marrow depression, diabetes mellitus (risk of exacerbation or ketoacidosis), hypereosinophilic disorders, low leucocyte count, low neutrophil count, myeloproliferative disease, paralytic ileus

**CAUTIONS, FURTHER INFORMATION**

- CNS and respiratory depression
  - With intramuscular use Blood pressure, pulse and respiratory rate should be monitored for at least 4 hours after intramuscular injection, particularly in those also receiving a benzodiazepine or another antipsychotic (leave
at least one hour between administration of olanzapine intramuscular injection and parenteral benzodiazepines).

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Common or very common** Arthralgia - hypercholesterolaemia - hypertyglyceridaemia - increased appetite - malaise - oedema
    - **Uncommon** Alopecia - amnesia - bradycardia - epistaxis
    - **Rare** Hepatitis - pancreatitis - rhabdomyolysis

- **SPECIFIC SIDE-EFFECTS**
  - With intramuscular use
    - Hypoventilation - sinus pause
  - **PREGNANCY** Use only if potential benefit outweighs risk; neonatal lethargy, tremor, and hypertonia reported when used in third trimester.
  - **BREAST FEEDING** Avoid—present in milk.
  - **HEPATIC IMPAIRMENT** Consider initial dose of 5 mg daily.
  - **RENAL IMPAIRMENT** Consider initial dose of 5 mg daily.

- **MONITORING REQUIREMENTS**
  - Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotic drugs. Patients taking olanzapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.
  - Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking olanzapine should have fasting blood glucose tested at baseline, after one month’s treatment, then every 4–6 months.

- **DIRECTIONS FOR ADMINISTRATION**
  - Olanzapine orodispersible tablet may be placed on the tongue and allowed to dissolve, or dispersed in water, orange juice, apple juice, milk, or coffee.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - With intramuscular use When prescribing, dispensing, or administering check that this injection is the correct preparation—this preparation is usually used in hospital for the rapid control of an acute episode and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer orodispersible tablets.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Table

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td><strong>Olanzapine (Non-proprietary)</strong></td>
<td></td>
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<tr>
<td>Olanzapine 2.5 mg Olanzapine 2.5mg tablets</td>
<td>28 tablet POM £21.85 DT price = £0.88</td>
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<td><strong>Zalasta</strong> (Consilient Health Ltd)</td>
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<td>Olanzapine 20 mg Zalasta 20mg tablets</td>
<td>28 tablet POM £135.06 DT price = £1.55</td>
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</tbody>
</table>

- **Zyprexa** (Eli Lilly and Company Ltd)
  - Olanzapine 2.5 mg Zyprexa 2.5mg tablets | 28 tablet POM £21.85 DT price = £0.88 |
  - Olanzapine 5 mg Zyprexa 5mg tablets | 28 tablet POM £43.70 DT price = £0.92 |
  - Olanzapine 7.5 mg Zyprexa 7.5mg tablets | 56 tablet POM £131.10 |
  - Olanzapine 10 mg Zyprexa 10mg tablets | 28 tablet POM £87.40 DT price = £1.09 |
  - Olanzapine 15 mg Zyprexa 15mg tablets | 28 tablet POM £119.18 DT price = £1.27 |
  - Olanzapine 20 mg Zyprexa 20mg tablets | 28 tablet POM £158.90 DT price = £1.55 |

- **Orodispersible tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 2
  - **EXCIPIENTS:** May contain Aspartame
  - **Olanzapine (Non-proprietary)**
    - Olanzapine 5 mg Olanzapine 5mg orodispersible tablets sugar-free | 28 tablet POM £4.99 DT price = £0.22 |
    - Olanzapine 10 mg Olanzapine 10mg orodispersible tablets | 28 tablet POM £5.99 DT price = £0.21 |
    - Olanzapine 10mg orodispersible tablets sugar-free-sugar-free | 28 tablet POM £2.33 DT price = £0.23 |
    - Olanzapine 15 mg Olanzapine 15mg orodispersible tablets sugar-free-sugar-free | 28 tablet POM £2.81 DT price = £0.22 |
    - Olanzapine 15mg orodispersible tablets | 28 tablet POM £6.99 DT price = £0.30 |
  - Olanzapine 20 mg Olanzapine 20mg orodispersible tablets sugar-free-sugar-free | 28 tablet POM £4.04 DT price = £0.33 |

- **Zyprexa Velotabs** (Eli Lilly and Company Ltd)
  - Olanzapine 5 mg Zyprexa 5mg Velotabs sugar-free | 28 tablet POM £48.07 DT price = £48.07 |
  - Olanzapine 10 mg Zyprexa 10mg Velotabs sugar-free | 28 tablet POM £40.85 DT price = £1.77 |
  - Olanzapine 10mg orodispersible tablets sugar-free-sugar-free | 28 tablet POM £74.29 DT price = £2.29 |
  - Olanzapine 15 mg Zyprexa 15mg Velotabs sugar-free | 28 tablet POM £111.43 DT price = £2.81 |
  - Olanzapine 15mg orodispersible tablets | 28 tablet POM £148.57 DT price = £4.04 |

- **Oral Lypophilate**
  - **Zyprexa Velotabs** (Eli Lilly and Company Ltd)
    - Olanzapine 5 mg Zyprexa 5mg Velotabs sugar-free | 28 tablet POM £48.07 DT price = £48.07 |
    - Olanzapine 10 mg Zyprexa 10mg Velotabs sugar-free | 28 tablet POM £87.40 DT price = £87.40 |
    - Olanzapine 15 mg Zyprexa 15mg Velotabs sugar-free | 28 tablet POM £131.10 DT price = £131.10 |
    - Olanzapine 20 mg Zyprexa 20mg Velotabs sugar-free | 28 tablet POM £174.79 DT price = £174.79 |

### Paliperidone

- **DRUG ACTION** Paliperidone is a metabolite of risperidone.

- **INDICATIONS AND DOSE**
  - **Maintenance in schizophrenia in patients previously responsive to paliperidone or risperidone**
    - **BY DEEP INTRAMUSCULAR INJECTION**
      - Adult: 150 mg for 1 dose on day 1, then 100 mg for 1 dose on day 8, to be injected into the deltoid muscle, dose subsequently adjusted at monthly intervals according to response; maintenance 75 mg once a month, alternatively maintenance 25–150 mg once a month, following the second dose, monthly maintenance doses can be administered into either the deltoid or gluteal muscle, for missed doses see product literature
  - **Schizophrenia | Psychotic or manic symptoms of schizoaffective disorder**
    - **BY MOUTH**
      - Adult: 6 mg once daily, dose to be taken in the morning, then adjusted in steps of 3 mg if required, dose to be adjusted over at least 5 days; usual dose 3–12 mg daily
Quetiapine

- **DRUG ACTION** Quetiapine is a dopamine D₂, dopamine D₆, 5-HT₂, alpha-1-receptor, and histamine-1 receptor antagonist.

- **INDICATIONS AND DOSE**
  - **Schizophrenia**
    - **By mouth using immediate-release medicines**
      - Adult: 25 mg twice daily for day 1, then 50 mg twice daily for day 2, then 100 mg twice daily for day 3, then 150 mg twice daily for day 4, then, adjusted according to response, usual dose 300–450 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 750 mg per day
    - **By mouth using modified-release medicines**
      - Adult: 300 mg once daily for day 1, then 600 mg once daily for day 2, then, adjusted according to response, usual dose 600 mg once daily, maximum dose under specialist supervision; maximum 800 mg per day
      - Elderly: Initially 50 mg once daily, adjusted according to response, adjusted in steps of 50 mg daily

- **Treatment of mania in bipolar disorder**
  - **By mouth using immediate-release medicines**
    - Adult: 50 mg twice daily for day 1, then 100 mg twice daily for day 2, then 150 mg twice daily for day 3, then 200 mg twice daily for day 4, then adjusted in steps of up to 200 mg daily, adjusted according to response, usual dose 400–800 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 800 mg per day
  - **By mouth using modified-release medicines**
    - Adult: 300 mg once daily for day 1, then 600 mg once daily for day 2, then, adjusted according to response, usual dose 400–800 mg once daily
    - Elderly: Initially 50 mg once daily, adjusted according to response, adjusted in steps of 50 mg daily

- **SIDE-EFFECTS**
  - **Common or very common** Anxiety, appetite changes, arthralgia, depression, epistaxis, hypertension, infection, malaise, myalgia, oedema, respiratory disorders, sleep disorders, toothache, urinary disorders
  - **Rare** Alopecia, elevated plasma-cholesterol concentrations, elevated plasma-triglyceride concentrations, hypoaesthesia, paraesthesia, taste disturbances, tinnitus, visual disorders

- **MONITORING REQUIREMENTS**
  - With intramuscular use Treatment requires careful monitoring for optimum effect.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intramuscular use Correct injection technique (including the use of z-track technique) and rotation of injection sites are essential.
  - With oral use Always take with breakfast or always take on an empty stomach.

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer paliperidone tablets.

  - **Missed doses**
    - With intramuscular use For missed doses see product literature.

- **CAUTIONS**
  - **General Cautions**
    - Cataract surgery (risk of intraoperative floppy iris syndrome) - elderly patients with dementia - elderly patients with risk factors for stroke - predisposition to gastrointestinal obstruction - prolactin-dependent tumours

- **Specific Cautions**
  - With intramuscular use When transferring from oral to depot therapy, the dose by mouth should be reduced gradually.

- **MEDICINAL FORMS**
  - **There can be variation in the licensing of different medicines containing the same drug.**

  - **Modified-release tablet**
    - **Cautionary and advisory labels** 2, 25
      - **Paliperidone (Non-proprietary)**
        - **Paliperidone 3 mg** Paliperidone 3mg modified-release tablets
        - **Paliperidone 6 mg** Paliperidone 6mg modified-release tablets
        - **Paliperidone 9 mg** Paliperidone 9mg modified-release tablets
      - **Invega** (Janssen-Cilag Ltd)
        - Paliperidone 3 mg Invega 3mg modified-release tablets
        - Paliperidone 6 mg Invega 6mg modified-release tablets
        - Paliperidone 9 mg Invega 9mg modified-release tablets

  - **Suspension for injection**
    - **Xeplion** (Janssen-Cilag Ltd)
      - Paliperidone (as Paliperidone palmitate) 100 mg per 1 ml Xeplion 150mg/1.5ml suspension for injection pre-filled syringes
      - Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes
      - Paliperidone 100mg/1ml suspension for injection pre-filled syringes

  - **Price per pack**
    - £392.59
    - £314.07
    - £183.92

- **General Side-effects**
  - **Common or very common** Anxiety, appetite changes, arthralgia, depression, epistaxis, hypertension, infection, malaise, myalgia, oedema, respiratory disorders, sleep disorders, toothache, urinary disorders

- **Renal Impairment**
  - Adults: 50–80 mL/minute/1.73 m². Initially 1.5 mg once daily if eGFR 10–50 mL/minute/1.73 m² (max. 3 mg once daily). Avoid if eGFR less than 10 mL/minute/1.73 m².
  - With intramuscular use Initial dose 100 mg on day 1 and then 75 mg on day 8 if eGFR 50–80 mL/minute/1.73 m²; recommended maintenance dose 50 mg (range 25–100 mg) monthly if eGFR 50–80 mL/minute/1.73 m². Avoid if eGFR less than 50 mL/minute/1.73 m².

- **Monitoring Requirements**
  - With intramuscular use Treatment requires careful monitoring for optimum effect.

- **Directions for Administration**
  - With intramuscular use Correct injection technique (including the use of z-track technique) and rotation of injection sites are essential.
  - With oral use Always take with breakfast or always take on an empty stomach.

- **Patient and carer advice** Patients or carers should be given advice on how to administer paliperidone tablets.

  - **Missed Doses**
    - With intramuscular use For missed doses see product literature.
Treatment of depression in bipolar disorder
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: 50 mg once daily for day 1, dose to be taken at bedtime, then 100 mg once daily for day 2, then 200 mg once daily for day 3, then 300 mg once daily for day 4, then, adjusted according to response; usual dose 300 mg once daily, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 600 mg per day
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 50 mg once daily for day 1, dose to be taken at bedtime, then 100 mg once daily for day 2, then 200 mg once daily for day 3, then 300 mg once daily for day 4, then, adjusted according to response; usual dose 300 mg once daily; maximum 600 mg per day

Prevention of mania and depression in bipolar disorder
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: Continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual dose 300–800 mg daily in 2 divided doses
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: Continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual dose 300–800 mg once daily

Adjunctive treatment of major depression
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 50 mg once daily for 2 days, dose to be taken at bedtime, then 150 mg once daily for 2 days, then, adjusted according to response, usual dose 150–300 mg once daily
  - Elderly: Initially 50 mg once daily for 3 days, then increased if necessary to 100 mg once daily for 4 days, then adjusted in steps of 50 mg, adjusted according to response, usual dose 50–300 mg once daily, dose of 300 mg should not be reached before day 22 of treatment

DOSE EQUIVALENT AND CONVERSION
- Patients can be switched from immediate-release to modified-release tablets at the equivalent daily dose; to maintain clinical response, dose titration may be required.

- CAUTIONS  Cerebrovascular disease • elderly • patients at risk of aspiration pneumonia • treatment of depression in patients under 25 years (increased risk of suicide)
- SIDE-EFFECTS
  - Common or very common  Asthenia • dysarthria • dyspnoea • elevated plasma–cholesterol concentrations • elevated plasma–triglyceride concentrations • increased appetite • irritability • peripheral oedema • sleep disorders
  - Uncommon  Hyponatraemia • hypothyroidism • restless legs syndrome • rhinitis
  - Rare  Hepatitis • pancreatitis
  - Very rare  Angioedema • inappropriate secretion of antidiuretic hormone • rhabdomyolysis • Stevens-Johnson syndrome
  - Frequency not known  Suicidal behaviour (particularly on initiation) • toxic epidermal necrolysis
- PREGNANCY  Use only if potential benefit outweighs risk.
- BREAST FEEDING  Manufacturer advises avoid.
- HEPATIC IMPAIRMENT  For immediate-release tablets, initially 25 mg daily, increased daily in steps of 25–50 mg. For modified-release tablets, initially 50 mg daily, increased daily in steps of 50 mg.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 2
- Quetiapine (Non-proprietary)
  - Quetiapine (as Quetiapine fumarate) 25 mg  Quetiapine 25mg tablets | 60 tablet (Pos) £38.05 DT price = £1.04
  - Quetiapine (as Quetiapine fumarate) 100 mg  Quetiapine 100mg tablets | 60 tablet (Pos) £107.45 DT price = £1.50
  - Quetiapine (as Quetiapine fumarate) 150 mg  Quetiapine 150mg tablets | 60 tablet (Pos) £110.45 DT price = £2.09
  - Quetiapine (as Quetiapine fumarate) 200 mg  Quetiapine 200mg tablets | 60 tablet (Pos) £107.45 DT price = £2.35
  - Quetiapine (as Quetiapine fumarate) 300 mg  Quetiapine 300mg tablets | 60 tablet (Pos) £161.50 DT price = £3.06

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 2, 23, 25
- Atrolak XL (Accord Healthcare Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg  Atrolak XL 50mg tablets | 60 tablet (Pos) £67.65 DT price = £67.66
  - Quetiapine (as Quetiapine fumarate) 200 mg  Atrolak XL 200mg tablets | 60 tablet (Pos) £113.09 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg  Atrolak XL 300mg tablets | 60 tablet (Pos) £169.99 DT price = £170.00
  - Quetiapine (as Quetiapine fumarate) 400 mg  Atrolak XL 400mg tablets | 60 tablet (Pos) £226.19 DT price = £226.20
- Biquelle XL (Aspire Pharma Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg  Biquelle XL 50mg tablets | 60 tablet (Pos) £29.45 DT price = £67.66
  - Quetiapine (as Quetiapine fumarate) 150 mg  Biquelle XL 150mg tablets | 60 tablet (Pos) £49.45 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 200 mg  Biquelle XL 200mg tablets | 60 tablet (Pos) £49.45 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg  Biquelle XL 300mg tablets | 60 tablet (Pos) £74.45 DT price = £170.00
  - Quetiapine (as Quetiapine fumarate) 400 mg  Biquelle XL 400mg tablets | 60 tablet (Pos) £98.95 DT price = £226.20
- Ebesque XL (Ethypharm UK Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg  Ebesque XL 50mg tablets | 60 tablet (Pos) £31.80 DT price = £67.66
  - Quetiapine (as Quetiapine fumarate) 200 mg  Ebesque XL 200mg tablets | 60 tablet (Pos) £53.16 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg  Ebesque XL 300mg tablets | 60 tablet (Pos) £79.90 DT price = £170.00
  - Quetiapine (as Quetiapine fumarate) 400 mg  Ebesque XL 400mg tablets | 60 tablet (Pos) £106.31 DT price = £226.20
- Mintreleq XL (CEB Pharma Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg  Mintreleq XL 50mg tablets | 60 tablet (Pos) £29.45 DT price = £67.66
  - Quetiapine (as Quetiapine fumarate) 150 mg  Mintreleq XL 150mg tablets | 60 tablet (Pos) £49.45 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 200 mg  Mintreleq XL 200mg tablets | 60 tablet (Pos) £49.45 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg  Mintreleq XL 300mg tablets | 60 tablet (Pos) £74.45 DT price = £170.00
  - Quetiapine (as Quetiapine fumarate) 400 mg  Mintreleq XL 400mg tablets | 60 tablet (Pos) £98.95 DT price = £226.20
- Psyquet XL (Sandoz Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg  Psyquet XL 50mg tablets | 60 tablet (Pos) £27.97 DT price = £67.66
  - Quetiapine (as Quetiapine fumarate) 150 mg  Psyquet XL 150mg tablets | 60 tablet (Pos) £46.97 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 200 mg  Psyquet XL 200mg tablets | 60 tablet (Pos) £46.97 DT price = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg  Psyquet XL 300mg tablets | 60 tablet (Pos) £70.72 DT price = £170.00
  - Quetiapine (as Quetiapine fumarate) 400 mg  Psyquet XL 400mg tablets | 60 tablet (Pos) £93.99 DT price = £226.20
Risperidone

**INDICATIONS AND DOSE**

### Schizophrenia and other psychoses in patients tolerant to risperidone by mouth and taking oral risperidone up to 4 mg daily

**BY DEEP INTRAMUSCULAR INJECTION**

- **Adult:** Initially 25 mg every 2 weeks, to be administered into the deltoid or gluteal muscle, adjusted in steps of 12.5 mg (max. per dose 50 mg every 2 weeks) at intervals of at least 4 weeks, during initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection

### Schizophrenia and other psychoses in patients tolerant to risperidone by mouth and taking oral risperidone over 4 mg daily

**BY DEEP INTRAMUSCULAR INJECTION**

- **Adult:** Initially 37.5 mg every 2 weeks, adjusted in steps of 12.5 mg (max. per dose 50 mg every 2 weeks) at intervals of at least 4 weeks, during initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection

### Acute and chronic psychosis

**BY MOUTH**

- **Adult:** 2 mg daily in 1–2 divided doses for day 1, then 4 mg daily in 1–2 divided doses for day 2, slower titration is appropriate in some patients, usual dose 4–6 mg daily, doses above 10 mg daily only if benefit considered to outweigh risk; maximum 16 mg per day

### Elderly

- **Initially:** 500 micrograms twice daily, then increased in steps of 500 micrograms twice daily, increased to 1–2 mg twice daily

### Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer’s dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others

**BY MOUTH**

- **Adult:** Initially 250 micrograms twice daily, then increased in steps of 250 micrograms twice a day on alternate days, adjusted according to response; usual dose 500 micrograms twice daily (max. per dose 1 mg twice daily)

### CAUTIONS

**GENERAL CAUTIONS**

Avoid in acute porphyrias p. 930 - cataract surgery (risk of intra-operative floppy iris syndrome) - dehydro- dementia with Lewy bodies - prolactin-dependent tumours

**SPECIFIC CAUTIONS**

- With intramuscular use When transferring from oral to depot therapy, the dose by mouth should be reduced gradually

### SIDE-EFFECTS

**GENERAL SIDE-EFFECTS**

- **Common or very common** Anxiety - appetite changes - arthralgia - depression - epistaxis - hypertension - infection - malaise - myalgia - oedema - respiratory disorders - sleep disorders - toothache - urinary disorders

- **Uncommon** Alopecia - elevated plasma-cholesterol concentrations - elevated plasma-triglyceride concentrations - hypoesthesia - paraesthesia - taste disturbances - tinnitus - visual disorders

- **Rare** Inappropriate antidiuretic hormone secretion - intestinal obstruction - intra-operative floppy iris syndrome - pancreatitis - pulmonary embolism - rhabdomyolysis

**SPECIFIC SIDE-EFFECTS**

- With intramuscular use Erythema - nODULES - pain at injection site - swelling

**SIDE-EFFECTS, FURTHER INFORMATION**

- With intramuscular use If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

**PREGNANCY** Use only if potential benefit outweighs risk.

**BREAST FEEDING** Use only if potential benefit outweighs risk—small amount present in milk.

**HEPATIC IMPAIRMENT**

- With intramuscular use If an oral dose of at least 2 mg daily tolerated, 25 mg as a depot injection can be given every 2 weeks.
- With oral use Initial and subsequent oral doses should be halved.

**RENAL IMPAIRMENT** Initial and subsequent oral doses should be halved.

**MONITORING REQUIREMENTS**

- With intramuscular use Treatment requires careful monitoring for optimum effect.
Olanzapine embonate
(Olanzapine pamoate)

**INDICATIONS AND DOSE**

Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 15 mg oral olanzapine daily)

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–75 years: Initially 210 mg every 2 weeks, alternatively initially 405 mg every 4 weeks, then maintenance 150 mg every 2 weeks, alternatively maintenance 300 mg every 4 weeks, maintenance dose to be started after 2 months of initial treatment, dose to be administered into the gluteal muscle, consult product literature if supplementation with oral olanzapine required

Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 20 mg oral olanzapine daily)

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–75 years: Initially 300 mg every 2 weeks, then maintenance 210 mg every 2 weeks, alternatively maintenance 405 mg every 4 weeks, maintenance dose to be started after 2 months of initial treatment, dose to be administered into the gluteal muscle, consult product literature if supplementation with oral olanzapine required

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose adjustment may be necessary if smoking started or stopped during treatment.

**IMPORTANT SAFETY INFORMATION**

When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be used for the rapid control of an acute episode.

- **CAUTIONS**
  - Bone-marrow depression, diabetes mellitus (risk of exacerbation or ketoacidosis), hyperesinophilic disorders, low leucocyte count, low neutrophil count, myeloproliferative disease, paralytic ileus, when transferring from oral to depot therapy, the dose by mouth should be reduced gradually.

### ANTIPSYCHOTICS > SECOND-GENERATION (DEPOT INJECTIONS)

See under individual antipsychotics, second-generation monographs above for details of other depot injections.
4 Movement disorders

4.1 Dystonias and other involuntary movements

Other drugs used for Dystonias and other involuntary movements
- Chlorpromazine hydrochloride, p. 361
- Clonidine hydrochloride, p. 361
- Clozapine, p. 371
- Diazepam, p. 321
- Haloperidol, p. 363
- Orphenadrine hydrochloride, p. 384
- Pericyazine, p. 364
- Pramipexole, p. 395
- Prochlorperazine, p. 365
- Procyclidine hydrochloride, p. 384
- Ropinirole, p. 396
- Rotigotine, p. 398
- Trifluoperazine, p. 366
- Trihexyphenidyl hydrochloride, p. 385

ANTIPSYCHOTICS > FIRST-GENERATION

Promazine hydrochloride

- INDICATIONS AND DOSE
  - Short-term adjunctive management of psychomotor agitation
    - BY MOUTH
    - Adult: 100–200 mg 4 times a day
    - Agitation and restlessness in elderly
      - BY MOUTH
      - Elderly: 25–50 mg 4 times a day

- CONTRA-INDICATIONS
  - CNS depression - comatose states - phaeochromocytoma
  - CAUTIONS
    - Cerebral arteriosclerosis
  - SIDE-EFFECTS
    - Haemolytic anaemia
  - HEPATIC IMPAIRMENT
    - Can precipitate coma;
      - phenothiazines are hepatotoxic.
  - REPRODUCTIVE IMPAIRMENT
    - Start with small doses in severe renal impairment because of increased cerebral sensitivity.
  - LESS SUITABLE FOR PRESCRIBING
    - Promazine hydrochloride is less suitable for prescribing.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  Tablet
  - Promazine hydrochloride (Non-proprietary)
    - Promazine hydrochloride 25 mg Promazine 25mg tablets | 100 tablet DT price = £47.99
    - Promazine hydrochloride 50 mg Promazine 50mg tablets | 100 tablet DT price = £64.49
  - Promazine hydrochloride 100 mg Promazine 100mg tablets | 100 tablet DT price = £132.00

  Oral solution
  - Promazine hydrochloride (Non-proprietary)
    - Promazine hydrochloride 5 mg per 1 ml Promazine 25mg/5ml syrup | 150 ml DT price = £13.00
    - Promazine hydrochloride 10 mg per 1 ml Promazine 50mg/5ml syrup | 150 ml DT price = £15.24

CNS STIMULANTS

Piracetam

- INDICATIONS AND DOSE
  - Adjunctive treatment of cortical myoclonus
    - BY MOUTH
    - Adult: Initially 7.2 g daily in 2–3 divided doses, then increased in steps of 4.8 g every 3–4 days, adjusted according to response, subsequently, attempts should be made to reduce dose of concurrent therapy; maximum 24 g per day

- CONTRA-INDICATIONS
  - Cerebral haemorrhage - Huntington’s chorea
  - CAUTIONS
    - Gastric ulcer - history of haemorrhagic stroke - increased risk of bleeding - major surgery - underlying disorders of haemostasis
  - INTERACTIONS
    - Caution with concomitant drugs that increase bleeding.

- SIDE-EFFECTS
  - Common or very common
    - Hyperkinesia - nervousness - weight gain
Uncommon Abdominal pain · anxiety · asthenia · ataxia · confusion · depression · dermatitis · diarrhoea · drowsiness · haemorrhagic disorder · hallucination · headache · insomnia · nausea · pruritus · urticaria · vertigo · vomiting

PREGNANCY Avoid.

BREAST FEEDING Avoid.

HEPATIC IMPAIRMENT Adjust dose if both hepatic and renal impairment.

RENAL IMPAIRMENT Use two-thirds of normal dose if eGFR 50–80 mL/minute/1.73 m²; use one-third of normal dose in 2 divided doses if eGFR 30–50 mL/minute/1.73 m²; use one-sixth of normal dose as a single dose if eGFR 20–30 mL/minute/1.73 m². Avoid if eGFR less than 20 mL/minute/1.73 m².

TREATMENT CESSATION Avoid abrupt withdrawal.

DIRECTIONS FOR ADMINISTRATION Follow the oral solution with a glass of water (or soft drink) to reduce bitter taste.

PRESCRIBING AND DISPENSING INFORMATION Piracetam has been used in children 16 years and over as adjunctive treatment for cortical myoclonus.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet CAUTIONARY AND ADVISORY LABELS 3

Nootropil (UCB Pharma Ltd)

Piracetam 1.2 gram Nootropil 1.2g tablets | 60 tablet £10.97

Piracetam 800 mg Nootropil 800mg tablets | 90 tablet £11.75

Oral solution CAUTIONARY AND ADVISORY LABELS 3

Piracetam (Non-proprietary)

Piracetam 333.3 mg per 1 mL Piracetam 333.3mg/ml oral solution sugar free sugar-free | 300 mL £16.31

Nootropil (UCB Pharma Ltd)

Piracetam 333.3 mg per 1 mL Nootropil 33% oral solution sugar-free | 300 mL £16.31

MUSCLE RELAXANTS > MUSCLE RELAXANTS, PERIPHERALLY ACTING > NEOUROTOXINS (BOTULINUM TOXINS)

Botulinum toxin type A

INDICATIONS AND DOSE Treatment of focal spasticity (including hand and wrist disability associated with stroke) (specialist use only) | Blepharospasm (specialist use only) | Hemifacial spasm (specialist use only) | Spasmodic torticolis (specialist use only) | Severe hyperhidrosis of the axillae (specialist use only) | Prophylaxis of headaches in adults with chronic migraine (specialist use only) | Temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years (specialist use only) | Ankle disability due to lower limb spasticity associated with stroke (specialist use only) | Management of bladder dysfunctions (specialist use only) | Temporary improvement of moderate to severe crow’s feet (specialist use only) | By subcutaneous injection, or by intramuscular injection (consult product literature)

DOSE EQUIVALENCE AND CONVERSION Important: information is specific to each individual preparation.

CONTRA-INDICATIONS Acute urinary retention (specific to use in bladder disorders only) | Catheterisation difficulties (specific to use in bladder disorders only) | Generalised disorders of muscle activity · infection at injection site · myasthenia gravis · presence of bladder calculi (specific to use in bladder disorders only) | Urinary tract infection (specific to use in bladder disorders only)

CAUTIONS GENERAL CAUTIONS Atrophy in target muscle · chronic respiratory disorder · elderly · excessive weakness in target muscle · history of

Rhabdomyolysis

Very rare Agitation · amnesia · ataxia · bradycardia · disorientation · dizziness · dry mouth · dyspepsia

PREGNANCY Avoid unless essential—toxicity in animal studies.

BREAST FEEDING Avoid.

HEPATIC IMPAIRMENT Use half initial dose and slower dose titration in mild to moderate impairment. Use with caution in severe impairment.

RENAL IMPAIRMENT Use with caution.

TREATMENT CESSATION Avoid abrupt withdrawal.

PATIENT AND CARER ADVICE Driving and skilled tasks May affect performance of skilled tasks (e.g. driving).

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet CAUTIONARY AND ADVISORY LABELS 2

Revocon (Sun Pharmaceuticals UK Ltd)

Tetrabenazine 25 mg Revocon 25mg tablets | 112 tablet £100.00 DT price = £100.00

Tetmodis (Beacon Pharmaceuticals Ltd)

Tetrabenazine 25 mg Tetmodis 25mg tablets | 112 tablet £100.00 DT price = £100.00

Xenazine (Alliance Pharmaceuticals Ltd)

Tetrabenazine 25 mg Xenazine 25 tablets | 112 tablet £100.00 DT price = £100.00

MONOAMINE DEPLETING DRUGS

Tetrabenazine

INDICATIONS AND DOSE Movement disorders due to Huntington’s chorea, hemiballismus, senile chorea, and related neurological conditions

BY MOUTH

Adult: Initially 25 mg 3 times a day, then increased, if tolerated, in steps of 25 mg every 3–4 days; maximum 200 mg per day

Elderly: Lower initial dose may be necessary

Moderate to severe tardive dyskinesia

BY MOUTH

Adult: Initially 12.5 mg daily, dose to be gradually increased according to response

CONTRA-INDICATIONS Depression · parkinsonism · phaeochromocytoma · prolactin-dependent tumours

CAUTIONS Susceptibility to QT-interval prolongation

INTERACTIONS Appendix 1 (tetrabenazine).

Caution with concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS

Common or very common Anxiety · confusion · constipation · depression · diarrhoea · drowsiness · dysphagia · hypotension · insomnia · nausea · parkinsonism · vomiting

Uncommon Altered consciousness level · extrapyramidal disorders · hyperthermia

Rare Neuroleptic malignant syndrome

Appendix 1

Appendix 3
aspiration · history of dysphagia · inflammation in target muscle · neurological disorders · neuromuscular disorders · off-label use (fatal adverse events reported)

**SPECIFIC CAUTIONS**

- When used for blepharospasm or hemifacial spasm Risk of angle-closure glaucoma

**CAUTIONS, FURTHER INFORMATION**

Neuromuscular or neurological disorders can lead to increased sensitivity and exaggerated muscle weakness including dysphagia and respiratory compromise.

- Blepharospasm or hemifacial spasm When used for blepharospasm and hemifacial spasm, reduced blinking can lead to corneal exposure, persistent epithelial defect and corneal ulceration (especially in those with VIIth nerve disorders)—careful testing of corneal sensation in previously operated eyes, avoidance of injection in lower lid area to avoid ectropion, and vigorous treatment of epithelial defect needed.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Excessive doses may paralyse distant muscles · increased electrophysiologic jitter in some distant muscles · influenza-like symptoms · misplaced injections may paralyse nearby muscle groups

- Rare Antibody formation (substantial deterioration in response) · arrhythmias · myocardial infarction · seizures

- Very rare Aspiration · dysphagia · dysphonia · exaggerated muscle weakness · respiratory disorders

**SPECIFIC SIDE-EFFECTS**

- Common or very common
  - When used for axillary hyperhidrosis Abnormal skin odour · alopecia · hot flushes · non-axillary sweating · paraesthesia · pruritus · subcutaneous nodule
  - When used for blepharospasm Dry eye · ecchymosis · facial oedema · irritation · keratitis · lacrimation · lagophthalmos · photophobia · ptosis
  - When used for focal upper-limb spasticity associated with stroke Dysphagia · hypertonia · purpura
  - When used for hemifacial spasm Dry eye · ecchymosis · facial oedema · irritation · keratitis · lacrimation · lagophthalmos · photophobia · ptosis
  - When used for spasmodic torticollis Back pain · dizziness · drowsiness · dry mouth · dysphagia and pooling of saliva (occurs most frequently after injection into sternomastoid muscle) · headache · hypertonia · malaise · nausea · numbness · rhinitis · stiffness · weakness
  - When used for temporary improvement of moderate to severe wrinkles between the eyebrows Facial oedema · headache · ptosis
  - When used for axillary hyperhidrosis Pain in extremities

- Uncommon
  - When used for axillary hyperhidrosis Joint pain · myalgia
  - When used for blepharospasm Conjunctivitis · dermatitis · diplopia · dizziness · drooping · dry mouth · ectropion · entropion · facial weakness · headache · paraesthesia · tiredness · visual disturbances
  - When used for focal upper-limb spasticity associated with stroke Amnesia · arthralgia · bursitis · cough · depression · dry mouth · dysaesthesia · haematoma · headache · insomnia · malaise · pain in extremities · paraesthesia · peripheral oedema · vertigo
  - When used for focal upper-limb specificity associated with stroke Nausea
  - When used for hemifacial spasm Conjunctivitis · dermatitis · diplopia · dizziness · drooping · dry mouth · ectropion · entropion · facial weakness · headache · paraesthesia · tiredness · visual disturbances
  - When used for spasmodic torticollis Collitis · diarrhoea · diplopia · dysphonia · eye pain · myalgia · ptosis · skeletal pain · sweating · tremor · voice alteration · vomiting

- When used for temporary improvement of moderate to severe wrinkles between the eyebrows Anxiety · asthenia · blepharitis · dizziness · dry mouth · dry skin · muscle cramp · nausea · paraesthesia · photosensitivity reactions · tinnitus · visual disturbances

- Rare
  - When used for blepharospasm Eyelid bruising and swelling (minimised by applying gentle pressure at injection site immediately after injection)
  - When used for hemifacial spasm Eyelid bruising and swelling (minimised by applying gentle pressure at injection site immediately after injection)

- Very rare
  - When used for blepharospasm Angle-closure glaucoma · corneal epithelial defect · corneal perforation · corneal ulceration
  - When used for hemifacial spasm Angle-closure glaucoma · corneal epithelial defect · corneal perforation · corneal ulceration

- Frequency not known
  - When used for focal lower-limb spasticity associated with stroke Arthralgia · peripheral oedema · rash

- CONCEPTION AND CONTRACEPTION Avoid in women of child-bearing age unless using effective contraception.

- PREGNANCY Avoid unless essential—toxicity in animal studies (manufacturer of Botox® advise avoid).

- BREAST FEEDING Low risk of systemic absorption but avoid unless essential.

- PRESCRIBING AND DISPENSING INFORMATION Preparations are not interchangeable.

- PATIENT AND CARER ADVICE Patients and carers should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties; they should be advised to seek immediate medical attention if swallowing, speech or breathing difficulties occur.

- NATIONAL FUNDING/access decisions

**NICE technology appraisals (Tas)**

- Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (June 2012) NICE TA260

Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine, defined as headaches on at least 15 days per month, of which at least 8 days are with migraine), that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.

- Scottish medicines consortium (SMC) decisions

The Scottish Medicines Consortium has advised (March 2011 and March 2013) that Botox® is not recommended for use within NHS Scotland for prophylaxis of headaches in adults with chronic migraine.

- The Scottish Medicines Consortium has advised that Azzalure® and Vistabel® (December 2010), and Bocouture® (February 2011) are not recommended for use within NHS Scotland.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Azzalure®** (Galderna (UK) Ltd)
  - Botulinum toxin type A 125 unit Powder for solution for injection vials | 1 vial | £64.00 | 2 vial | £128.00

- **Bocouture®** (Merz Pharma UK Ltd)
  - Botulinum toxin type A 50 unit Powder for solution for injection vials | 1 vial | £72.00

- **Botox®** (Allergan Ltd)
  - Botulinum toxin type A 50 unit Powder for solution for injection vials | 1 vial | £77.50
Botulinum toxin type B

**INDICATIONS AND DOSE**

- **Spasmodic torticollis (cervical dystonia)** (specialist use only)
  - BY INTRAMUSCULAR INJECTION
    - Adult: Initially 5000–10 000 units, adjusted according to response, dose to be divided between 2–4 most affected muscles
  - **DOSE EQUIVALENCE AND CONVERSION**
    - Important: information specific to each individual preparation.

- **CONTRA-INDICATIONS** Neuromuscular disorders - neuromuscular junctional disorders

- **CAUTIONS** History of dysphagia or aspiration - off-label use (risk of toxin spread) - tolerance may occur

- **SIDE-EFFECTS**
  - Common or very common
    - Dry mouth - dyspepsia - dysphagia - dysphonia - headache - increased electrophysiologic jitter in some distant muscles - influenza-like symptoms - myasthenia - neck pain - taste disturbances - visual disturbances - worsening torticollis
  - Frequency not known
    - Aspiration pneumonia - constipation - exaggerated muscle weakness - malaise - ptosis - respiratory disorders - vomiting

- **PREGNANCY** Low risk of systemic absorption but avoid unless essential.

- **BREAST FEEDING** Low risk of systemic absorption but avoid unless essential.

- **DIRECTIONS FOR ADMINISTRATION** Injection may be diluted with sodium chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION** Important: not interchangeable with other botulinum toxin preparations.

- **PATIENT AND CARER ADVICE** Patients should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties; they should be advised to seek immediate medical attention if swallowing, speech or breathing difficulties occur.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **NeuroBloc** (Eisai Ltd)
      - Botulinum toxin type B 5000 unit per 1 ml NeuroBloc 5 000 units/1ml solution for injection vials | 1 vial £148.27 (Hospital only)
      - NeuroBloc 10 000 units/2ml solution for injection vials | 1 vial £197.69 (Hospital only)
      - NeuroBloc 2 500 units/0.5ml solution for injection vials | 1 vial £111.20 (Hospital only)

# NEUROPROTECTIVE DRUGS

**Tafamidis**

- **INDICATIONS AND DOSE**
  - Treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in patients with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment (initiated under specialist supervision)
    - BY MOUTH
      - Adult: 20 mg once daily

- **SIDE-EFFECTS** Abdominal pain - diarrhoea - urinary tract infection - vaginal infection

- **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment and ensure effective contraception during and for one month after stopping treatment.

- **PREGNANCY** Avoid (toxicity in animal studies).

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Caution in severe impairment—no information available.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Tafamidis should be prescribed in addition to standard treatment, but before liver transplantation; it should be discontinued in patients who undergo liver transplantation.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - **CAUTIONARY AND ADVISORY LABELS** 25
    - **Vyndaqel** (Pfizer Ltd)
    - **Tafamidis 20 mg** Vyndaqel 20 mg capsules | 30 capsules £10,685.00

## 4.2 Parkinson’s disease

### Parkinson’s disease and related disorders

#### Parkinson’s disease

In idiopathic Parkinson’s disease, the progressive degeneration of pigmented neurones in the substantia nigra leads to a deficiency of the neurotransmitter dopamine. The resulting neurochemical imbalance in the basal ganglia causes the characteristic signs and symptoms of the illness. Drug therapy does not prevent disease progression, but it improves most patients’ quality of life.

Patients with suspected Parkinson’s disease should be referred to a specialist to confirm the diagnosis; the diagnosis should be reviewed every 6–12 months.

Features resembling those of Parkinson’s disease can occur in diseases such as progressive supranuclear palsy and multiple system atrophy, but they do not normally show a sustained response to the drugs used in the treatment of idiopathic Parkinson’s disease.

When initiating treatment, patients should be advised about its limitations and possible side-effects. About 5–10% of patients with Parkinson’s disease respond poorly to treatment.

Treatment is usually not started until symptoms cause significant disruption of daily activities. **Levodopa, non-ergot-derived dopamine-receptor agonists, or monoamine-oxidase-B inhibitors** can be prescribed for initial treatment in early Parkinson’s disease. Therapy with two or more antiparkinsonian drugs may be necessary as the disease progresses. Most patients eventually require levodopa and subsequently develop motor complications.
Elderly
Antiparkinsonian drugs can cause confusion in the elderly. It is particularly important to initiate treatment with low doses and to increase the dose gradually.

Dopaminergic drugs used in Parkinson's disease

Dopamine-receptor agonists
The dopamine-receptor agonists have a direct action on dopamine receptors. Initial treatment of Parkinson's disease is often with the dopamine–receptor agonists pramipexole p. 395, ropinirole p. 396, and rotigotine p. 398. The ergot-derivative dopamine–receptor agonists bromocriptine p. 391, cabergoline p. 393, and pergolide p. 394 are rarely used because of the risk of fibrotic reactions.

When used alone, dopamine–receptor agonists cause fewer motor complications in long-term treatment compared with levodopa treatment but the overall motor performance improves slightly less. The dopamine–receptor agonists are associated with more psychiatric side-effects than levodopa.

Dopamine–receptor agonists are also used with levodopa in more advanced disease. If a dopamine–receptor agonist is added to levodopa therapy, the dose of levodopa needs to be reduced.

Apomorphine hydrochloride p. 390 is a potent dopamine–receptor agonist that is sometimes helpful in advanced disease for patients experiencing unpredictable 'off' periods with levodopa treatment. Apomorphine hydrochloride should be initiated in a specialist clinic. After an overnight withdrawal of oral antiparkinsonian medication to induce an 'off' episode, the threshold dose of apomorphine hydrochloride is determined. Oral antiparkinsonian medication is then restarted. The patient must be taught to self-administer apomorphine hydrochloride by subcutaneous injection into the lower abdomen or outer thigh at the first sign of an 'off' episode. Once treatment has been established it may be possible to gradually reduce other antiparkinsonian medications.

Levodopa
Levodopa, the amino-acid precursor of dopamine, acts by replenishing depleted striatal dopamine. It is given with an extracerebral dopa-decarboxylase inhibitor, which reduces the peripheral conversion of levodopa to dopamine, thereby limiting side-effects such as nausea, vomiting, and cardiovascular effects; additionally, effective brain-dopamine concentrations are achieved with lower doses of levodopa. The extracerebral dopa-decarboxylase inhibitors used with levodopa are benserazide (in co-beneldopa p. 387) and carbidopa (in co-careldopa p. 388).

Levodopa, in combination with a dopa-decarboxylase inhibitor, is useful in the elderly or frail, in patients with other significant illnesses, and in those with more severe symptoms. It is effective and well tolerated in the majority of patients.

Levodopa therapy should be initiated at a low dose and increased in small steps; the final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual patient.

Nausea and vomiting with co-beneldopa or co-careldopa are rarely dose-limiting and domperidone p. 402 can be useful in controlling these effects.

Levodopa treatment is associated with potentially troublesome motor complications including response fluctuations and dyskinesias. Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period. 'End-of-dose' deterioration with progressively shorter duration of benefit also occurs. Modified-release preparations may help with 'end-of-dose' deterioration or nocturnal immobility and rigidity. Motor complications are particularly problematic in young patients treated with levodopa.

Monoamine-oxidase-B inhibitors
Rasagiline p. 399 and selegiline hydrochloride p. 399 are monoamine-oxidase-B inhibitors used in Parkinson's disease. Early treatment with selegiline hydrochloride alone can delay the need for levodopa therapy.

Antimuscarinic drugs used in parkinsonism
Antimuscarinic drugs can be useful in drug-induced parkinsonism, but they are generally not used in idiopathic Parkinson's disease because they are less effective than dopaminergic drugs and they are associated with cognitive impairment.

The antimuscarinic drugs orphenadrine hydrochloride p. 384, procyclidine hydrochloride p. 384, and trihexyphenidyl hydrochloride p. 385 reduce the symptoms of parkinsonism induced by antipsychotic drugs, but there is no justification for giving them routinely in the absence of parkinsonian side-effects. Tardive dyskinesia is not improved by antimuscarinic drugs and may be made worse.

In idiopathic Parkinson's disease, antimuscarinic drugs reduce tremor and rigidity but they have little effect on bradykinesia. They may be useful in reducing sialorrhoea. There are no important differences between the antimuscarinic drugs, but some patients tolerate one better than another.

Procyclidine hydrochloride can be given parenterally and is effective emergency treatment for acute drug-induced dystonic reactions.

If treatment with an antimuscarinic is ineffective, intravenous diazepam p. 321 can be given for life-threatening acute drug-induced dystonic reactions.

Drugs used in essential tremor, chorea, tics, and related disorders
Tetrabenazine p. 380 is mainly used to control movement disorders in Huntington's chorea and related disorders. Tetrabenazine can also be prescribed for the treatment of tardive dyskinesia if switching or withdrawing the causative antipsychotic drug is not effective. It acts by depleting nerve endings of dopamine. It is effective in only a proportion of patients and its use may be limited by the development of depression.

Haloperidol p. 363 [unlicensed indication], olanzapine p. 373 [unlicensed indication], risperidone p. 377 [unlicensed indication], and quetiapine p. 375 [unlicensed indication], can also be used to suppress chorea in Huntington's disease.

Haloperidol can also improve motor tics and symptoms of Tourette syndrome and related choreas. Other treatments for Tourette syndrome include pimozide p. 364 [unlicensed indication] (important: ECG monitoring required), clonidine hydrochloride p. 136 [unlicensed indication], and sulpiride p. 366 [unlicensed indication]. Trihexyphenidyl hydrochloride in high dosage can also improve some movement disorders; it is sometimes necessary to build the dose up over many weeks. Chlorpromazine hydrochloride p. 361 and haloperidol are used to relieve intractable hiccup.

Propranolol hydrochloride p. 142 or another beta-adrenoceptor blocking drug may be useful in treating essential tremor or tremors associated with anxiety or thyrotoxicosis.

Primidone p. 313 in some cases provides relief from benign essential tremor; the dose is increased slowly to reduce side-effects.

Piracetam p. 379 is used as an adjunctive treatment for myoclonus of cortical origin. After an acute episode, attempts should be made every 6 months to decrease or discontinue treatment.

Riluzole p. 983 is used to extend life in patients with motor neurone disease who have amyotrophic lateral sclerosis.

Torsion dystonia and other involuntary movements
Treatment with botulinum toxin type A p. 380 can be considered after an acquired non-progressive brain injury if
rapid-onset spasticity causes postural or functional difficulties.

**ANTIMUSCARINICS**

**Orphenadrine hydrochloride**

- **DRUG ACTION** Orphenadrine exerts its antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.

- **INDICATIONS AND DOSE**
  - **Parkinsonism** | Drug-induced extrapyramidal symptoms (but not tardive dyskinesia)
    - **BY MOUTH**
      - Adult: Initially 150 mg daily in divided doses, then increased in steps of 50 mg every 2–3 days, adjusted according to response; usual dose 150–300 mg daily in divided doses; maximum 400 mg per day
      - Elderly: Preferably dose at lower end of range

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 | gastrointestinal obstruction | myasthenia gravis
- **CAUTIONS** Cardiovascular disease | elderly | hypertension | in patients susceptible to angle-closure glaucoma | liable to abuse | prostatic hypertrophy | psychotic disorders | pyrexia
- **INTERACTIONS** → Appendix 1 (antimuscarinics).
  Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urinary retention, and constipation. Concomitant use of other drugs with antimuscarinic effects can also lead to confusion in the elderly.
- **SIDE-EFFECTS**
  - Common or very common | Urinary retention
  - Uncommon | Drowsiness | impaired coordination | insomnia | seizures
  - Very rare | Angle-closure glaucoma
  - Frequency not known | Anxiety | blurred vision | confusion | constipation | dizziness | dry mouth | euphoria | hallucinations | impaired memory | nausea | rash | restlessness | tachycardia | vomiting
- **PREGNANCY** Caution.
- **BREAST FEEDING** Caution.
- **HEPATIC IMPAIRMENT** Use with caution.
- **RENAL IMPAIRMENT** Use with caution.
- **TREATMENT CESSATION** Avoid abrupt withdrawal in patients taking long-term treatment.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    May affect performance of skilled tasks (e.g. driving).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution
  - **Tablet**
    - **EXCIPIENTS**: May contain Tartrazine
      - **Orphenadrine hydrochloride (Non-proprietary)**
        - Orphenadrine hydrochloride 50 mg. Orphenadrine 50mg tablets | 100 tablet PO | £0.80 | 250 tablet PO | no price available
      - **Oral solution**
        - **Orphenadrine hydrochloride (Non-proprietary)**
          - Orphenadrine hydrochloride 10 mg per 1 ml Orphenadrine 50mg/5ml oral solution sugar free sugar-free | 150 ml PO | £36.80 DT price = £35.65
  - **Procyclidine hydrochloride**
    - **DRUG ACTION** Procyclidine exerts its antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.
    - **INDICATIONS AND DOSE**
      - Parkinsonism | Extrapyramidal symptoms (but not tardive dyskinesia)
        - **BY MOUTH**
          - Adult: 2.5 mg 3 times a day, then increased in steps of 2.5–5 mg daily if required; increased if necessary up to 30 mg daily in 2–4 divided doses, to be increased at 2–3 day intervals. Maximum daily dose only to be used in exceptional circumstances; maximum 60 mg per day
          - Elderly: Lower end of range preferable
      - **Acute dystonia**
        - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
          - Adult: 5–10 mg, occasionally, more than 10 mg, dose usually effective in 5–10 minutes but may need 30 minutes for relief
          - Elderly: Lower end of range preferable
    - **CONTRA-INDICATIONS** Gastro-intestinal obstruction | myasthenia gravis
    - **CAUTIONS** Cardiovascular disease | elderly | hypertension | liable to abuse | prostatic hypertrophy | psychotic disorders | pyrexia | those susceptible to angle-closure glaucoma
    - **INTERACTIONS** → Appendix 1 (antimuscarinics).
      Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urinary retention, and constipation. Concomitant use of other drugs with antimuscarinic effects can also lead to confusion in the elderly.
    - **SIDE-EFFECTS**
      - Angle-closure glaucoma | anxiety | blurred vision | confusion | constipation | dizziness | dry mouth | euphoria | gingivitis | hallucinations | impaired memory | nausea | rash | restlessness | tachycardia | urinary retention | vomiting
    - **PREGNANCY** Use only if potential benefit outweighs risk.
    - **BREAST FEEDING** No information available.
    - **HEPATIC IMPAIRMENT** Use with caution.
    - **RENAL IMPAIRMENT** Use with caution.
    - **TREATMENT CESSATION** Avoid abrupt withdrawal in patients taking long-term treatment.
    - **PATIENT AND CARER ADVICE**
      - Driving and skilled tasks
        May affect performance of skilled tasks (e.g. driving).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
  - **Tablet**
    - **Procyclidine hydrochloride (Non-proprietary)**
      - Procyclidine hydrochloride 5 mg. Procyclidine 5mg tablets | 28 tablet PO | £14.25 DT price = £13.40 | 100 tablet PO | £50.00 | 500 tablet PO | £239.29
      - Kemadrin (Aspen Pharma Trading Ltd)
        - Procyclidine hydrochloride 5 mg. Kemadrin 5mg tablets | 100 tablet PO | £4.72 | 500 tablet PO | £23.62
  - **Oral solution**
    - **Procyclidine hydrochloride (Non-proprietary)**
      - Procyclidine hydrochloride 1 mg per 1 ml Procyclidine 5mg/5ml oral solution sugar free sugar-free | 150 ml PO | £11.54 DT price = £11.54
      - Procyclidine hydrochloride 500 microgram per 1 ml Procyclidine 2.5mg/5ml oral solution sugar free sugar-free | 150 ml PO | £6.22 DT price = £6.22
Trihexyphenidyl hydrochloride

(Benzhexol hydrochloride)

**DRUG ACTION**: Trihexyphenidyl exerts its effects by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.

**INDICATIONS AND DOSE**

**Parkinson’s disease (if used in combination with co-careldopa or co-beneldopa)**
- **Adult**: Maintenance 2–6 mg daily in divided doses, use not recommended because of toxicity in the elderly and the risk of aggravating dementia.
- **Parkinsonism**: Drug-induced extrapyramidal symptoms (but not tardive dyskinesia)
  - **BY MOUTH**: Adult: 1 mg daily, then increased in steps of 2 mg every 3–5 days, adjusted according to response; maintenance 5–15 mg daily in 3–4 divided doses, not recommended for use in Parkinson’s disease because of toxicity in the elderly and the risk of aggravating dementia; maximum 20 mg per day.
  - **Elderly**: Lower end of range preferable, not recommended for use in Parkinson’s disease because of toxicity in the elderly and the risk of aggravating dementia.

**CONTRA-INDICATIONS**: Gastro-intestinal obstruction · myasthenia gravis

**CAUTIONS**: Cardiovascular disease · elderly · hypertension · liable to abuse · prostatic hypertrophy · psychotic disorders · pyrexia · those susceptible to angle-closure glaucoma

**INTERACTIONS**: Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation. Concomitant use of other drugs with antimuscarinic effects can also lead to confusion in the elderly.

**SIDE-EFFECTS**
- **Very rare** · Angle-closure glaucoma
- **Frequency not known** · Anxiety · blurred vision · confusion · constipation · dizziness · dry mouth · euphoria · hallucinations · impaired memory · nausea · rash · restlessness · tachycardia · urinary retention · vomiting

**PREGNANCY**: Use only if potential benefit outweighs risk.

**BREAST FEEDING**: Avoid.

**HEPATIC IMPAIRMENT**: Use with caution.

**RENAL IMPAIRMENT**: Use with caution.

**TREATMENT CESSATION**: Avoid abrupt withdrawal in patients taking long-term treatment.

**DIRECTIONS FOR ADMINISTRATION**: Tablets should be taken with or after food.

**PATIENT AND CARER ADVICE**: Driving and skilled tasks may affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Table

<table>
<thead>
<tr>
<th><strong>Trihexyphenidyl hydrochloride (Non-proprietary)</strong></th>
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<tr>
<td>Trihexyphenidyl hydrochloride 2 mg</td>
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<td>84 tablet (Pos)</td>
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**DOPAMINERGIC DRUGS** > CATECHOL-O-METHYLTRANSFERASE INHIBITORS

Entacapone

**DRUG ACTION**: Entacapone prevents the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain.

**INDICATIONS AND DOSE**

**Adjunct to co-beneldopa or co-careldopa in Parkinson’s disease with ‘end-of-dose’ motor fluctuations (under expert supervision)**
- **BY MOUTH**: Adult: 200 mg, dose to be given with each dose of levodopa with dopa-decarboxylase inhibitor; maximum 2 g per day.

**CONTRA-INDICATIONS**: History of neuroleptic malignant syndrome · history of non-traumatic rhabdomyolysis · phaeochromocytoma

**CAUTIONS**: Concurrent levodopa dose may need to be reduced by about 10–30% · ischaemic heart disease

**INTERACTIONS**: Appendix 1 (entacapone). Avoid iron-containing products at the same time of day.

**SIDE-EFFECTS**
- **Common or very common** · Abdominal pain · abnormal dreams · confusion · constipation · diarrhoea · dizziness · dry mouth · dyskinesia · dystonia · fatigue · hallucinations · insomnia · ischaemic heart disease · nausea · sweating · urine may be coloured reddish-brown · vomiting
- **Uncommon** · Myocardial infarction
- **Rare** · Rash
- **Very rare** · Agitation · anorexia · urticaria · weight loss
- **Frequency not known** · Colitis · hepatitis · neuroleptic malignant syndrome · rhabdomyolysis · skin, hair, and nail discoloration

**PREGNANCY**: Avoid—no information available.

**BREAST FEEDING**: Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**: Avoid.

**TREATMENT CESSATION**: Avoid abrupt withdrawal.

**PATIENT AND CARER ADVICE**: Patient counselling is advised (may colour urine reddish-brown, concomitant iron containing products).

**MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Tablet**

<table>
<thead>
<tr>
<th><strong>Entacapone (Non-proprietary)</strong></th>
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<tr>
<td>Entacapone 200 mg</td>
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<td>Comtess (Oriion Pharma (UK) Ltd)</td>
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<tr>
<td>Entacapone 200 mg</td>
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</tbody>
</table>

**Combinations available**: Carbidopa with entacapone and levodopa, p. 386
Tolcapone

- **DRUG ACTION** Tolcapone prevents the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain.

- **INDICATIONS AND DOSE**
  Adjunct to co-beneldopa or co-careldopa in Parkinson’s disease with ‘end-of-dose’ motor fluctuations if another inhibitor of peripheral catechol-O-methyltransferase inappropriate (under expert supervision)
  - **BY MOUTH**
  - Adult: 100 mg 3 times a day (max. per dose 200 mg 3 times a day) continuing beyond 3 weeks only if substantial improvement, leave 6 hours between each dose; first daily dose should be taken at the same time as levodopa with dopa-decarboxylase inhibitor, dose maximum only in exceptional circumstances

- **CONTRA-INDICATIONS** Phaeochromocytoma · previous history of hyperthermia · previous history of neuroleptic malignant syndrome · previous history of rhabdomyolysis · severe dyskinesia

- **CAUTIONS** Most patients receiving more than 600 mg levodopa daily require reduction of levodopa dose by about 30%

- **CAUTIONS, FURTHER INFORMATION**
  - Hepatotoxicity: Potentially life-threatening hepatotoxicity including fulminant hepatitis reported rarely, usually in women and during the first 6 months, but late-onset liver injury also reported; discontinue if abnormal liver function tests or symptoms of liver disorder; do not re-introduce tolcapone once discontinued.

- **INTERACTIONS** \(\rightarrow\) Appendix 1 (tolcapone).

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain · anorexia · chest pain · confusion · constipation · diarrhoea · dizziness · drowsiness · dyskinesia · dyspepsia · dystonia · excessive dreaming · hallucinations · headache · hepatotoxicity · nausea · sleep disturbances · sweating · syncope · urinary discoloration · vomiting · xerostomia
  - Frequency not known Neuroleptic malignant syndrome reported on dose reduction or withdrawal · rhabdomyolysis reported on dose reduction or withdrawal

- **PREGNANCY** Toxicity in animal studies—use only if potential benefit outweighs risk.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Avoid.

- **RENAI PROIRMENT** Caution if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS** Test liver function before treatment, and monitor every 2 weeks for first year, every 4 weeks for next 6 months and then every 8 weeks thereafter (restart monitoring schedule if dose increased).

- **TREATMENT CESSATION** Avoid abrupt withdrawal.

- **PATIENT AND CARER ADVICE** Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 14, 25
  - **Tasmar (Meda Pharmaceuticals Ltd)**
  - **Tolcapone 100 mg** Tasmar 100mg tablets | 100 tablet [Pack] £95.20

**DOPAMINERGIC DRUGS > DOPAMINE PRECURSORS**

**Carbidopa with entacapone and levodopa**

The properties listed below are those particular to the combination only. For the properties of the components please consider, co-careldopa p. 388, entacapone p. 385.

- **INDICATIONS AND DOSE**
  - **STALEVO® 100/25/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 10 tablets per day
  - **STALEVO® 125/31.25/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 10 tablets per day
  - **STALEVO® 150/37.5/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 10 tablets per day
  - **STALEVO® 175/43.75/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 8 tablets per day
  - **STALEVO® 200/50/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 7 tablets per day
  - **STALEVO® 50/12.5/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 10 tablets per day
  - **STALEVO® 75/18.75/200**
    Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment
    - **BY MOUTH**
    - Adult: 1 tablet for each dose; maximum 10 tablets per day

- **PRESCRIBING AND DISPENSING INFORMATION** Patients receiving standard-release co-careldopa or co-beneldopa alone, initiate Stalevo® at a dose that provides similar (or slightly lower) amount of levodopa.

  Patients with dyskinesia or receiving more than 800 mg levodopa daily, introduce entacapone before transferring.
to Stalevo® (levodopa dose may need to be reduced by 10–30% initially).

Patients receiving entacapone and standard-release co-careldopa or co-beneldopa, initiate Stalevo® at a dose that provides similar (or slightly higher) amount of levodopa.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**

Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with carbidopa with entacapone and levodopa. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

10, 14 (urine reddish-brown), 25

- **Stalevo®** (Orion Pharma (UK) Ltd)
  - Carbidopa 25 mg, Levodopa 100 mg, Entacapone 200 mg
  - Stalevo 100mg/25mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31
  - Carbidopa 18.75 mg, Levodopa 75 mg, Entacapone 200 mg
  - Stalevo 75mg/18.75mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31
  - Carbidopa 37.5 mg, Levodopa 150 mg, Entacapone 200 mg
  - Stalevo 150mg/37.5mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31
  - Carbidopa 12.5 mg, Levodopa 50 mg, Entacapone 200 mg
  - Stalevo 50mg/12.5mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31
  - Carbidopa 31.25 mg, Levodopa 125 mg, Entacapone 200 mg
  - Stalevo 125mg/31.25mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31
  - Carbidopa 43.75 mg, Levodopa 175 mg, Entacapone 200 mg
  - Stalevo 175mg/43.75mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31
  - Carbidopa 50 mg, Entacapone 200 mg, Levodopa 200 mg
  - Stalevo 200mg/50mg/200mg tablets | 30 tablet (POM) £20.79 | 100 tablet (POM) £69.31

**Co-beneldopa**

**INDICATIONS AND DOSE**

**Parkinson's disease**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 50 mg 3–4 times a day, then increased in steps of 100 mg daily, dose to be increased once or twice weekly according to response; maintenance 400–800 mg daily in divided doses
  - Elderly: Initially 50 mg 1–2 times a day, then increased in steps of 50 mg daily, dose to be increased every 3–4 days according to response

**Parkinson's disease (in advanced disease)**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 100 mg 3 times a day, then increased in steps of 100 mg daily, dose to be increased once or twice weekly according to response; maintenance 400–800 mg daily in divided doses

**Parkinson's disease (patients not taking levodopa/dopa-decarboxylase inhibitor therapy)**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 1 capsule 3 times a day; maximum 6 capsules per day

**IMPORTANT SAFETY INFORMATION**

**IMPULSE CONTROL DISORDERS**

Treatment with levodopa is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. If the patient develops an impulse control disorder, levodopa should be withdrawn or the dose reduced until the symptoms resolve.

**SIDE-EFFECTS**

- **Common or very common** Abnormal dreams, anorexia, anxiety, arrhythmias, chorea, confusion, dementia, depression, dizziness, drowsiness, dry mouth, dyskinesia, dystonia, euphoria, fatigue, insomnia, nausea, palpitations, postural hypotension, psychosis, syncope, taste disturbances, vomiting

- **Uncommon** Ataxia, chest pain, constipation, diarrhoea, dysphagia, flatulence, hand tremor, hoarseness, hypersalivation, hypertension, malaise, muscle cramps, oedema, reddish discoloration of the urine and other body fluids, weakness, weight changes

- **Rare** Abdominal pain, activation of Homer's syndrome, activation of malignant melanoma, agitation, agranulocytosis, alopecia, blepharospasm, blurred vision, bruxism, convulsions, diplopia, disorientation, duodenal ulcer, dyspepsia, dysphonia, exanthema, flushing, gastro-intestinal bleeding, haemolytic anaemia, headache, Henoch-Schönlein purpura, hiccup, leucopenia, neuroleptic malignant syndrome (associated with abrupt withdrawal), non-haemolytic anaemia, oculogyric crisis, paraesthesia, phlebitis, priapism, pupil dilatation, reduced mental acuity, sweating, thrombocytopenia, trismus, urinary incontinence, urinary retention

- **Very rare** Angle-closure glaucoma, suicidal ideation

- **Frequency not known** Compulsive behaviour

**PREGNANCY** Caution in pregnancy—toxicity has occurred in animal studies.

**BREAST FEEDING** May suppress lactation; present in milk—avoid.

**HEPATIC IMPAIRMENT** Use with caution.

**RENAL IMPAIRMENT** Use with caution.

**Parkinson's disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 1 capsule substituted for every 100 mg of levodopa and given at same dosage frequency, increased every 2–3 days according to response; average increase of 50% needed over previous levodopa dose and titration may take up to 4 weeks, supplementary dose of immediate-release Madopar® may be needed with first morning dose; if response still poor to total daily dose of Madopar® CR plus Madopar® corresponding to 1.2 g levodopa—consider alternative therapy.

**DOSE EQUIVALENT AND CONVERSION**

- **Dose is expressed as levodopa.**
EFFECT ON LABORATORY TESTS False positive tests for urinary ketones have been reported.

TREATMENT CESSION Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis).

DIRECTIONS FOR ADMINISTRATION The dispersible tablets can be dispersed in water or orange squash (not orange juice) or swallowed whole.

PRESCRIBING AND DISPENSING INFORMATION Co-beneldopa is a mixture of benserazide hydrochloride and levodopa in mass proportions corresponding to 1 part of benserazide and 4 parts of levodopa.

When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued 12 hours before (although interval can be shorter).

When switching from modified-release levodopa to dispersible co-beneldopa, reduce dose by approximately 30%.

When administered as an adjunct to other antiparkinsonian drugs, once therapeutic effect apparent, the other drugs may be reduced or withdrawn.

PATIENT AND CARER ADVICE Patients or carers should be counselled on improving sleep behaviour.

Driving and skilled tasks Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with co-beneldopa.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution dispersible tablet.

Dispersible tablet CAUTIONARY AND ADVISORY LABELS 10, 14, 21

- Madopar (Roche Products Ltd)
  Benserazide (as Benserazide hydrochloride) 12.5 mg, Levodopa 50 mg Madopar 50mg/12.5mg dispersible tablets sugar-free | 100 tablet (PO) £5.90 DT price = £5.90
  Benserazide (as Benserazide hydrochloride) 25 mg, Levodopa 100 mg Madopar 100mg/25mg dispersible tablets sugar-free | 100 tablet (PO) £10.45 DT price = £10.45

Capsule CAUTIONARY AND ADVISORY LABELS 10, 14, 21

- Co-beneldopa (Non-proprietary)
  Benserazide (as Benserazide hydrochloride) 12.5 mg, Levodopa 50 mg Co-beneldopa 12.5mg/50mg capsules | 100 capsule (PO) £4.73-£4.96 DT price = £4.96
  Benserazide (as Benserazide hydrochloride) 25 mg, Levodopa 100 mg Co-beneldopa 25mg/100mg capsules | 100 capsule (PO) £6.56-£6.91 DT price = £6.91
  Benserazide (as Benserazide hydrochloride) 50 mg, Levodopa 200 mg Co-beneldopa 50mg/200mg capsules | 100 capsule (PO) £11.19-£11.78 DT price = £11.78

- Madopar (Roche Products Ltd)
  Benserazide (as Benserazide hydrochloride) 12.5 mg, Levodopa 50 mg Madopar 50mg/12.5mg dispersible tablets | 100 capsule (PO) £4.96 DT price = £4.96
  Benserazide (as Benserazide hydrochloride) 25 mg, Levodopa 100 mg Madopar 100mg/25mg dispersible tablets | 100 capsule (PO) £6.91 DT price = £6.91
  Benserazide (as Benserazide hydrochloride) 50 mg, Levodopa 200 mg Madopar 200mg/50mg capsules | 100 capsule (PO) £11.78 DT price = £11.78

Co-careldopa

INDICATIONS AND DOSE Parkinson’s disease

BY MOUTH

Adult: Initially 25/100 mg 3 times a day, then increased in steps of 12.5/50 mg once daily or on alternate days, alternatively increased in steps of 25/100 mg once daily or on alternate days, dose to be adjusted according to response; dose increased until 800 mg levodopa (with 200 mg carbidopa) daily in divided doses is reached, then maintenance up to 200/2000 mg daily in divided doses, adjusted according to response, when co-careldopa is used, the total daily dose of carbidopa should be at least 70 mg. A lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects

Parkinson’s disease—alternative regimen

BY MOUTH

Adult: Initially 12.5/50 mg 3–4 times a day, alternatively initially 10/100 mg 3–4 times a day, then increased in steps of 12.5/50 mg once daily or on alternate days, adjusted according to response, alternatively increased in steps of 10/100 mg once daily or on alternate days, adjusted according to response, dose increased until 800 mg levodopa (with up to 200 mg carbidopa) daily in divided doses is reached, then maintenance up to 200/2000 mg daily in divided doses, adjusted according to response, when co-careldopa is used, the total daily dose of carbidopa should be at least 70 mg. A lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects

DOSE EQUIVALENCE AND CONVERSION

The proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively.

- 2 tablets Sinemet® 12.5/50 mg is equivalent to 1 tablet Sinemet® Plus 25 mg/100 mg.

CARAMET® CR Parkinson’s disease (patients not receiving levodopa/dopa-decarboxylase inhibitor preparations, expressed as levodopa)

BY MOUTH USING MODIFIED-RELEASE TABLETS

Adult: Initially 100–200 mg twice daily, dose to be given at least 6 hours apart; dose adjusted according to response at intervals of at least 2 days

Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)

BY MOUTH USING MODIFIED-RELEASE TABLETS

Adult: Discontinue previous preparation at least 12 hours before first dose of CarameT® CR; substitute CarameT® CR to provide a similar amount of levodopa daily and extend dosing interval by 30–50%; dose then adjusted according to response at intervals of at least 2 days.

DUODOPA®

Severe Parkinson’s disease inadequately controlled by other preparations

Adult: Administered as intestinal gel, for use with enteral tube (consult product literature)
HALF SINEMET® CR
Parkinson’s disease (for fine adjustment of Sinemet® CR dose)
▶ BY MOUTH
▶ Adult: (consult product literature)

SINEMET® CR
Parkinson’s disease (patients not receiving levodopa/dopa-decarboxylase inhibitor therapy)
▶ BY MOUTH
▶ Adult: Initially 1 tablet twice daily, both dose and interval then adjusted according to response at intervals of not less than 3 days

Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)
▶ BY MOUTH
▶ Adult: 1 tablet twice daily, dose can be substituted for a daily dose of levodopa 300–400 mg in immediate-release Sinemet® tablets (substitute Sinemet® CR to provide approximately 10% more levodopa per day and extend dosing interval by 30–50%); dose and interval then adjusted according to response at intervals of not less than 3 days.

IMPORTANT SAFETY INFORMATION
IMPULSE CONTROL DISORDERS
Treatment with levodopa is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. If the patient develops an impulse control disorder, levodopa should be withdrawn or the dose reduced until the symptoms resolve.

● CAUTIONS
  - Cushing’s syndrome
  - Diabetes mellitus
  - Endocrine disorders
  - History of convulsions
  - History of myocardial infarction with residual arrhythmia
  - History of peptic ulcer
  - Hypothyroidism
  - Osteomalacia
  - Phaeochromocytoma
  - Psychiatric illness (avoid if severe and discontinue if deterioration)
  - Severe cardiovascular disease
  - Severe pulmonary disease
  - Susceptibility to angle-closure glaucoma

● INTERACTIONS
  ▶ Appendix 1 (co-careldopa, levodopa).

● SIDE-EFFECTS
  ▶ Common or very common
    - Abnormal dreams
    - Anorexia
    - Anxiety
    - Arrhythmias
    - Chorea
    - Confusion
    - Dementia
    - Depression
    - Dizziness
    - Drowsiness
    - Dry mouth
    - Dyskinesia
    - Dystonia
    - Euphoria
    - Fatigue
    - Insomnia
    - Nausea
    - Palpitations
    - Postural hypotension
    - Psychosis
    - Syncope
    - Taste disturbances
    - Vomiting

  ▶ Uncommon
    - Ataxia
    - Chest pain
    - Constipation
    - Diarrhoea
    - Dysphagia
    - Flatulence
    - Hand tremor
    - Hoarseness
    - Hypersalivation
    - Hypertension
    - Malaise
    - Muscle cramps
    - Oedema
    - Reddish discoloration of the urine and other body fluids
    - Weakness
    - Weight changes

  ▶ Rare
    - Abdominal pain
    - Activation of Horner’s syndrome
    - Activation of malignant melanoma
    - Agitation
    - Agranulocytosis
    - Alopecia
    - Blepharospasm
    - Blurred vision
    - Bruxism
    - Convulsions
    - Diplopia
    - Disorientation
    - Duodenal ulcer
    - Dyspepsia
    - Dysphonia
    - Exanthema
    - Flushing
    - Gastro-intestinal bleeding
    - Haemolytic anaemia
    - Headache
    - Henoch–Schönlein purpura
    - Hiccups
    - Leucopenia
    - Neuropathic pain
    - Neuroleptic malignant syndrome (associated with abrupt withdrawal)
    - Non-haemolytic anaemia
    - Oculogyric crisis
    - Paraesthesia
    - Phlebitis
    - Priapism
    - Pupil dilatation
    - Reduced mental acuity
    - Sweating
    - Thrombocytopenia
    - Trismus
    - Urinary incontinence
    - Urinary retention

  ▶ Very rare
    - Angio-oedema
    - Suicidal ideation

  ▶ Frequency not known
    - Compulsive behaviour

● PREGNANCY
  - Use with caution—toxicity has occurred in animal studies.

● BREAST FEEDING
  - May suppress lactation; present in milk—avoid.

● HEPATIC IMPAIRMENT
  - Use with caution.

● RENAL IMPAIRMENT
  - Use with caution.

● EFFECT ON LABORATORY TESTS
  - False positive tests for urinary ketones have been reported.

● TREATMENT CESSION
  - Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis).

● PRESCRIBING AND DISPENSING INFORMATION
  - Co-careldopa is a mixture of carbidopa and levodopa; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively.

  - When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued at least 12 hours before.

  - Co-careldopa 25/100 provides an adequate dose of carbidopa when low doses of levodopa are needed.

● PATIENT AND CARER ADVICE

Driving and skilled tasks
Sudden onset of sleep
  - Excessive daytime sleepiness and sudden onset of sleep can occur with co-careldopa.

  - Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

  - Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or comitant medication. Patients should be counselled on improving sleep behaviour.

● NATIONAL FUNDING/ACCESS DECISIONS

DUODOPA®

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2016) that Duodopa® intestinal gel is accepted for restricted use within NHS Scotland, within its licensed indication, only in patients not eligible for deep brain stimulation. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS
10, 14
▶ Co-careldopa (Non-proprietary)
Carbidopa (as Carbidopa monohydrate) 12.5 mg, Levodopa 50 mg
Co-careldopa 12.5mg/50mg tablets | 90 tablet (Pom) £6.28
DT price = £6.28

Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg
Co-careldopa 25mg/100mg tablets | 100 tablet (Pom) £26.99
DT price = £13.91

Carbidopa (as Carbidopa monohydrate) 10 mg, Levodopa 100 mg
Co-careldopa 10mg/100mg tablets | 100 tablet (Pom) £8.68
DT price = £8.40

Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 250 mg
Co-careldopa 25mg/250mg tablets | 100 tablet (Pom) £35.00
DT price = £34.98

Sinemet (Merck Sharp & Dohme Ltd)
Carbidopa (as Carbidopa monohydrate) 12.5 mg, Levodopa 50 mg
Sinemet 12.5mg/50mg tablets | 90 tablet (Pom) £6.28
DT price = £6.28

Carbidopa (as Carbidopa monohydrate) 10 mg, Levodopa 100 mg
Sinemet 10mg/100mg tablets | 100 tablet (Pom) £7.30
DT price = £8.40

4
Nervous system
Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 250 mg Sinemet 25mg/250mg tablets | 100 tablet £18.29 DT price = £34.98
- Sinemet CR (Merck Sharp & Dohme Ltd)
Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Sinemet Plus 25mg/100mg tablets | 100 tablet £12.88 DT price = £13.91

Modiﬁed-release tablet
CAUTIONARY AND ADVISORY LABELS 10, 14, 25
- Caramet CR (Teva UK Ltd)
Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Caramet 25mg/100mg CR tablets | 60 tablet £11.47 DT price = £11.60
Carbidopa (as Carbidopa monohydrate) 50 mg, Levodopa 200 mg Caramet 50mg/200mg CR tablets | 60 tablet £11.47 DT price = £11.60
- Half Sinemet CR (Merck Sharp & Dohme Ltd)
Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Half Sinemet CR 25mg/100mg tablets | 60 tablet £11.60 DT price = £11.60
Carbidopa (as Carbidopa monohydrate) 50 mg, Levodopa 200 mg Lecadox 200mg/50mg modified-release tablets | 60 tablet £9.86 DT price = £11.60
- Sinemet CR (Merck Sharp & Dohme Ltd)
Carbidopa (as Carbidopa monohydrate) 50 mg, Levodopa 200 mg Sinemet CR 50mg/200mg tablets | 60 tablet £11.60 DT price = £11.60

Gel
CAUTIONARY AND ADVISORY LABELS 10, 14
- Duovent (AbbVie Ltd)
Carbidopa (as Carbidopa monohydrate) 5 mg per 1 mL, Levodopa 20 mg per 1 mL Duovent gel 100mL bottle | 1 bag £7.00 7 bag no price available

DOPAMINERGIC DRUGS > DOPAMINE RECEPTOR AGONISTS

Amantadine hydrochloride

- DRUG ACTION Amantadine is a weak dopamine agonist with modest antiparkinsonian effects.

- INDICATIONS AND DOSE Parkinson’s disease
  - BY MOUTH
    - Adult: 100 mg daily for 1 week, then increased to 100 mg twice daily, usually administered in conjunction with other treatment. Some patients may require higher doses; maximum 400 mg per day
    - Elderly: 100 mg daily, adjusted according to response

Post-herpetic neuralgia
- BY MOUTH
  - Adult: 100 mg twice daily for 14 days (continued for another 14 days if necessary)

Treatment of influenza A (but not recommended)
- BY MOUTH
  - Adult: 100 mg daily 4–5 days

Prophylaxis of influenza A (but not recommended)
- BY MOUTH
  - Adult: 100 mg daily usually for 6 weeks or with influenza vaccination for 2–3 weeks after vaccination

- CONTRA-INDICATIONS Epilepsy · history of gastric ulceration
- CAUTIONS Confused or hallucinatory states · congestive heart disease (may exacerbate oedema) · elderly · tolerance to the effects of amantadine may develop in Parkinson’s disease
- INTERACTIONS → Appendix 1 (amantadine).
- SIDE-EFFECTS
  - Common or very common Anorexia · anxiety · dizziness · dry mouth · gastrointestinal disturbances · hallucinations · headache · impaired concentration · insomnia · lethargy · livedo reticularis · mood changes · myalgia · palpitation · peripheral oedema · postural hypotension · slurred speech · sweating
  - Uncommon Confusion · movement disorders · neuroleptic malignant syndrome · psychosis · rash · seizure · tremor · urinary incontinence · urinary retention · visual disturbances
  - Frequency not known Heart failure · leucopenia · photosensitisation

- PREGNANCY Avoid; toxicity in animal studies.
- BREAST FEEDING Avoid; present in milk; toxicity in infant reported.
- HEPATIC IMPAIRMENT Use with caution.
- RENAL IMPAIRMENT Reduce dose. Avoid if eGFR less than 15 mL/minute/1.73 m².
- TREATMENT CESSATION Avoid abrupt withdrawal in Parkinson’s disease.

- PATIENT AND CARER ADVICE Driving and skilled tasks May affect performance of skilled tasks (e.g. driving).
- NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) NICE TA158 Amantadine is not recommended for prophylaxis of influenza.
  www.nice.org.uk/TA158
- Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009) NICE TA168 Amantadine is not recommended for treatment of influenza.
  www.nice.org.uk/TA168

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

Capsule
- Amantadine hydrochloride (Non-proprietary) Amantadine hydrochloride 100 mg Amantadine 100mg capsules | 14 capsule £10.25 | 56 capsule £41.00 DT price = £41.00

Oral solution
- Amantadine hydrochloride (Non-proprietary) Amantadine hydrochloride 10 mg per 1 mL Amantadine 50mg/5m solution sugar free sugar-free | 150 mL £138.18–£140.00 DT price = £138.64

Apomorphine hydrochloride

- INDICATIONS AND DOSE

Refactory motor fluctuations in Parkinson’s disease (off” episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (for capable and motivated patients) (under expert supervision)
- BY SUBCUTANEOUS INJECTION
  - Adult: Initially 1 mg, dose to be administered at the first sign of “off” episode, then 2 mg after 30 minutes, dose to be given if inadequate or no response following initial dose, thereafter increase dose at minimum 40-minute intervals until satisfactory response obtained, this determines threshold dose; usual dose 3–30 mg daily in divided doses (max. per dose 10 mg), subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses; maximum 100 mg per day
Bromocriptine is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary.

**INDICATIONS AND DOSE**

- **Prevention of lactation**
  - **BY MOUTH**
    - Adult: Initially 2.5 mg daily for 1 day, then 2.5 mg twice daily for 14 days

**DRUG ACTION**

- Bromocriptine is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary.

**TREATMENT CESSION**

- Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

**PATIENT AND CARER ADVICE**

- **Driving and skilled tasks**
  - **Sudden onset of sleep** Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.
    - Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

- **Drugs and driving** Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

2015 legislation regarding driving whilst taking certain drugs, may also apply to apomorphine, see Drugs and driving under Guidance on prescribing p. 1.

**Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

**Solution for injection**

- **CAUTIONARY AND ADVISORY LABELS**
- **EXCIPIENTS**: May contain Sulfites
- **APO-go (Britannia Pharmaceuticals Ltd)**
  - Apomorphine hydrochloride 10 mg per 1 ml APO-go 50mg/5ml solution for injection ampoules | 5 ampoule | £73.11 DT price = £73.11
  - Apomorphine hydrochloride 10 mg per 1 ml APO-go Pen 30mg/3ml solution for injection | 5 pre-filled disposable injection | £123.91 DT price = £123.91

**Solution for infusion**

- **CAUTIONARY AND ADVISORY LABELS**
- **EXCIPIENTS**: May contain Sulfites
- **APO-go PFS (Britannia Pharmaceuticals Ltd)**
  - Apomorphine hydrochloride 5 mg per 1 ml APO-go PFS 50mg/10ml solution for infusion pre-filled syringes | 5 pre-filled disposable injection | £73.11 DT price = £73.11

**IMPORTANT SAFETY INFORMATION**

**IMPULSE CONTROL DISORDERS**

- Treatment with dopamine-receptor agonists are associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.

**CONTRA-INDICATIONS** Avoid if ‘on’ response to levodopa marred by severe dyskinesia or dystonia · dementia · psychosis · respiratory depression.

**CAUTIONS** Cardiovascular disease · history of postural hypotension (special care on initiation) · neuropsychiatric conditions · pulmonary disease · susceptibility to QT-interval prolongation.

**INTERACTIONS** → Appendix 1 (apomorphine).

**SIDE-EFFECTS**

- **Common or very common** Confusion · drowsiness · hallucinations · nausea · sudden onset of sleep · vomiting · yawning.
- **Uncommon** Dyskinesia during ‘on’ periods (may require discontinuation) · dysphagia · haemolytic anaemia (with levodopa) · postural hypotension · rash · thrombocytopenia (with levodopa).
- **Rare** Eosinophilia.
- **Frequency not known** Compulsive behaviour · dizziness · peripheral oedema.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of hypersensitivity to opioids.

**PREGNANCY** Avoid unless clearly necessary.

**BREAST FEEDING** No information available; may suppress lactation.

**HEPATIC IMPAIRMENT** Avoid.

**RENAL IMPAIRMENT** Use with caution.

**MONITORING REQUIREMENTS**

- Monitor hepatic, haemopoietic, renal, and cardiovascular function.
- With concomitant levodopa test initially and every 6 months for haemolytic anaemia and thrombocytopenia (development calls for specialist haematological care with dose reduction and possible discontinuation).

**REFRACTORY MOTOR FLUCTUATIONS** In Parkinson’s disease (‘off’ episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (in patients requiring division into more than 10 injections daily) (under expert supervision)

- **BY CONTINUOUS SUBCUTANEOUS INFUSION**
- Adult: Initially 1 mg/hour, adjusted according to response, then increased in steps of up to 500 micrograms/hour, dose to be increased at intervals not more often than every 4 hours; usual dose 1–4 mg/hour, alternatively usual dose 15–60 micrograms/kg/hour, change infusion site every 12 hours and give during waking hours only (tolerance may occur unless there is a 4-hour treatment-free period at night—24-hour infusions not recommended unless severe night time symptoms); intermittent bolus doses may be needed; maximum 100 mg per day
Suppression of lactation
- **BY MOUTH**
- **Adult:** Initially 2.5 mg daily for 2–3 days, then 2.5 mg twice daily for 14 days

Hypogonadism | Galactorrhoea | Infertility
- **BY MOUTH**
- **Adult:** Initially 1–1.25 mg daily, dose to be taken at bedtime, increased dose gradually; usual dose 7.5 mg daily in divided doses, increased if necessary up to 30 mg daily, usual dose in infertility without hyperprolactinaemia is 2.5 mg twice daily

Acromegaly
- **BY MOUTH**
- **Adult:** Initially 1–1.25 mg daily, dose to be taken at bedtime, then increased to 5 mg every 6 hours, increase dose gradually

Prolactinoma
- **BY MOUTH**
- **Adult:** Initially 1–1.25 mg daily, dose to be taken at bedtime, then increased to 5 mg every 6 hours, increase dose gradually. Occasionally patients may require up to 30 mg daily

Parkinson’s disease
- **BY MOUTH**
- **Adult:** Initially 1–1.25 mg daily for 1 week, dose to be taken at night, then 2–2.5 mg daily for 1 week, dose to be taken at night, then 2.5 mg twice daily for 1 week, then 2.5 mg 3 times a day for 1 week, then increased in steps of 2.5 mg every 3–14 days, adjusted according to response; maintenance 10–30 mg daily

**IMPORTANT SAFETY INFORMATION**

**FIBROTIC REACTIONS**
Bromocriptine has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson’s disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful.

**IMPALE CONTROL DISORDERS**
Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

- **CONTRA-INDICATIONS** Avoid in pre-eclampsia, cardiac valvulopathy (exclude before treatment), hypertension in postpartum women or in puerperium

- **CONTRA-INDICATIONS, FURTHER INFORMATION**
- Postpartum or puerperium: Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease, or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and mental disorders have been reported in postpartum women given bromocriptine for lactation suppression — caution with antihypertensive therapy and avoid other ergot alkaloids. Discontinue immediately if hypertension, unremitting headache, or signs of CNS toxicity develop.

- **CAUTIONS** Acute porphyrias. p. 930 · cardiovascular disease · history of peptic ulcer (particularly in acromegalic patients) · history of serious mental disorders (especially psychotic disorders) · Raynaud’s syndrome

- **CAUTIONS, FURTHER INFORMATION**
- Hyperprolactinaemic patients. In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e., exclude pituitary tumour before treatment).

- **INTERACTIONS** → Appendix 1 (bromocriptine).
- Tolerance may be reduced by alcohol.

- **SIDE-EFFECTS**
- **Common or very common** Constipation · headache · nasal congestion · nausea
- **Uncommon** Confusion (particularly with high doses) · dizziness · dry mouth · fatigue · hallucinations (particularly with high doses) · postural hypotension · psychomotor excitation (particularly with high doses) · vomiting
- **Rare** Abdominal pain · arrhythmia · bradycardia · diarrhea · gastric ulcer · gastrointestinal bleeding · insomnia · paraesthesia · psychosis · tachycardia · tinnitus · visual disturbances
- **Very rare** Neuroleptic malignant syndrome on withdrawal · vasospasm of fingers and toes (particularly in patients with Raynaud’s syndrome)

- **Frequency not known** Allergic skin reactions · alopecia · cardiac valvulopathy · constrictive pericarditis · drowsiness · dryness · dyskinesia · hypersexuality · hyponatraemia · hypotension · increased libido · leg cramps · leucopenia · pathological gambling · pericardial effusion · peripheral oedema · pleural effusion · pleural fibrosis · pleuritis · pulmonary fibrosis · retroperitoneal fibrosis · reversible hearing loss · thrombocytopenia · urinary incontinence

- **SIDE-EFFECTS, FURTHER INFORMATION**
- Gastro-intestinal bleeding · Treatment should be withdrawn if gastro-intestinal bleeding occurs.

- **ALLERGIC AND CROSS-SENSITIVITY** Bromocriptine should not be used in patients with hypersensitivity to ergot alkaloids.

- **CONCEPTION AND CONTRACEPTION** Caution — provide contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration).

- **BREAST FEEDING** Suppresses lactation; avoid breast feeding for about 5 days if lactation prevention fails.

- **HEPATIC IMPAIRMENT** Dose reduction may be necessary.

- **MONITORING REQUIREMENTS**
- Specialist evaluation—monitor for pituitary enlargement, particularly during pregnancy; monitor visual field to detect secondary field loss in macroprolactinoma.
- Monitor for fibrotic disease.
- Monitor blood pressure for a few days after starting treatment and following dosage increase.

- **TREATMENT CESSATION** Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

- **PATIENT AND CARER ADVICE**

  **Driving and skilled tasks**
  Sudden onset of sleep · Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

  Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have
experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 10, 21**

- **Bromocriptine** (as Bromocriptine mesilate) 1 mg Bromocriptine 1mg tablets | 100 tablet | price = £76.62
- **Bromocriptine** (as Bromocriptine mesilate) 2.5 mg Bromocriptine 2.5mg tablets | 30 tablet | price = £74.89

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 10, 21**

- **Parlodol** (Meda Pharmaceuticals Ltd) Bromocriptine (as Bromocriptine mesilate) 5 mg Parlodol 5mg capsules | 100 capsule | price = £37.57

**INDICATIONS AND DOSE**

**Prevention of lactation**

- **BY MOUTH**
- Adult: 1 mg, to be taken as a single dose on the first day postpartum

**Suppression of established lactation**

- **BY MOUTH**
- Adult: 250 micrograms every 12 hours for 2 days

**Hyperprolactinaemic disorders**

- **BY MOUTH**
- Adult: Initially 500 micrograms once weekly, dose may be taken as a single dose or as 2 divided doses on separate days, then increased in steps of 500 micrograms every month until optimal therapeutic response reached, increase dose following monthly monitoring of serum prolactin levels; usual dose 0.25–2 mg once weekly, usually 1 mg weekly; reduce initial dose and increase more gradually if patient intolerant, doses over 1 mg weekly to be given as divided dose; maximum 4.5 mg per week

**Alone or as adjunct to co-beneldopa or co-careldopa in Parkinson’s disease where dopamine-receptor agonists other than ergot derivative not appropriate**

- **BY MOUTH**
- Adult: Initially 1 mg daily, then increased in steps of 0.5–1 mg every 7–14 days, concurrent dose of levodopa may be decreased gradually while dose of cabergoline is increased; maximum 3 mg per day

**Cabergoline**

**DRUG ACTION** Cabergoline is a stimulant of dopamine receptors in the brain and it also inhibits release of prolactin by the pituitary.

**INDICATIONS AND DOSE**

**FIBROTIC REACTIONS**

Cabergoline has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions.

Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson’s disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

**IMPULSE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists are associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

**CONTRA-INDICATIONS** Avoid in pre-eclampsia · cardiac valvulopathy (exclude before treatment) · history of pericardial fibrotic disorders · history of puerperal psychosis · history of pulmonary fibrotic disorders · history of retroperitoneal fibrotic disorders

**CAUTIONS** Acute porphyrias p. 930 · cardiovascular disease · history of peptic ulcer (particularly in acromegalic patients) · history of serious mental disorders (especially psychotic disorders) · Raynaud’s syndrome

**CAUTIONS, FURTHER INFORMATION**

Hyperprolactinaemic patients in hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

**INTERACTIONS** → Appendix 1 (cabergoline). Tolerance may be reduced by alcohol.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · angina · breast pain · confusion · constipation · depression · dyspepsia · epigastric pain · gastritis · hallucinations · headache · nausea · syncope
- **Rare** Digital vasospasm · epistaxis · hot flushes · muscle weakness · palpitation · paraesthesia · transient hemianopia · vomiting
- **Frequency not known** Allergic skin reactions · alopecia · cardiac valvulopathy · constictive pericarditis · drowsiness · dyskinesia · erythroamelalgia · hypersexuality · hypotension · increased libido · leg cramps · pathological gambling · pericardial effusion · peripheral oedema · pleural effusion · pleural fibrosis · pleuritis · pulmonary fibrosis · retroperitoneal fibrosis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Gastro-intestinal bleeding Treatment should be withdrawn if gastro-intestinal bleeding occurs.

**ALLERGY AND CROSS-SENSITIVITY** Cabergoline should not be used in patients with hypersensitivity to ergot alkaloids.
CONCEPTION AND CONTRACEPTION  Exclude pregnancy before starting and perform monthly pregnancy tests during the amenorrhoeic period. Caution—advise non-hormonal contraception if pregnancy not desired. Discontinue 1 month before intended conception (ovulatory cycles persist for 6 months).

PREGNANCY  Discontinue if pregnancy occurs during treatment (specialist advice needed).

BREAST FEEDING  Suppresses lactation; avoid breast-feeding if lactation prevention fails.

HEPATIC IMPAIRMENT  Reduce dose in severe hepatic impairment.

MONITORING REQUIREMENTS

Monitor for

- MONITORING REQUIREMENTS

TREATMENT CESSATION  Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PRESCRIBING AND DISPENSING INFORMATION  Dispense in original container (contains desiccant).

PATIENT AND CARER ADVICE

Driving and skilled tasks

Sudden onset of sleep  Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions  Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10, 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabergoline (Non-proprietary)</td>
<td></td>
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<tr>
<td>Cabergoline 1 mg</td>
<td>Cabergoline 1mg tablets</td>
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<td>Cabergoline 2 mg</td>
<td>Cabergoline 2mg tablets</td>
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<td>Dostinex (Pfizer Ltd)</td>
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<tr>
<td>Dostinex 500 microgram</td>
<td>Dostinex 500microgram tablets</td>
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</tbody>
</table>

**INDICATIONS AND DOSE**

Monotherapy in Parkinson’s disease where dopamine-receptor agonists other than ergot derivative not appropriate

BY MOUTH

Adult: Initially 50 micrograms once daily for day 1, dose to be taken at bedtime, then 50 micrograms twice daily for days 2–4, then increased in steps of 100–250 micrograms daily, dose to be increased at intervals of 3–4 days, increased to 1.5 mg daily in 3 divided doses at day 28, then increased in steps of up to 250 micrograms every 3–4 days, this increase to be started after day 30; maintenance 2.1–2.5 mg daily; maximum 3 mg per day

Adjunctive therapy with co-beneldopa or co-careldopa in Parkinson’s disease where dopamine-receptor agonists other than ergot derivative not appropriate

BY MOUTH

Adult: Initially 50 micrograms daily for 2 days, then increased in steps of 100–150 micrograms every 3 days, dose to be adjusted over next 12 days following initial dose and usually given in 3 divided doses, then increased in steps of 250 micrograms every 3 days, during pergolide titration, levodopa dose may be reduced cautiously; maximum 3 mg per day

**IMPORTANT SAFETY INFORMATION**

**FIBROTIC REACTIONS**

Pergolide has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with pergolide; it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking pergolide should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

**IMPULSE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.

**CONTRA-INDICATIONS**

Cardiac valvulopathy (exclude before treatment) - history of fibrotic disorders

**CAUTIONS**

Acute porphyrias p. 930 - arrhythmias - dyskinesia (may exacerbate) - hallucinations - history of confusion - psychosis - underlying cardiac disease

**INTERACTIONS**  Appendix 1 (pergolide).

**SIDE-EFFECTS**  Abdominal pain - atrial premature contractions - compulsive behaviour - confusion - constipation - diarrhoea - diplopia - dizziness - drowsiness - dyskinesia - dyspepsia - dysphoria - erythromelalgia - fever - hallucinations - hiccup - hypotension - insomnia - nausea -
palpitation · rash · Raynaud’s phenomenon · rhinitis · sudden onset of sleep · syncope · tachycardia · vomiting

- **PREGNANCY** Use only if potential benefit outweighs risk.
- **BREAST FEEDING** May suppress lactation.
- **TREATMENT CESSATION** Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

- **PATIENT AND CARER ADVICE**

  **Driving and skilled tasks**

  Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

  Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

  Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

  **Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  **CAUTIONARY AND ADVISORY LABELS**

  10

  ▶ **Pergolide (Non-proprietary)**

  | Pergolide (as Pergolide mesilate) | mg | Pergolide 1mg tablets | 100 tablet (PO) | £12.50–£135.00 DT price = £31.16

  | Pergolide (as Pergolide mesilate) | 50 microgram | Pergolide | 50 microgram tablets | 100 tablet (PO) | £32.02 DT price = £32.01

  | Pergolide (as Pergolide mesilate) | 250 microgram | Pergolide | 250 microgram tablets | 100 tablet (PO) | £36.00–£39.00 DT price = £38.00

### Pramipexole

- **INDICATIONS AND DOSE**

  **Parkinson’s disease, used alone or as an adjunct to cobeneldopa or co-careldopa**

  ▶ **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

  - **Adult:** Initially 88 micrograms 3 times a day, if tolerated dose to be increased by doubling dose every 5–7 days, increased to 350 micrograms 3 times a day, then increased in steps of 180 micrograms 3 times a day if required, dose to be increased at weekly intervals, during dose titration and maintenance, levodopa dose may be reduced, maximum daily dose to be given in 3 divided doses; maximum 3.3 mg per day

  ▶ **BY MOUTH USING MODIFIED-RELEASE MEDICINES**

  - **Adult:** Initially 260 micrograms once daily, dose to be increased by doubling dose every 5–7 days, increased to 1.05 mg once daily, then increased in steps of 520 micrograms every week if required, during dose titration and maintenance, levodopa dose may be reduced according to response; maximum 3.15 mg per day

  **Moderate to severe restless legs syndrome**

  ▶ **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

  - **Adult:** Initially 88 micrograms once daily, dose to be taken 2–3 hours before bedtime, dose to be increased by doubling dose every 4–7 days if necessary, repeat dose titration if restarting treatment after an interval of more than a few days; maximum 540 micrograms per day

  **DOSE EQUIVALENCE AND CONVERSION**

  ▶ Doses and strengths are stated in terms of pramipexole (base).

  ▶ Equivalent strengths of pramipexole (base) in terms of pramipexole dihydrochloride monohydrate (salt) for immediate-release preparations are as follows:

    - 88 micrograms base = 125 micrograms salt
    - 180 micrograms base = 250 micrograms salt
    - 350 micrograms base = 500 micrograms salt
    - 700 micrograms base = 1 mg salt.

  ▶ Equivalent strengths of pramipexole (base) in terms of pramipexole dihydrochloride monohydrate (salt) for modified-release preparations are as follows:

    - 260 micrograms base = 375 micrograms salt
    - 520 micrograms base = 750 micrograms salt
    - 1.05 mg base = 1.5 mg salt
    - 1.57 mg base = 2.25 mg salt
    - 2.1 mg base = 3 mg salt
    - 2.62 mg base = 3.75 mg salt
    - 3.15 mg base = 4.5 mg salt.

### IMPORTANT SAFETY INFORMATION

**IMPULSE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine–receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

- **CAUTIONS** Psychotic disorders · risk of visual disorders (ophthalmological testing recommended) · severe cardiovascular disease

- **INTERACTIONS** → Appendix 1 (pramipexole).

- **SIDE-EFFECTS**

  ▶ **Common or very common** Confusion · constipation · decreased appetite · dizziness · drowsiness · dyskinesia · hallucinations · headache · hyperkinesia · hypotension · nausea · peripheral oedema · postural hypotension · restless sleep disturbances · sudden onset of sleep · visual disturbances · vomiting · weight changes

  ▶ **Uncommon** Amnesia · binge eating · cardiac failure · compulsive behaviour · delusion · dysphoria · hiccup · paranoia · pneumonia · pruritus · rash · syncope

  ▶ **Frequency not known** Paroxysmal worsening of restless legs syndrome

- **PREGNANCY** Use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING** May suppress lactation; avoid—present in milk in animal studies.

- **RENAL IMPAIRMENT** For immediate-release tablets in Parkinson’s disease, initially 88 micrograms twice daily (max. 1.57 mg daily in 2 divided doses) if eGFR 20–50 mL/minute/1.73 m²; initially 88 micrograms once daily (max. 1.1 mg once daily) if eGFR less than 20 mL/minute/1.73 m². If renal function declines during treatment, reduce dose by the same percentage as the decline in eGFR. For immediate-release tablets in restless legs syndrome, reduce dose if eGFR less than 20 mL/minute/1.73 m². For modified-release tablets, initially 260 micrograms on alternate days if eGFR
Medicinal Forms

- **Mirapexin**
  - **Pramipexole (as Pramipexole dihydrochloride monohydrate)**
  - **Pramipexole** 88 microgram tablets: 30 tablet pack = £8.60 DT price = £1.22
  - **Pramipexole** 180 microgram tablets: 30 tablet pack = £17.19 DT price = £1.89 | 100 tablet pack = £6.30
  - **Pramipexole** 350 microgram tablets: 30 tablet pack = £34.38 DT price = £11.56 | 100 tablet pack = £38.40
  - **Pramipexole** 700 microgram tablets: 30 tablet pack = £76.40 DT price = £2.14 | 100 tablet pack = £254.69
  - **Mirapexin** (Boehringer Ingelheim Ltd)
    - **Pramipexole** 88 microgram tablets: 30 tablet pack = £11.24 DT price = £1.22
    - **Pramipexole** 180 microgram tablets: 30 tablet pack = £18.89 | 100 tablet pack = £74.95
    - **Pramipexole** 350 microgram tablets: 30 tablet pack = £44.97 DT price = £11.56 | 100 tablet pack = £149.90
    - **Pramipexole** 700 microgram tablets: 30 tablet pack = £89.94 DT price = £2.14 | 100 tablet pack = £299.82

- **Oprymea** (Consilient Health Ltd)
  - **Pramipexole** 88 microgram tablets: 30 tablet pack = £3.23 DT price = £1.22
  - **Pramipexole** 180 microgram tablets: 30 tablet pack = £6.09 DT price = £1.89 | 100 tablet pack = £15.46
  - **Pramipexole** 350 microgram tablets: 30 tablet pack = £11.56 | 100 tablet pack = £108.43
  - **Pramipexole** 700 microgram tablets: 30 tablet pack = £18.26 DT price = £2.14 | 100 tablet pack = £117.63

**CAUTIONARY AND ADVISORY LABELS**

Some patients taking dopamine-receptor agonists; these should refrain from driving or operating machinery until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**Hypotensive Reactions**

Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

### Modified-release tablet

**CAUTIONARY AND ADVISORY LABELS**

- **Pramipexole**
  - **Pramipexole (as Pramipexole dihydrochloride monohydrate)**
    - 260 microgram tablets: 30 tablet pack = £30.87–£32.49 DT price = £32.49
    - **Pramipexole** 520 microgram tablets: 30 tablet pack = £61.73–£64.98 DT price = £64.98
    - **Pramipexole** 1.05 mg tablets: 30 tablet pack = £246.91–£259.91 DT price = £259.91
    - **Pramipexole** 1.57 mg tablets: 30 tablet pack = £192.24–£202.36 DT price = £202.36
    - **Pramipexole** 2.62 mg tablets: 30 tablet pack = £320.41–£337.27 DT price = £337.27
    - **Pramipexole** 3.15 mg tablets: 30 tablet pack = £370.38–£389.87 DT price = £389.87

- **Mirapexin** (Boehringer Ingelheim Ltd)
  - **Pramipexole** 2.62 mg tablets: 30 tablet pack = £327.27 DT price = £337.27
  - **Pramipexole** 3.15 mg tablets: 30 tablet pack = £389.87 DT price = £389.87

- **Oprymea** (Consilient Health Ltd)
  - **Pramipexole** 88 microgram tablets: 30 tablet pack = £102.28 DT price = £129.96
  - **Pramipexole** 180 microgram tablets: 30 tablet pack = £159.26 DT price = £182.36
  - **Pramipexole** 350 microgram tablets: 30 tablet pack = £259.91 DT price = £259.91
  - **Pramipexole** 700 microgram tablets: 30 tablet pack = £64.98 DT price = £64.98

- **Oprymea** (Consilient Health Ltd)
  - **Pramipexole** 10.05 mg tablets: 30 tablet pack = £102.28 DT price = £129.96
  - **Pramipexole** 1.57 mg tablets: 30 tablet pack = £202.36 DT price = £202.36
  - **Pramipexole** 2.1 mg tablets: 30 tablet pack = £337.27 DT price = £337.27
  - **Pramipexole** 2.62 mg tablets: 30 tablet pack = £389.87 DT price = £389.87

### Ropinirole

**INDICATIONS AND DOSE**

Parkinson's disease, either used alone or as an adjunct to co-beneldopa or co-careldopa.

- **By mouth using immediate-release medicines**
  - **Adult**: Initially 750 micrograms daily in 3 divided doses, then increased in steps of 750 micrograms daily, dose
to be increased at weekly intervals, increased to 3 mg daily in 3 divided doses, then increased in steps of 1.5–3 mg daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 9–16 mg daily in 3 divided doses, higher doses may be required if used with levodopa, when administered as adjunct to levodopa, concurrent dose of levodopa may be reduced by approx. 20%, daily maximum dose to be given in 3 divided doses; maximum 24 mg per day

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - **Adult:** Initially 2 mg once daily for 1 week, then 4 mg once daily, increased in steps of 2 mg at intervals of at least 1 week, adjusted according to response, increased to up to 8 mg once daily, dose to be increased further if still no response; increased in steps of 2–4 mg at intervals of at least 2 weeks if required; maximum 24 mg per day

**Parkinson's disease in patients transferring from ropinirole immediate-release tablets**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - **Adult:** Initially ropinirole modified-release once daily substituted for total daily dose equivalent of ropinirole immediate-release tablets; if control not maintained after switching, titrate dose, consider slower titration in patients over 75 years, when administered as adjunct to levodopa, concurrent dose of levodopa may gradually be reduced by approx. 30%, if treatment interrupted for 1 day or more, consider re-initiation with immediate-release tablets

**Moderate to severe restless legs syndrome**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult:** Initially 250 micrograms once daily for 2 days, increased if tolerated to 500 micrograms once daily for 5 days, then increased if tolerated to 1 mg once daily for 7 days, then increased in steps of 500 micrograms daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 2 mg once daily, doses to be taken at night, repeat dose titration if restarting after interval of more than a few days; maximum 4 mg per day

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose adjustment may be necessary if smoking started or stopped during treatment.

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**UNLICENSED USE**

Doses in the BNF may differ from those in product literature.

---

**IMPORTANT SAFETY INFORMATION**

**IMPULSE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

**CAUTIONS**

- Elderly • major psychotic disorders • severe cardiovascular disease (risk of hypotension—monitor blood pressure)

**INTERACTIONS**

- Appendix 1 (ropinirole).

**SIDE-EFFECTS**

- **Common or very common**
  - Abdominal pain • confusion • constipation • dizziness • drowsiness • dyskinesia • dyspepsia • fatigue • gastro-oesophageal reflux disease • hallucinations • hypotension • nausea • nervousness • peripheral oedema • sudden onset of sleep • syncope • vomiting

- **Uncommon**
  - Compulsive behaviour • psychosis

- **Very rare**
  - Hepatic disorders

- **Frequency not known**
  - Paradoxical worsening of restless legs syndrome

- **PREGNANCY**
  - Avoid unless potential benefit outweighs risk—toxicity in animal studies.

- **BREAST FEEDING**
  - May suppress lactation—avoid.

- **HEPATIC IMPAIRMENT**
  - Avoid—no information available.

- **RENAL IMPAIRMENT**
  - Avoid if eGFR less than 30 ml/minute/1.73 m².

- **TREATMENT CESSATION**
  - Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

- **PATIENT AND CARER ADVICE**

  **Driving and skilled tasks**

  - Sudden onset of sleep
  - Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

  Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

  - Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or comitant medication. Patients should be counselled on improving sleep behaviour.

- **Hypotensive reactions**

  - Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium has advised (June 2006) that Adartrel™ should be restricted for use in patients with a baseline score of 24 points or more on the International Restless Legs Scale.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

<table>
<thead>
<tr>
<th>Cautionary and Advisory Labels</th>
<th>10, 21</th>
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<tbody>
<tr>
<td>Ropinirole (Non-proprietary)</td>
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<tr>
<td>Ropinirole (as Ropinirole hydrochloride) 5 mg</td>
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<tr>
<td>Ropinirole (as Ropinirole hydrochloride) 5 mg</td>
<td>ReQuip 5mg tablets</td>
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</table>
Rotigotine

**INDICATIONS AND DOSE**

**Monotherapy in Parkinson's disease**

- **Adult:** Initially 2 mg/24 hours, then increased in steps of 2 mg/24 hours every week if required; maximum 8 mg/24 hours per day

**Adjunctive therapy with co-beneldopa or co-careldopa in Parkinson's disease**

- **Adult:** Initially 4 mg/24 hours, then increased in steps of 2 mg/24 hours every week if required; maximum 16 mg/24 hours per day

**Moderate to severe restless legs syndrome**

- **By transdermal application using patches**

  - Adult: Initially 1 mg/24 hours, then increased in steps of 1 mg/24 hours every week if required; maximum 3 mg/24 hours per day

**IMPORTANT SAFETY INFORMATION**

**IMPALE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

**CAUTIONS**

- Avoid exposure of patch to heat - remove patch (aluminium-containing) before magnetic resonance imaging or cardioversion

**INTERACTIONS**

- → Appendix 1 (rotigotine)

**SIDE-EFFECTS**

- **Common or very common** Abnormal behaviour - abnormal thinking - aggression - application site reactions - confusion - constipation - dizziness - drowsiness - dry mouth - dyskinesia - dyspepsia - hallucinations - headache - hiccup - hypertension - malaise - nausea - palpititation - paranoea - peripheral oedema - postural hypotension - pruritus - psychosis - rash - sleep disturbances - sudden onset of sleep - sweating - syncope - vomiting - weight changes

- **Uncommon** Abdominal pain - atrial fibrillation - erectile dysfunction - hypotension - impulse control disorders - visual disturbances

- **Rare** Irritability - obsessive compulsive disorder - seizures - tachycardia

**PREGNANCY**

- Avoid — no information available.

**BREAST FEEDING**

- May suppress lactation; avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

- Caution in severe impairment — no information available.

**MONITORING REQUIREMENTS**

- Ophthalmic testing recommended.

**TREATMENT CESSATION**

- Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

**DIRECTIONS FOR ADMINISTRATION**

- Apply patch to dry, non-irritated skin on torso, thigh, or upper arm, removing after 24 hours and siting replacement patch on a different area (avoid using the same area for 14 days).

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**

- Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

  - Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

  - Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as
depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypnotic reactions Hypnotic reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium (SMC) has advised that Neupro® is accepted for restricted use for the treatment of advanced Parkinson’s disease in combination with levodopa where the transdermal route would facilitate treatment (July 2007).

  The Scottish Medicines Consortium has advised that Neupro® is accepted as monotherapy for the treatment of early-stage idiopathic Parkinson’s disease (June 2007). The Scottish Medicines Consortium has advised (April 2009) that rotigotine (Neupro®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults with a baseline score of 15 points or more on the International Restless Legs Scale.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Transdermal patch**

  **CAUTIONARY AND ADVISORY LABELS 10**

  » Neupro (UCB Pharma Ltd)

  Rotigotine 1 mg per 24 hour Neupro 1mg/24hours transdermal patches | 28 patch | £77.24

  Rotigotine 2 mg per 24 hour Neupro 2mg/24hours transdermal patches | 7 patch | no price available | 28 patch | £81.10

  DT price = £81.10

  Rotigotine 3 mg per 24 hour Neupro 3mg/24hours transdermal patches | 28 patch | £102.35

  Rotigotine 4 mg per 24 hour Neupro 4mg/24hours transdermal patches | 7 patch | no price available | 28 patch | £123.60

  DT price = £123.60

  Rotigotine 6 mg per 24 hour Neupro 6mg/24hours transdermal patches | 7 patch | no price available | 28 patch | £149.93

  DT price = £149.93

  Rotigotine 8 mg per 24 hour Neupro 8mg/24hours transdermal patches | 7 patch | no price available | 28 patch | £149.93

  DT price = £149.93

  **DOPAMINERGIC DRUGS > MONOAMINE-OXIDASE B INHIBITORS**

  **Rasagiline**

  » **DRUG ACTION** Rasagiline is a monoamine-oxidase B inhibitor.

  » **INDICATIONS AND DOSE**

   Parkinson’s disease, used alone or as adjunct to co-beneldopa or co-careldopa to reduce ‘end of dose’ fluctuations

   » BY MOUTH

   Adult: 1 mg daily

  » **INTERACTIONS** → Appendix 1 (rasagiline).

  » **SIDE-EFFECTS**

   » Common or very common Abnormal dreams · angina · anorexia · arthralgia · conjunctivitis · constipation · depression · dry mouth · dyspepsia · flatulence · hallucinations · headache · influenza-like symptoms · leucopenia · rash · rhinitis · skin carcinoma · urinary urgency · vertigo · weight loss

   » Uncommon Cerebrovascular accident · myocardial infarction

  » **PREGNANCY** Use with caution.

  » **BREAST FEEDING** Use with caution—may suppress lactation.

  » **HEPATIC IMPAIRMENT** Use with caution in mild impairment. Avoid in moderate to severe impairment.

  » **TREATMENT CESSATION** Avoid abrupt withdrawal.

  » **MEDICINAL FORMS**

   There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

   **Tablet**

   » Rasagiline (Non-proprietary)

   Rasagiline 1 mg Rasagiline 1mg tablets | 28 tablet | £70.72 DT price = £13.38

   Azilect (Teva UK Ltd)

   Rasagiline 1 mg Azilect 1mg tablets | 28 tablet | £70.72 DT price = £13.38

  **Selegiline hydrochloride**

  » **DRUG ACTION** Selegiline is a monoamine-oxidase-B inhibitor.

  » **INDICATIONS AND DOSE**

   Parkinson’s disease, used alone or as adjunct to co-beneldopa or co-careldopa to reduce ‘end of dose’ deterioration | Symptomatic parkinsonism

   » BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

   Adult: Initially 5 mg once daily for 2–4 weeks, then increased if tolerated to 10 mg daily, dose to be taken in the morning

   » BY MOUTH USING ORAL LYOPHILISATE

   Adult: 1.25 mg once daily, dose to be taken before breakfast

   **DOSE EQUIVALENCE AND CONVERSION**

   1.25-mg oral lyophilisate is equivalent to 10-mg tablet.

   Patients receiving 10 mg conventional selegiline hydrochloride tablets can be switched to oral lyophilisates (Zelapar®) 1.25 mg.

  » **CONTRA-INDICATIONS** Active duodenal ulceration · active gastric ulceration · avoid or use with great caution in postural hypotension (when used in combination with levodopa)

  » **CAUTIONS** Angina · arrhythmias · avoid in acute porphyrias · p. 930 · duodenal ulceration · gastric ulceration · history of hepatic dysfunction · patients predisposed to confusion and psychosis · psychosis · uncontrolled hypertension

  » **INTERACTIONS** → Appendix 1 (selegiline). Avoid with drugs that increase blood pressure.

  » **SIDE-EFFECTS**

   » Common or very common Arthralgia · bradycardia · confusion · constipation · depression · diarrhoea · dizziness · dry mouth · fatigue · hair loss · headache · hypertension · hypotension · impaired balance · mouth ulcers · movement disorders · muscle cramps · myalgia · myopathy · nasal congestion · nausea · psychosis · sleeping disorders · stomatitis · sweating · tremor

   » Uncommon Agitation · angina · ankle oedema · anxiety · arrhythmias · blurred vision · dyspnoea · leucocytopenia · loss of appetite · micturition difficulties · palpitation · postural hypotension · skin reactions · supraventricular tachycardia · thrombocytopenia

   » **Frequency not known** Hypersexuality

   **SIDE-EFFECTS, FURTHER INFORMATION**

   Side-effects of levodopa may be increased—concurrent levodopa dosage can be reduced by 10–30% in steps of 10% every 3–4 days.

  » **PREGNANCY** Avoid—no information available.

  » **BREAST FEEDING** Avoid—no information available.

  » **HEPATIC IMPAIRMENT** Use with caution in severe impairment.
400 Nausea and labyrinth disorders

5 Nausea and labyrinth disorders

Nausea and labyrinth disorders

Drug treatment

Antiemetics should be prescribed only when the cause of vomiting is known because otherwise they may delay diagnosis, particularly in children. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin p. 103 or antiepileptic overdose.

If antiemetic drug treatment is indicated, the drug is chosen according to the aetiology of vomiting.

Antihistamines are effective against nausea and vomiting resulting from many underlying conditions. There is no evidence that any one antihistamine is superior to another. Evidence that any one antihistamine is superior to another is based on many underlying conditions. There is no evidence that any one antihistamine is superior to another.

Other antipsychotic drugs including haloperidol p. 363 and levomepromazine p. 411 are used for the relief of nausea and vomiting in terminal illness.

Metoclopramide hydrochloride p. 403 is an effective antiemetic and its activity closely resembles that of the phenothiazines. Metoclopramide hydrochloride also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease.

Domperidone p. 402 acts at the chemoreceptor trigger zone; it is licensed only for the relief of nausea and vomiting. It has the advantage over metoclopramide hydrochloride and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood-brain barrier. In Parkinson’s disease, it can be used to treat nausea caused by dopaminergic drugs.

Granisetron p. 405 and ondansetron p. 406 are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting. Palonosetron p. 407 is licensed for prevention of nausea and vomiting associated with moderately or highly emetogenic cytotoxic chemotherapy. Palonosetron is also available in combination with netupitant, a neurokinin 1-receptor antagonist, for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy and highly emetogenic cisplatin-based chemotherapy.

Dexamethasone p. 618 has antiemetic effects and it is used in vomiting associated with cancer chemotherapy. It can be used alone or with metoclopramide hydrochloride, prochlorperazine, lorazepam p. 317, or a 5HT3-receptor antagonist.

Aprepitant p. 404 and fosaprepitant p. 404 are neurokinin 1-receptor antagonists licensed for the prevention of acute and delayed nausea and vomiting associated with cisplatin-based cytotoxic chemotherapy; they are given with dexamethasone and a 5HT3-receptor antagonist.

Nabilone p. 402 is a synthetic cannabinoid with antiemetic properties. It may be used for nausea and vomiting caused by cytotoxic chemotherapy that is unresponsive to conventional antiemetics.

Vomiting during pregnancy

Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy. On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as promethazine, may be required. Prochlorperazine or metoclopramide hydrochloride are alternatives. If symptoms do not settle in 24 to 48 hours then specialist opinion should be sought. Hyperemesis gravidarum is a more serious condition, which requires regular antiemetic therapy, intravenous fluid and electrolyte replacement and sometimes nutritional support.

Supplementation with thiamine p. 950 must be considered in order to reduce the risk of Wernicke’s encephalopathy.

Postoperative nausea and vomiting

The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, and the type and duration of surgery. Other risk factors include female sex, non-smokers, a history of postoperative nausea and vomiting or motion sickness, and intraoperative and postoperative use of opioids. Therapy to prevent...
postoperative nausea and vomiting should be based on the assessed risk of postoperative nausea and vomiting in each patient. Drugs used include 5HT3-receptor antagonists, droperidol p. 410, dexamethasone, some phenothiazines (e.g. prochlorperazine), and antihistamines (e.g. cyclizine below). A combination of two or more antiemetic drugs that have different mechanisms of action is often indicated in those at high risk of postoperative nausea and vomiting or where postoperative vomiting presents a particular danger (e.g. in some types of surgery). When a prophylactic antiemetic drug has failed, postoperative nausea and vomiting should be treated with one or more drugs from a different class.

**Motion sickness**

Antiemetics should be given to prevent motion sickness rather than after nausea or vomiting develop. The most effective drug for the prevention of motion sickness is hyoscine hydrobromide p. 409. The sedating antihistamines are slightly less effective against motion sickness, but are generally better tolerated than hyoscine. If a sedative effect is desired promethazine is useful, but generally a slightly less sedating antihistamine such as cyclizine or cinnarizine p. 408 is preferred. Domperidone, metoclopramide hydrochloride, 5HT3-receptor antagonists, and the phenothiazines (except the antihistamine phenothiazine promethazine) are ineffective in motion sickness.

**Other vestibular disorders**

Management of vestibular diseases is aimed at treating the underlying cause as well as treating symptoms of the balance disturbance and associated nausea and vomiting. Vertigo and nausea associated with Ménière’s disease and middle-ear surgery can be difficult to treat.

Betahistine dihydrochloride p. 411 is an analogue of histamine and is claimed to reduce endolymphatic pressure by improving the microcirculation. Betahistine dihydrochloride is licensed for vertigo, tinnitus, and hearing loss associated with Ménière’s disease.

A diuretic alone or combined with salt restriction may provide some benefit in vertigo associated with Ménière’s disease; antihistamines (such as cinnarizine), and phenothiazines (such as prochlorperazine) are also used. Where possible, prochlorperazine should be reserved for the treatment of acute symptoms.

**Cytotoxic chemotherapy, palliative care, and migraine**

Antiemetics have a role in the management of nausea and vomiting induced by cytotoxic chemotherapy, in palliative care, and associated with migraine.

**Other drugs used for Nausea and labyrinth disorders**

Paracetamol with metoclopramide, p. 439. Promethazine hydrochloride, p. 269

**ANTIEMETICS AND ANTI NAUSEANTS**

**ANTIHISTAMINES**

<table>
<thead>
<tr>
<th>Cyclizine</th>
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<tr>
<td><strong>INDICATIONS AND DOSE</strong></td>
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<tr>
<td><strong>Nausea</strong></td>
</tr>
<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>Adult: 50 mg up to 3 times a day, for motion sickness, take 1–2 hours before departure</td>
</tr>
<tr>
<td><strong>BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION</strong></td>
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<tr>
<td>Adult: 50 mg 3 times a day</td>
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</tbody>
</table>

**Nausea and vomiting of known cause**

**Nausea and vomiting associated with vestibular disorders and palliative care**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Child 1 month–5 years: 0.5–1 mg/kg up to 3 times a day (max. per dose 25 mg), intravenous injection to be given over 3–5 minutes, for motion sickness, take 1–2 hours before departure
  - Child 6–11 years: 25 mg up to 3 times a day, intravenous injection to be given over 3–5 minutes, for motion sickness, take 1–2 hours before departure
  - Child 12–17 years: 50 mg up to 3 times a day, intravenous injection to be given over 3–5 minutes, for motion sickness, take 1–2 hours before departure
- **BY CONTINUOUS INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INFUSION**
  - Child 1–23 months: 3 mg/kg, dose to be given over 24 hours
  - Child 2–5 years: 12.5 mg up to 3 times a day
  - Child 6–11 years: 25 mg up to 3 times a day
  - Child 12–17 years: 50 mg up to 3 times a day

**Nausea and vomiting associated with palliative care**

- **BY SUBCUTANEOUS INFUSION**
  - Adult: 150 mg, dose to be given over 24 hours
- **BY MOUTH**
  - Adult: 50 mg up to 3 times a day

**UNLICENSED USE** Tablets not licensed for use in children under 6 years. Injection not licensed for use in children.

**CONTRA-INDICATIONS** Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

**CAUTIONS** Epilepsy - glaucoma (in children) - may counteract haemodynamic benefits of opioids - neuromuscular disorders—increased risk of transient paralysis with intravenous use - prostatic hypertrophy (in adults) - pyloroduodenal obstruction - severe heart failure—may cause fall in cardiac output and associated increase in heart rate, mean arterial pressure and pulmonary wedge pressure - susceptibility to angle-closure glaucoma (in adults) - urinary retention

**INTERACTIONS** → Appendix 1 (antihistamines).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Drowsiness
- **Rare** Anaphylaxis - angioedema - angle-closure glaucoma - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - palpitation - paradoxical stimulation (especially with high doses in children) - paradoxical stimulation (especially with high doses in the elderly) - photosensitivity reactions - rashes - sleep disturbances - tremor
- **Frequency not known** Antimuscarinic effects - blurred vision - dry mouth - gastro-intestinal disturbances - hallucinations - headache - hypertension - movement disorders - oculogyric crisis - paraesthesia - psychomotor impairment - tachycardia - transient speech disorders - twitching - urinary retention

**SPECIFIC SIDE-EFFECTS**

- **Rare**
  - With intravenous use: Transient paralysis
  - Frequency not known
  - With subcutaneous use: Local irritation
SIDE-EFFECTS, FURTHER INFORMATION

Children and the elderly are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

- **PREGNANCY** Manufacturer advises avoid; however, there is no evidence of teratogenicity. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

- **BREAST FEEDING** No information available. Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.

- **DIRECTIONS FOR ADMINISTRATION** For administration by mouth, tablets may be crushed. Mixing and compatibility for the use of syringe drivers in palliative care Cyclizine may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9% or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.

- **PATIENT AND CARER ADVICE**

  **Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g., cycling, driving); effects of alcohol enhanced.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

  **Capsule**

  **CAUTIONARY AND ADVISORY LABELS 2**

  **Nabilone (Non-proprietary)**

  Nabilone 1 mg Nabilone 1mg capsules | 20 capsule | £196.00–

  **DOPAMINE RECEPTOR ANTAGONISTS**

  **Antiemetics and Antinauseants**

  **CANNIBINOIDS**

  **Nabilone**

  - **INDICATIONS AND DOSE**

    **Nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics (preferably in hospital setting) (under close medical supervision)**

    - **BY MOUTH**

      - **Adult:** Initially 1 mg twice daily, increased if necessary to 2 mg twice daily throughout each cycle of cytotoxic therapy and, if necessary, for 48 hours after the last dose of each cycle, the first dose should be taken the night before initiation of cytotoxic treatment and the second dose 1–3 hours before the first dose of cytotoxic drug, daily dose maximum should be given in 3 divided doses; maximum 6 mg per day

    - **CAUTIONS** Adverse effects on mental state can persist for 48–72 hours after stopping • elderly • heart disease • history of psychiatric disorder • hypertension

  - **SIDE-EFFECTS**

    - **Common or very common** Ataxia • concentration difficulties • drowsiness • dry mouth • dysphoria • euphoria • headache • hypotension • nausea • sleep disturbance • vertigo • visual disturbance

    - **Frequency not known** Abdominal pain • confusion • decreased appetite • decreased coordination • depression • disorientation • hallucinations • psychosis • tachycardia • tremors

- **SIDE-EFFECTS, FURTHER INFORMATION**

  Drowsiness and dizziness occur frequently with standard doses.

  - **PREGNANCY** Avoid unless essential.

  - **BREAST FEEDING** Avoid—no information available.

  - **HEPATIC IMPAIRMENT** Avoid in severe impairment.

  - **PATIENT AND CARER ADVICE**

    **Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g., driving). Effects of alcohol enhanced.

    For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including nabilone, see Drugs and driving under Guidance on prescribing p. 1. Behavioural effects Patients should be made aware of possible changes of mood and other adverse behavioural effects.

  - **MEDICINAL FORMS**

    There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule
● Domperidone is contra-indicated for use in conditions where cardiac conduction is, or could be, impaired, or where there is underlying cardiac disease, when administered concomitantly with drugs that prolong the QT interval or potent CYP3A4 inhibitors, and in severe hepatic impairment;

● The recommended dose in adults and adolescents over 12 years and over 35 kg is 10 mg up to 3 times daily;

● The recommended dose in children under 35 kg is 250 micrograms/kg up to 3 times daily;

● Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy. This advice does not apply to unlicensed uses of domperidone (e.g. palliative care).

● CONTRA-INDICATIONS Cardiac disease - conditions where cardiac conduction is, or could be, impaired (in adults) - gastro-intestinal haemorrhage (in children) - if increased gastrointestinal motility harmful (in adults) - mechanical obstruction (in children) - mechanical perforation (in children) - predisposition to cardiac conduction disorders (in children) - prolactinoma

● CAUTIONS Children - if there are cardiac concerns, obtain ECG before and during treatment (in children) - patients over 60 years - increased risk of ventricular arrhythmia (in adults)

● INTERACTIONS ▶ Appendix 1 (domperidone). Contra-indicated with concomitant use of drugs that prolong the QT interval. Contra-indicated with concomitant use of potent CYP3A4 inhibitors.

● SIDE-EFFECTS

▶ Common or very common Drowsiness - dry mouth - malaise

▶ Uncommon Anxiety - breast pain - decreased libido - diarrhoea - galactorrhoea - headache - pruritus - rash

▶ Frequency not known Agitation - amenorrhoea - convulsions - extrapyramidal disorders - gynaecomastia - nervousness - oculogyric crisis - QT-interval prolongation - sudden cardiac death - urinary retention - ventricular arrhythmias

● PREGNANCY Use only if potential benefit outweighs risk.

● BREAST FEEDING Amount too small to be harmful.

● HEPATIC IMPAIRMENT Avoid in moderate or severe impairment.

● RENAL IMPAIRMENT Reduce frequency.

● PRESCRIBING AND DISPENSING INFORMATION Palliative care For further information on the use of domperidone in palliative care, see www.palliativedrugs.com/formulary/en/domperidone.html.

● PATIENT AND CARER ADVICE Arrhythmia Patients and their carers should be told how to recognise signs of arrhythmia and advised to seek medical attention if symptoms such as palpitation or syncpe develop.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

| CAUTIONARY AND ADVISORY LABELS 22 |
| Domperidone (non-proprietary) ▼ |
| Domperidone (as Domperidone maleate) 10 mg Domperidone 10mg tablets | 30 tablet (PoS) £2.71 DT price = £9.87 | 100 tablet (PoS) £9.04 DT price = £29.90 |
| Motilium (Zentiva) ▼ |
| Domperidone (as Domperidone maleate) 10 mg Motilium 10mg tablets | 30 tablet (PoS) £2.71 DT price = £9.87 | 100 tablet (PoS) £9.04 DT price = £29.90 |

## Metoclopramide hydrochloride 21-Nov-2016

● INDICATIONS AND DOSE
Symptomatic treatment of nausea and vomiting including that associated with acute migraine | Delayed (but not acute) chemotherapy-induced nausea and vomiting | Radiotherapy-induced nausea and vomiting | Prevention of postoperative nausea and vomiting

▶ BY MOUTH, OR BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION

Adult (body-weight up to 60 kg): Up to 500 micrograms/kg daily in 3 divided doses, when administered by slow intravenous injection, to be given over at least 3 minutes

Adult (body-weight 60 kg and above): 10 mg up to 3 times a day, when administered by slow intravenous injection, to be given over at least 3 minutes

Hiccups in palliative care

▶ BY MOUTH, OR BY INTRAMUSCULAR INJECTION, OR BY SUBCUTANEOUS INJECTION

Adult: 10 mg every 6–8 hours

Nausea and vomiting in palliative care

▶ BY MOUTH

Adult: 10 mg 3 times a day

▶ BY SUBCUTANEOUS INFUSION

Adult: 30–100 mg/24 hours

## IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE—METOCLOPRAMIDE: RISK OF NEUROLOGICAL ADVERSE EFFECTS—RESTRICTED DOSE AND DURATION OF USE (AUGUST 2013)
The benefits and risks of metoclopramide have been reviewed by the European Medicines Agency’s Committee on Medicinal Products for Human Use, which concluded that the risk of neurological effects such as extrapyramidal disorders and tardive dyskinesia outweigh the benefits in long-term or high-dose treatment. To help minimise the risk of potentially serious neurological adverse effects, the following restrictions to indications, dose, and duration of use have been made:

● In adults over 18 years, metoclopramide should only be used for prevention of postoperative nausea and vomiting, radiotherapy-induced nausea and vomiting, delayed (but not acute) chemotherapy-induced nausea and vomiting, and symptomatic treatment of nausea and vomiting, including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics);

● Metoclopramide should only be prescribed for short-term use (up to 5 days);

Usual dose is 10 mg, repeated up to 3 times daily; max. daily dose is 500 micrograms/kg;

Intravenous doses should be administered as a slow bolus over at least 3 minutes;

Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy. This advice does not apply to unlicensed uses of metoclopramide (e.g. palliative care).

● CONTRA-INDICATIONS 3–4 days after gastrointestinal surgery · gastro-intestinal haemorrhage · gastro-intestinal obstruction · gastro-intestinal perforation · phaeochromocytoma

## Oral suspension

| CAUTIONARY AND ADVISORY LABELS 22 |
| Domperidone (non-proprietary) ▼ |
| Domperidone 1 mg per 1 ml Domperidone 5mg/5ml oral suspension sugar free sugar-free | 200 ml (PoS) £13.43 DT price = £13.43 |
Nervous system

404 Nausea and labyrinth disorders

**CAUTIONS** Asthma - atopic allergy - bradycardia - cardiac conduction disturbances - children - elderly - epilepsy - may mask underlying disorders such as cerebral irritation - Parkinson’s disease - uncorrected electrolyte imbalance - young adults (15–19 years old)

**INTERACTIONS** → Appendix 1 (metoclopramide).

Caution with concomitant use of other drugs affecting cardiac conduction.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

▶ **Common or very common** Extrapyramidal effects (especially in children and young adults (15–19 years old)) - galactorrhoea - gynaecomastia - hyperprolactinaemia - menstrual changes

▶ Very rare Depression - methaemoglobinaemia (more severe in G6PD deficiency) - neuroleptic malignant syndrome

▶ Frequency not known Anxiety - confusion - diarrhoea - dizziness - drowsiness - dysphoria - hypotension - oedema - pruritus - rash - restlessness - tardive dyskinesia on prolonged administration - tremor - urticaria - visual disturbances

**SPECIFIC SIDE-EFFECTS**

▶ Very rare

▶ With intravenous use Cardiac conduction abnormalities

**SIDE-EFFECTS, FURTHER INFORMATION**

Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine will abort dystonic attacks.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Small amount present in milk; avoid.

**HEPATIC IMPAIRMENT** Reduce dose.

**RENAL IMPAIRMENT** Avoid or use small dose in severe impairment; increased risk of extrapyramidal reactions.

**DIRECTIONS FOR ADMINISTRATION** Oral liquid preparation to be given via a graduated oral dosing syringe.

**PRESCRIBING AND DISPENSING INFORMATION**

Palliative care For further information on the use of metoclopramide hydrochloride in palliative care, see www.palliativemedic.com/formulary/en/metoclopramide.html.

**PATIENT AND CARER ADVICE** Counselling on use of pipette advised with oral solution.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

▶ Metoclopramide hydrochloride (Non-proprietary) Metoclopramide hydrochloride 10 mg Metoclopramide 10mg tablets | 28 tablet [Pcm] £1.23 DT price = £0.74

▶ Maxolon (AMCo) Metoclopramide hydrochloride 10 mg Maxolon 10mg tablets | 84 tablet [Pcm] £5.24

**Oral solution**

▶ Metoclopramide hydrochloride (Non-proprietary) Metoclopramide hydrochloride 1 mg per 1 ml Metoclopramide 5mg/5ml oral solution sugar free sugar-free | 150 ml [Pcm] £19.77 DT price = £13.77

**Solution for injection**

▶ Metoclopramide hydrochloride (Non-proprietary) Metoclopramide hydrochloride 5 mg per 1 ml Metoclopramide 10mg/2ml solution for injection ampoules | 5 ampoule [Pcm] £1.31 | 10 ampoule [Pcm] £3.30 DT price = £3.29

▶ Maxolon (AMCo) Metoclopramide hydrochloride 5 mg per 1 ml Maxolon 10mg/2ml solution for injection ampoules | 12 ampoule [Pcm] £3.21 Maxolon High Dose 100mg/20ml solution for injection ampoules | 10 ampoule [Pcm] £26.68

**COMBINATIONS AVAILABLE** Metoclopramide hydrochloride 10 mg

**ANTIEMETICS AND ANTIAGUSTANTS**

**NEUROKININ RECEPTOR ANTAGONISTS**

**Aprepitant**

**INDICATIONS AND DOSE** Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

▶ BY MOUTH

▶ Adult: Initially 125 mg, dose to be taken 1 hour before chemotherapy, then 80 mg once daily for 2 days, consult product literature for dose of concomitant corticosteroid and 5HT3-antagonist

**SIDE-EFFECTS**

▶ Very rare

▶ With intravenous use Cardiac conduction abnormalities

**SIDE-EFFECTS, FURTHER INFORMATION**

Fosaprepitant is a prodrug of aprepitant.

▶ **Common or very common** Anorexia - asthenia - constipation - diarrhoea - dizziness - dyspepsia - headache - hiccups


▶ **Frequency not known** Dysarthria - dysphoria - insomnia - Stevens-Johnson syndrome - urticaria - visual disturbances

**CONCEPTION AND CONTRACEPTION** Effectiveness of hormonal contraceptives reduced—effective non-hormonal methods of contraception necessary during treatment and for 2 months after stopping aprepitant.

**PREGNANCY** Avoid unless potential benefit outweighs risk—no information available.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Caution in moderate to severe impairment.

**MEDITICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Capsule**

▶ Emend (Merck Sharp & Dohme Ltd) Aprepitant 80 mg Emend 80mg capsules | 2 capsule [Pcm] £31.61 Aprepitant 125 mg Emend 125mg capsules | 1 capsule [Pcm] no price available | 5 capsule [Pcm] £79.03

**Fosaprepitant**

**DRUG ACTION** Fosaprepitant is a prodrug of aprepitant.

**INDICATIONS AND DOSE** Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

▶ BY INTRAVENOUS INFUSION

▶ Adult: 150 mg, dose to be administered over 20–30 minutes and given 30 minutes before chemotherapy on day 1 of cycle only, consult product literature for dose of concomitant corticosteroid and 5HT3-receptor antagonist
Treatment of postoperative nausea and vomiting
▶ BY INTRAVENOUS INJECTION
▶ Adult: 1 mg, dose to be diluted to 5 mL and given over 30 seconds; maximum 3 mg per day

Management of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy
▶ BY MOUTH
▶ Adult: 1–2 mg, to be taken within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses for up to 1 week following treatment, when intravenous route also used, maximum combined total dose 9 mg in 24 hours
▶ BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
▶ Adult: 10–40 micrograms/kg (max. per dose 3 mg), to be given 5 minutes before start of treatment, dose may be repeated if necessary, further maintenance doses must not be given less than 10 minutes apart, for intravenous injection, each 1 mg granisetron diluted to 5 mL and given over not less than 30 seconds, for intravenous infusion, to be given over 5 minutes; maximum 9 mg per day

Antiemetics and Antinauseants (5HT3) Receptor Antagonists

Granisetron

Drug Action
Granisetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

INDICATIONS AND DOSE
Nausea and vomiting induced by cytotoxic chemotherapy for planned duration of 3–5 days where oral antiemetics cannot be used
▶ BY TRANSDERMAL APPLICATION USING PATCHES
▶ Adult: Apply 3.1 mg/24 hours, apply patch to clean, dry, non-irritated, non-hairy skin on upper arm (or abdomen if upper arm cannot be used) 24–48 hours before treatment. Patch may be worn for up to 7 days; remove at least 24 hours after completing chemotherapy

Prevention of postoperative nausea and vomiting
▶ BY INTRAVENOUS INJECTION
▶ Adult: 1 mg, to be administered before induction of anaesthesia, dose to be diluted to 5 mL and given over 30 seconds

Medicinal forms

Granisetron (as Granisetron hydrochloride)

1 mg
Granisetron 1mg tablets | 10 tablet | £51.20
Granisetron 2mg tablets | 5 tablet | £52.39

Kytril (Roche Products Ltd)

Granisetron (as Granisetron hydrochloride) 1 mg | Kytril 1mg tablets | 10 tablet | £52.29
Granisetron (as Granisetron hydrochloride) 2 mg | Kytril 2mg tablets | 5 tablet | £52.39

Solution for injection
Granisetron (as Granisetron hydrochloride) 1 mg per 1ml
Granisetron 3mg/3ml concentrate for solution for injection ampoules | 5 ampoule | £24.00
Granisetron 1mg/1ml concentrate for solution for injection ampoules | 5 ampoule | £8.00

Caution Subacute intestinal obstruction · susceptibility to QT-interval prolongation (including electrolyte disturbances)

INTERACTIONS
▶ Appendix 1 (5HT3-receptor Antagonists). Caution with concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
▶ Common or very common Constipation · diarrhoea · headache · insomnia
▶ Uncommon Extrapyramidal reactions · QT-interval prolongation · rash

SPECIFIC SIDE-EFFECTS
▶ Uncommon
▶ With transdermal use · Application-site reactions
▶ PREGNANCY Manufacturer advises avoid.
▶ BREAST FEEDING Avoid—no information available.

Nervous system

Granisetron (as Granisetron hydrochloride) 1 mg
Granisetron 1mg tablets | 10 tablet | £51.20
Granisetron 2mg tablets | 5 tablet | £52.39

Kytril (Roche Products Ltd)

Granisetron (as Granisetron hydrochloride) 1 mg | Kytril 1mg tablets | 10 tablet | £52.29
Granisetron (as Granisetron hydrochloride) 2 mg | Kytril 2mg tablets | 5 tablet | £52.39

Solution for injection
Granisetron (as Granisetron hydrochloride) 1 mg per 1ml
Granisetron 3mg/3ml concentrate for solution for injection ampoules | 5 ampoule | £24.00
Granisetron 1mg/1ml concentrate for solution for injection ampoules | 5 ampoule | £8.00

Nausea and labyrinth disorders 405

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion
▶ Ivemend (Merck Sharp & Dohme Ltd)
Ivemend 150mg powder for solution for infusion vials | 1 vial | £47.42

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2011) that fosaprepitant (Ivemend®) is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy.

Contra-indications
Acute porphyrias p. 930

Interactions
▶ Appendix 1 (fosaprepitant).

Side-effects

Common or very common Anorexia · asthenia · constipation · diarrhoea · dizziness · dyspepsia · headache · hiccup

Uncommon Abdominal pain · abnormal dreams · acne · anaemia · anxiety · bradycardia · chills · colitis · confusion · conjunctivitis · cough · drowsiness · dry mouth · duodenal ulcer · dysuria · euphoria · flatulence · flushing · haematuria · hyperglycaemia · hypotension · myalgia · neutropenia · oedema · palpitations · pharyngitis · photosensitivity · polyuria · pruritus · rash · sneezing · stomatitis · sweating · taste disturbance · thirst · tinnitus · weight changes

Frequency not known Dysarthria · dysphagia · insomnia · Stevens-Johnson syndrome · urticaria · visual disturbances

Conception and contraception Effectiveness of hormonal contraceptives reduced—effective non-hormonal methods of contraception necessary during treatment and for 2 months after stopping fosaprepitant.

Pregnancy
Avoid unless potential benefit outweighs risk—no information available.

Breast feeding
Avoid—present in milk in animal studies.

Hepatic impairment
Caution in moderate to severe impairment.

Directions for administration
For intravenous infusion (Ivemend®), give interminently in Sodium chloride 0.9%; reconstitute each 150-mg vial with 5 mL Sodium chloride 0.9% gently without shaking to avoid foaming, then dilute in 145 mL infusion fluid; give over 20–30 minutes.

National funding/access decisions

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2011) that fosaprepitant (Ivemend®) is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion
▶ Ivemend (Merck Sharp & Dohme Ltd)
Ivemend 150mg powder for solution for infusion vials | 1 vial | £47.42

Antiemetics and Antinauseants (5HT3) Receptor Antagonists

Granisetron

Drug action
Granisetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

Indications and dose
Nausea and vomiting induced by cytotoxic chemotherapy for planned duration of 3–5 days where oral antiemetics cannot be used
▶ By transdermal application using patches
▶ Adult: Apply 3.1 mg/24 hours, apply patch to clean, dry, non-irritated, non-hairy skin on upper arm (or abdomen if upper arm cannot be used) 24–48 hours before treatment. Patch may be worn for up to 7 days; remove at least 24 hours after completing chemotherapy

Prevention of postoperative nausea and vomiting
▶ By intravenous injection
▶ Adult: 1 mg, to be administered before induction of anaesthesia, dose to be diluted to 5 mL and given over 30 seconds

Caution Subacute intestinal obstruction · susceptibility to QT-interval prolongation (including electrolyte disturbances)

Interactions
▶ Appendix 1 (5HT3-receptor Antagonists). Caution with concomitant use of drugs that prolong QT interval.

Side-effects
General side-effects
▶ Common or very common Constipation · diarrhoea · headache · insomnia
▶ Uncommon Extrapyramidal reactions · QT-interval prolongation · rash

Specific side-effects
▶ Uncommon
▶ With transdermal use · Application-site reactions
▶ Pregnancy Manufacturer advises avoid.
▶ Breast feeding Avoid—no information available.

Hepatic impairment
Manufacturer advises use with caution.

Directions for administration
▶ With intravenous use For intravenous infusion, give interminently in Glucose 5% or Sodium Chloride 0.9%; dilute up to 3 mL in 20–50 mL infusion fluid; give over 5 minutes.

Patient and carer advice
▶ With transdermal use Patients should be advised not to expose the site of the patch to sunlight during use and for 10 days after removal.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Tablet
▶ Granisetron (Non-proprietary)
Granisetron (as Granisetron hydrochloride) 1 mg
Granisetron 1mg tablets | 10 tablet | £51.20
Granisetron 2mg tablets | 5 tablet | £52.39

Kytril (Roche Products Ltd)

Granisetron (as Granisetron hydrochloride) 1 mg
Granisetron 1mg tablets | 10 tablet | £52.29
Granisetron 2mg tablets | 5 tablet | £52.39
**Nervous system**

**Adult:** Initially 8 mg, dose to be taken 1–2 hours before treatment, then 8 mg every 12 hours for up to 5 days

**BY MOUTH**

**Adult:** Initially 16 mg, dose to be taken 1–2 hours before treatment, then 16 mg daily for up to 5 days

**INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**

**Adult:** Initially 8 mg, dose to be administered immediately before treatment, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**INITIALLY BY INTRAMUSCULAR INJECTION, OR BY INTRAVENTRICULAR INJECTION**

**Elderly:** Initially 8 mg, dose to be administered immediately before treatment, intravenous infusion to be given over at least 15 minutes, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**Severely emetogenic chemotherapy (consult product literature for dose of concomitant corticosteroid)**

**BY MOUTH**

**Adult:** 24 mg, dose to be taken 1–2 hours before treatment, then 8 mg every 12 hours for up to 5 days

**BY RECTUM**

**Adult:** 16 mg, dose to be administered 1–2 hours before treatment, then 16 mg daily for up to 5 days

**INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**

**Adult:** Initially 8 mg, dose to be administered immediately before treatment, followed by (by intramuscular injection or by slow intravenous injection) 8 mg every 4 hours if required for 2 doses, alternatively, followed by (by continuous intravenous infusion) 1 mg/hour for up to 24 hours, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**INITIALLY BY INTRAMUSCULAR INJECTION**

**Adult 65–74 years:** Initially 8 mg, to be given immediately before treatment, followed by (by intramuscular injection) 8 mg every 4 hours if required for 2 doses, alternatively, followed by (by continuous intravenous infusion) 1 mg/hour for up to 24 hours, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**INITIALLY BY INTRAVENOUS INFUSION**

**Adult:** Initially 16 mg, immediately before treatment (over at least 15 minutes), followed by (by intramuscular injection or by slow intravenous injection) 8 mg every 4 hours if required for 2 doses, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**Adult 75 years and over:** Initially 8 mg, immediately before treatment (over at least 15 minutes), followed by (by intravenous infusion) 8 mg every 4 hours if required for 2 doses, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**Prevention of postoperative nausea and vomiting**

**INITIALLY BY MOUTH**

**Adult:** 16 mg, dose to be taken 1 hour before anaesthesia, alternatively (by intramuscular injection or by slow intravenous injection) 4 mg, dose to be administered at induction of anaesthesia

**BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**

**Adult:** 4 mg for 1 dose

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Constipation • flushing • headache • injection site-reactions
- **Uncommon** Arrhythmias • bradycardia • chest pain • hiccups • hypotension • movement disorders • seizures

**SPECIFIC SIDE-EFFECTS**

- **Rare**
  - With intravenous use Dizziness • transient visual disturbances
  - With intravenous use Transient blindness
  - Frequency not known
  - With rectal use Rectal irritation

**PREGNANCY** No information available; avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Present in milk in animal studies—avoid.

**HEPATIC IMPAIRMENT** Maximum 8 mg daily in moderate or severe impairment.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion (Zofran®), give continuously or intermittently in Glucose 5% or Glucose 5% with Potassium chloride 0.3% or Sodium chloride 0.9% or Sodium chloride 0.9% with Potassium chloride 0.3% or Mannitol 10% or Ringers solution; for intermittent infusion, dilute the required dose in 50–100 mL of infusion fluid and give over at least 15 minutes
- With oral use Orodispersible films and lyophilisates should be placed on the tongue, allowed to disperse and swallowed

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include strawberry.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer orodispersible films and lyophilisates.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Ondansetron (Non-proprietary)**
  - Ondansetron (as Ondansetron hydrochloride) 4 mg
  - Ondansetron 4 mg tablets | 10 tablet (PO) £25.46 DT price = £1.19 | 30 tablet (PO) £76.38
  - Ondansetron (as Ondansetron hydrochloride) 8 mg
  - Ondansetron 8 mg tablets | 10 tablet (PO) £47.99 DT price = £2.27

**Transdermal patch**

- **Sancuso (Kyowa Kirin Ltd)**
  - Granisetron 3.1 mg per 24 hour Sancuso 3.1 mg/24 hours transdermal patches | 1 patch (PO) £56.00
**Nausea and labyrinth disorders**  407

**Ondansetron**

**Adult:** Palonosetron

**Suppository** Zofran Flexi-amp

**Oral solution** Setofilm

**Ondansetron (Non-proprietary)**

**Oral solution**

- **Ondansetron (Non-proprietary)**
  - 800 microgram per 1 ml Ondansetron 8mg/5ml oral solution sugar-free free sugar-free | 50 ml (PoM) £38.08 DT price = £38.05
  - 800 microgram per 1 ml Zofran 8mg/5ml syrup sugar-free | 50 ml (PoM) £35.97 DT price = £35.97
- **Ondansetron (Non-proprietary)**
  - 2 mg per 1 ml Ondansetron 8mg/4ml solution for injection ampoules | 5 ampoule (PoM) £58.45
  - 2 mg per 1 ml Zofran Flexi-amp 8mg/4ml solution for injection | 5 ampoule (PoM) £59.95
- **Zofran Flexi-amp** (Novartis Pharmaceuticals UK Ltd)
  - 2 mg per 1 ml Ondansetron (as Ondansetron hydrochloride) 8 mg Zofran 8mg tablets | 10 tablet (PoM) £71.94 DT price = £72.27

**Common or very common** Constipation - diarrhoea - dizziness - headache


**Pregnancy**

Avoid—no information available.

**Breast feeding**

Avoid—no information available.

**Driving and skilled tasks** Dizziness or drowsiness may affect performance of skilled tasks (e.g. driving).

**Medicinal forms**

- **Capsule**
  - Alox (Sinclair Is Pharma Plc)
    - Palonosetron (as Palonosetron hydrochloride) 500 microgram Alox 500microgram capsules | 1 capsule (PoM) £55.89
- **Solution for injection**
  - Palonosetron (Non-proprietary)
    - Palonosetron (as Palonosetron hydrochloride) 50 microgram per 1 ml Palonosetron 250micrograms/5ml solution for injection vials | 1 vial (PoM) £55.89
  - Alox (Sinclair Is Pharma Plc)
    - Palonosetron (as Palonosetron hydrochloride) 50 microgram per 1 ml Alox 250micrograms/5ml solution for injection vials | 1 vial (PoM) £55.89

**Palonosetron with netupitant**

The properties listed below are those particular to the combination only. For the properties of the components please consider, palonosetron above.

**Indications and dose**

**Moderately emetogenic chemotherapy**

- **Initially by mouth**
  - Adult: 500 micrograms, dose to be taken 1 hour before treatment, alternatively (by intravenous injection) 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment
- **Severely emetogenic chemotherapy**
  - Adult: 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment

**Side-effects**

- **Common or very common** Fatigue
- **Uncommon** Alopecia - blood disorders - cardiomyopathy - conduction disorder - decreased appetite - urticaria - vertigo
- **Rare** Back pain - blurred vision - conjunctivitis - cystitis - dysphagia - hypoaesthesia - hypokalaemia - non-cardiac chest pain - psychosis (acute) - sleep disorder

**Conception and contraception**

Manufacturer recommends exclude pregnancy before treatment in females of childbearing age; ensure effective contraception during treatment and for one month after treatment.

**Clinical trials**

- **Summary**
  - 375 patients with moderately emetogenic chemotherapy
  - 51 patients with severely emetogenic chemotherapy

**Pharmacological properties**

- **Drug action**
  - Palonosetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

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  - **Severely emetogenic chemotherapy**
    - **By intravenous injection**
      - Adult: 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment

**Side-effects**

- **Common or very common**
  - Fatigue
- **Uncommon**
  - Alopecia - blood disorders - cardiomyopathy - conduction disorder - decreased appetite - urticaria - vertigo
- **Rare**
  - Back pain - blurred vision - conjunctivitis - cystitis - dysphagia - hypoaesthesia - hypokalaemia - non-cardiac chest pain - psychosis (acute) - sleep disorder

**Conception and contraception**

Manufacturer recommends exclude pregnancy before treatment in females of childbearing age; ensure effective contraception during treatment and for one month after treatment.
Nervous system

**SIDE-EFFECTS, FURTHER INFORMATION**
Children and the elderly are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**PREGNANCY** Manufacturer advises avoid; however, there is no evidence of teratogenicity. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.

**RENA L IMPAIRMENT** Use with caution—no information available.

**PATIENT AND CARER ADVICE**

- **Driving and skilled tasks**
  - Drowsiness may affect performance of skilled tasks (e.g. cycling, driving); sedating effects enhanced by alcohol.

**MEDICINAL FORMS**

| BNF 73 |
| Nausea and labyrinth disorders |

**Antihistamines**

### Cinnarizine

**INDICATIONS AND DOSE**
Relief of symptoms of vestibular disorders, such as vertigo, tinnitus, nausea, and vomiting in Ménière’s disease

- **BY MOUTH**
  - Child 5–11 years: 15 mg 3 times a day
  - Child 12–17 years: 30 mg 3 times a day
  - Adult: 30 mg 3 times a day

**Motion sickness**

- **BY MOUTH**
  - Child 5–11 years: Initially 15 mg, dose to be taken 2 hours before travel, then 7.5 mg every 8 hours if required, dose to be taken during journey
  - Child 12–17 years: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey
  - Adult: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey

**CONTRA-INDICATIONS**
Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

**CAUTIONS**
Epilepsy · glaucoma (in children) · Parkinson’s disease (in adults) · prostatic hypertrophy (in adults) · pyloroduodenal obstruction · susceptibility to angle-closure glaucoma (in adults) · urinary retention

**SIDE-EFFECTS**

- **Common or very common**
  - Drowsiness
  - Dry mouth
  - Gastro-intestinal disturbances · headache · psychomotor impairment · urinary retention

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Antimuscarinic effects**
  - Blurred vision · dry mouth · gastro-intestinal disturbances · headache · psychomotor impairment · urinary retention

**Promethazine teoclolate**

**INDICATIONS AND DOSE**

- **NAUSEA | VOMITING | LABYRINTHINE DISORDERS**
  - **BY MOUTH**
    - Child 5–9 years: 12.5–37.5 mg daily
    - Child 10–17 years: 25–75 mg daily; maximum 100 mg per day
    - Adult: 25–75 mg daily; maximum 100 mg per day

**Antihistamines**

- **SEDATING ANTIHISTAMINES**

### Cinnarizine with dimenhydrinate

The properties listed below are those particular to the combination only. For the properties of the components please consider, cinnarizine above.

**INDICATIONS AND DOSE**

- **VERTIGO**
  - **BY MOUTH**
    - Adult: 1 tablet 3 times a day

**MEDICINAL FORMS**

- **Tablet**
  - **Cinnarizine 15 mg**
    - Cinnarizine 15 mg tablets: 84 tablet £15.40
  - **Stugeron**
    - Stugeron 20 mg capsules: 930 tablet £24.00

**Antihistamines**

- **SEDATING ANTIHISTAMINES**

### Cinnarizine

**INDICATIONS AND DOSE**
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**Motion sickness**

- **BY MOUTH**
  - Child 5–11 years: Initially 15 mg, dose to be taken 2 hours before travel, then 7.5 mg every 8 hours if required, dose to be taken during journey
  - Child 12–17 years: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey
  - Adult: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey

**CONTRA-INDICATIONS**
Avoid in acute porphyrias p. 930 (some antihistamines are thought to be safe)

**CAUTIONS**
Epilepsy · glaucoma (in children) · Parkinson’s disease (in adults) · prostatic hypertrophy (in adults) · pyloroduodenal obstruction · susceptibility to angle-closure glaucoma (in adults) · urinary retention

**SIDE-EFFECTS**

- **Common or very common**
  - Drowsiness
### Motion sickness prevention (acts longer than promethazine hydrochloride)

- **BY MOUTH**
  - Child 5–9 years: 12.5 mg once daily, dose to be taken at bedtime on night before travel or 1–2 hours before travel
  - Child 10–17 years: 25 mg once daily, dose to be taken at bedtime on night before travel or 1–2 hours before travel
  - Adult: 25 mg once daily, dose to be taken at bedtime on night before travel or 1–2 hours before travel

### Motion sickness treatment (acts longer than promethazine hydrochloride)

- **BY MOUTH**
  - Child 5–9 years: 12.5 mg, dose to be taken at onset of motion sickness, then 12.5 mg daily for 2 days, dose to be taken at bedtime
  - Child 10–17 years: 25 mg, dose to be taken at onset of motion sickness, then 25 mg once daily for 2 days, dose to be taken at bedtime
  - Adult: 25 mg, dose to be taken at onset of motion sickness, then 25 mg once daily for 2 days, dose to be taken at bedtime

### IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009) OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN**

Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

- **CAUTIONS** Acute porphyrias p. 930 · asthma · bronchiectasis · bronchitis · epilepsy · prostatic hypertrophy (in adults) · pyloroduodenal obstruction · Reye’s syndrome · severe coronary artery disease · susceptibility to angle-closure glaucoma · urinary retention

- **INTERACTIONS** → Appendix 1 (antihistamines).

- **SIDE-EFFECTS**
  - Rare: Anaphylaxis · angioedema · angle-closure glaucoma · arrhythmias · blood disorders · bronchospasm · confusion · convulsions · depression · dizziness · extrapyramidal effects · hypersensitivity reactions · hypotension · liver dysfunction · palpitation · photosensitivity reactions · rashes · sleep disturbances · tremor

- **Frequency not known** Antimuscarinic effects · blurred vision · drowsiness · dry mouth · gastro-intestinal disturbances · headache · injection pain · psychomotor impairment · restlessness · urinary retention

**SIDE-EFFECTS, FURTHER INFORMATION**

Children and the elderly are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.

- **RENAL IMPAIRMENT** Use with caution.

### PATIENT AND CARER ADVICE

**Driving and skilled tasks**

Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- **Avomine** (Manx Healthcare Ltd) Promethazine teoclote 25 mg Avomine 25mg tablets | 10 tablet £1.13 | 28 tablet £3.13 DT price = £3.13

### ANTIMUSCARINICS

#### Hyoscine hydrobromide

**(Scopolamine hydrobromide)**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th>Motion sickness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
<td>Child 4–9 years: 75–150 micrograms, dose to be taken up to 30 minutes before the start of journey, then 75–150 micrograms every 6 hours if required; maximum 450 micrograms per day</td>
</tr>
<tr>
<td></td>
<td>Child 10–17 years: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day</td>
</tr>
<tr>
<td></td>
<td>Adult: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day</td>
</tr>
<tr>
<td></td>
<td><strong>BY TRANSDERMAL APPLICATION</strong></td>
</tr>
<tr>
<td></td>
<td>Child 10–17 years: Apply 1 patch, apply behind ear 5–6 hours before journey, then apply 1 patch after 72 hours if required, remove old patch and site replacement patch behind the other ear</td>
</tr>
<tr>
<td></td>
<td>Adult: Apply 1 patch, apply behind ear 5–6 hours before journey, then apply 1 patch after 72 hours if required, remove old patch and site replacement patch behind the other ear</td>
</tr>
</tbody>
</table>

**Hypersalivation associated with clozapine therapy**

- **BY MOUTH**
  - Adult: 300 micrograms up to 3 times a day; maximum 900 micrograms per day

**Excessive respiratory secretion (in palliative care)**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 400 micrograms every 4 hours as required, hourly use is occasionally necessary, particularly in excessive respiratory secretions
  - **BY CONTINUOUS SUBCUTANEOUS INFUSION**
    - Adult: 1.2–2 mg/24 hours

**Bowel colic in palliative care**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 400 micrograms every 4 hours as required, hourly use is occasionally necessary
  - **BY SUBCUTANEOUS INFUSION**
    - Adult: 1.2–2 mg/24 hours

**Bowel colic pain in palliative care**

- **BY MOUTH USING SUBLINGUAL TABLETS**
  - Adult: 300 micrograms 3 times a day, as Kwells®

**Premedication**

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 200–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia
Hyoscine hydrobromide 600 microgram per 1 ml
Hyoscine hydrobromide 600 micrograms/1ml solution for injection ampoules
10 ampoule (P) £56.50 DT price = £53.93

Transdermal patch

SCOPODERM (Novartis Consumer Health UK Ltd)
Hyoscine 1 mg per 72 hour Scopoderm 1.5mg patches
2 patch (P) £4.52 DT price = £4.52

ANTIPSYCHOTICS > FIRST-GENERATION

**Droperidol**

**DRUG ACTION** Droperidol is a butyrophenone, structurally related to haloperidol, which blocks dopamine receptors in the chemoreceptor trigger zone.

**INDICATIONS AND DOSE**
Prevention and treatment of postoperative nausea and vomiting

- **BY INTRAVENOUS INJECTION**
  - Adult: 0.625–1.25 mg, dose to be given 30 minutes before end of surgery, then 0.625–1.25 mg every 6 hours as required
  - Elderly: 625 micrograms, dose to be given 30 minutes before end of surgery, then 625 micrograms every 6 hours as required

Prevention of nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia (PCA)

- **BY INTRAVENOUS INJECTION**
  - Adult: 15–50 micrograms of droperidol for every 1 mg of morphine in PCA, reduce dose in elderly; maximum 5 mg per day

**CONTRA-INDICATIONS**
Bradycardia • CNS depression • comatose states • hypokalaemia • hypomagnesaemia • phaeochromocytoma • QT-interval prolongation

**CAUTIONS**
Chronic obstructive pulmonary disease • electrolyte disturbances • history of alcohol abuse • respiratory failure

**INTERACTIONS**
- Appendix 1 (droperidol). Avoid concomitant administration of drugs that prolong QT interval.

**SIDE-EFFECTS**
Anxiety • cardiac arrest • hallucinations • inappropriate antidiuretic hormone secretion

**BREAST FEEDING**
Limited information available—avoid repeated administration.

**HEPATIC IMPAIRMENT**
In postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required.

For nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose.

**RENAL IMPAIRMENT**
In postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required.

For nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose.

**MONITORING REQUIREMENTS**
Continuous pulse oximetry required if risk of ventricular arrhythmia—continue for 30 minutes following administration.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
CAUTIONARY AND ADVISORY LABELS 2

- **Hyoscine hydrobromide (Non-proprietary)**
  - Hyoscine hydrobromide 300 microgram tablets
  - 12 tablet (P) no price available DT price = £1.67

- **Kwells (Bayer Plc)**
  - Hyoscine hydrobromide 150 microgram Kwells Kids 150 microgram tablets
  - 12 tablet (P) £1.67 DT price = £1.67

- **Travel Calm (The Boots Company Plc)**
  - Hyoscine hydrobromide 300 microgram Travel Calm 300 microgram tablets
  - 12 tablet (P) no price available DT price = £1.67

**Chewable tablet**
CAUTIONARY AND ADVISORY LABELS 2, 24

- **Joy-Rides (Forest Laboratories UK Ltd)**
  - Hyoscine hydrobromide 150 microgram chewable tablets sugar-free
  - 12 tablet (P) £1.55

**Solution for injection**

- **Hyoscine hydrobromide (Non-proprietary)**
  - Hyoscine hydrobromide 400 microgram per 1 ml
  - Hyoscine hydrobromide 400 micrograms/1ml solution for injection ampoules
  - 10 ampoule (P) £25.00-£48.50 DT price = £47.21

**CAUTIONS**
Epilepsy

**ANTIPSYCHOTICS > FIRST-GENERATION**

**Droperidol**

**DRUG ACTION**

**INDICATIONS AND DOSE**

**CONTRA-INDICATIONS**

**CAUTIONS**

**INTERACTIONS**

**SIDE-EFFECTS**

**BREAST FEEDING**

**HEPATIC IMPAIRMENT**

**RENAL IMPAIRMENT**

**MONITORING REQUIREMENTS**

**MEDICINAL FORMS**

**IMMEDIATE SAFETY INFORMATION**

**PRESCRIBING AND DISPENSING INFORMATION**

**With systemic use**
Anticholinergic syndrome

**With transdermal use in children**

**RENAL IMPAIRMENT**
Use with caution.

**BREAST FEEDING**
Amount too small to be harmful.

**PREGNANCY**
Use only if potential benefit outweighs risk. Injection may depress neonatal respiration.

**HEPATIC IMPAIRMENT**
Use with caution.

**DIRECTIONS FOR ADMINISTRATION**
With transdermal use in children. Patch applied to hairless area of skin behind ear; if less than whole patch required either cut with scissors along full thickness ensuring membrane is not peeled away or cover portion to prevent contact with skin.

With oral use in children. For administration by mouth, injection solution may be given orally.

**PRESCRIBING AND DISPENSING INFORMATION**
Flavours of chewable tablet formulations may include raspberry.

**Palliative care**
For further information on the use of hyoscine hydrobromide in palliative care, see www.palliativedrugs.com/formulary/en/hyoscine-hydrobromide.html.

**PATIENT AND CARER ADVICE**
With transdermal use. Explain accompanying instructions to patient and in particular emphasis to wash hands after handling and to wash application site after removing, and to use one patch at a time.

Driving and skilled tasks
Drowsiness may persist for up to 24 hours or longer after removal of patch; effects of alcohol enhanced.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
CAUTIONARY AND ADVISORY LABELS 2

- **Hyoscine hydrobromide (Non-proprietary)**
  - Hyoscine hydrobromide 300 microgram tablets
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- **Kwells (Bayer Plc)**
  - Hyoscine hydrobromide 150 microgram Kwells Kids 150 microgram tablets
  - 12 tablet (P) £1.67 DT price = £1.67

- **Travel Calm (The Boots Company Plc)**
  - Hyoscine hydrobromide 300 microgram Travel Calm 300 microgram tablets
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**Solution for injection**

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**CAUTIONS**
Epilepsy

**ANTIPSYCHOTICS > FIRST-GENERATION**

**Droperidol**

**DRUG ACTION**

**INDICATIONS AND DOSE**

**CONTRA-INDICATIONS**

**CAUTIONS**

**INTERACTIONS**

**SIDE-EFFECTS**

**BREAST FEEDING**

**HEPATIC IMPAIRMENT**

**RENAL IMPAIRMENT**

**MONITORING REQUIREMENTS**

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Xomolix (Kyowa Kirin Ltd)**
  - Droperidol 2.5 mg per 1 ml
  - Xomolix 2.5mg/1ml solution for injection ampoules
  - 10 ampoule (P) £39.40

**IMMEDIATE SAFETY INFORMATION**

**PRESCRIBING AND DISPENSING INFORMATION**

**With systemic use**
Anticholinergic syndrome

**With transdermal use**

**CAUTIONARY AND ADVISORY LABELS**

**Travel Calm**

**Kwells**

**Tablet**
Levomepromazine
(Methotrimeprazine)

12-Dec-2016

● INDICATIONS AND DOSE

Pain in palliative care (reserved for distressed patients with severe pain unresponsive to other measures)
- By continuous subcutaneous infusion, or by intramuscular injection, or by intravenous injection
- Adult: Seek specialist advice

Restlessness and confusion in palliative care
- By continuous subcutaneous infusion
- Child 1–11 years: 0.35–3 mg/kg, to be administered over 24 hours
- Child 12–17 years: 12.5–200 mg, to be administered over 24 hours
- By mouth
- Adult: 6 mg every 2 hours as required
- By subcutaneous infusion
- Adult: 6.25 mg every 2 hours as required
- By subcutaneous infusion
- Adult: Initially 12.5–50 mg/24 hours, titrated according to response (doses greater than 100 mg/24 hours should be given under specialist supervision)

Nausea and vomiting in palliative care
- By continuous intravenous infusion, or by subcutaneous infusion
- Child 1 month–11 years: 100–400 micrograms/kg, to be administered over 24 hours
- Child 12–17 years: 5–25 mg, to be administered over 24 hours
- By mouth
- Adult: 6 mg once daily, dose to be taken at bedtime, increased if necessary to 12.5–25 mg twice daily
- By subcutaneous injection
- Adult: 6.25 mg once daily, dose to be given at bedtime, increased if necessary to 12.5–25 mg twice daily
- By subcutaneous infusion
- Adult: 5–25 mg/24 hours, sedation can limit the dose

Schizophrenia (bed patients)
- By mouth
- Adult: Initially 100–200 mg daily in 3 divided doses, increased if necessary to 1 g daily

Schizophrenia
- By mouth
- Adult: Initially 25–50 mg daily in divided doses, dose can be increased as necessary

● CONTRA-INDICATIONS

- CNS depression • comatose states • phaeochromocytoma

- CAUTIONS

- Diabetes • patients receiving large initial doses should remain supine

- CAUTIONS, FURTHER INFORMATION

- In adults: Risk of postural hypotension; not recommended for ambulant patients over 50 years unless risk of hypotensive reaction assessed.

- SIDE-EFFECTS

- Raised erythrocyte sedimentation rate

- HEPATIC IMPAIRMENT

- Can precipitate coma; phenothiazines are hepatotoxic.

- RENAL IMPAIRMENT

- Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- DIRECTIONS FOR ADMINISTRATION

- With subcutaneous use in children: For administration by subcutaneous infusion dilute with a suitable volume of Sodium Chloride 0.9%.

● PRESCRIBING AND DISPENSING INFORMATION

Palliative care
For further information on the use of levomepromazine in palliative care, see www.palliativedrugs.com/formulary/en/levomepromazine.html.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

| CAUTIONARY AND ADVISORY LABELS | 2 |
| Levomepromazine (Non-proprietary) |
| Levomepromazine maleate 100 mg | Nozinan 100mg tablets | 100 tablet (£0.04) no price available |
| Nozinan (Sanofi) |
| Levomepromazine maleate 25 mg | Nozinan 25mg tablets | 84 tablet (£0.26 DT price = £0.26) |

Solution for injection

| Levomepromazine (Non-proprietary) |
| Levomepromazine hydrochloride 25 mg per 1 ml | 25mg/1ml solution for injection ampoules | 10 ampoule (£0.13 DT price = £0.13) |
| Nozinan (Sanofi) |
| Levomepromazine hydrochloride 25 mg per 1 ml | Nozinan 25mg/1ml solution for injection ampoules | 10 ampoule (£0.26 DT price = £0.26) |

5.1 Menière’s disease

HISTAMINE ANALOGUES

Betaistine dihydrochloride

● INDICATIONS AND DOSE

Vertigo, tinnitus and hearing loss associated with Ménière’s disease
- By mouth
- Adult: Initially 16 mg 3 times a day, dose preferably taken with food; maintenance 24–48 mg daily

● CONTRA-INDICATIONS

- Phaeochromocytoma

● CAUTIONS

- Asthma • history of peptic ulcer

● INTERACTIONS

- Appendix 1 (betaistine).

● SIDE-EFFECTS

- Gastro-intestinal disturbances • headache • pruritus • rashes

● PREGNANCY

- Avoid unless clearly necessary—no information available.

● BREAST FEEDING

- Use only if potential benefit outweighs risk—no information available.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

| CAUTIONARY AND ADVISORY LABELS | 21 |
| Betaistine dihydrochloride 8 mg | Betaistine 8mg tablets | 84 tablet (£0.13 DT price = £0.13) |
| Betaistine dihydrochloride 16 mg | Betaistine 16mg tablets | 84 tablet (£1.51 DT price = £1.51) |
| Nozinan (Sanofi) |
| Betahistine dihydrochloride 8 mg | Betahistine 8mg tablets | 120 tablet (£0.04) |
| Betahistine dihydrochloride 16 mg | Betahistine 16mg tablets | 84 tablet (£1.51 DT price = £1.51) |
6 Pain

Analgesics

Drugs used for pain
The non-opioid drugs, paracetamol p. 414 and aspirin p. 114 (and other NSAIDs), are particularly suitable for pain in musculoskeletal conditions, whereas the opioid analgesics are more suitable for moderate to severe pain, particularly of visceral origin.

Pain in sickle-cell disease
The pain of mild sickle-cell crises is managed with paracetamol, a NSAID, codeine phosphate p. 421, or dihydrocodeine tartrate p. 423. Severe crises may require the use of morphine p. 429 or diamorphine hydrochloride p. 423; concomitant use of a NSAID may potentiate analgesia and allow lower doses of the opioid to be used. Pethidine hydrochloride p. 434 should be avoided if possible because accumulation of a neurotoxic metabolite can precipitate seizures; the relatively short half-life of pethidine hydrochloride necessitates frequent injections.

Dental and orofacial pain
Analgesics should be used judiciously in dental care as a temporary measure until the cause of the pain has been dealt with.

Dental pain of inflammatory origin, such as that associated with pulpitis, apical infection, localised osteitis or pericoronitis is usually best managed by treating the infection, providing drainage, restorative procedures, and other local measures. Analgesics provide temporary relief of pain (usually for about 1 to 7 days) until the causative factors have been brought under control. In the case of pulpitis, intra-osseous infection or abscess, reliance on analgesics alone is usually inappropriate.

Similarly the pain and discomfort associated with acute problems of the oral mucosa (e.g. acute herpetic gingivostomatitis, erythema multiforme) may be relieved by benzylamine hydrochloride mouthwash or spray p. 1069 until the cause of the mucosal disorder has been dealt with. However, where a patient is febrile, the antipyretic action of paracetamol or ibuprofen p. 999 is often helpful.

The choice of an analgesic for dental purposes should be based on its suitability for the patient. Most dental pain is relieved effectively by non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs that are used for dental pain include ibuprofen, diclofenac sodium p. 993, and aspirin.

Paracetamol has analgesic and antipyretic effects but no anti-inflammatory effect. Opioid analgesics such as dihydrocodeine tartrate act on the central nervous system and are traditionally used for moderate to severe pain. However, opioid analgesics are relatively ineffective in dental pain and their side-effects can be unpleasant. Paracetamol, ibuprofen, or aspirin are adequate for most cases of dental pain and an opioid is rarely required.

Combining a non-opioid with an opioid analgesic can provide greater relief of pain than either analgesic given alone. However, this applies only when an adequate dose of each analgesic is used. Most combination analgesic preparations have not been shown to provide greater relief of pain than an adequate dose of the non-opioid component given alone. Moreover, combination preparations have the disadvantage of an increased number of side-effects.

Any analgesic given before a dental procedure should have a low risk of increasing postoperative bleeding. In the case of pain after the dental procedure, taking an analgesic before the effect of the local anaesthetic has worn off can improve control. Postoperative analgesia with ibuprofen or aspirin is usually continued for about 24 to 72 hours.

Temporomandibular dysfunction can be related to anxiety in some patients who may clench or grind their teeth (bruxism) during the day or night. The muscle spasm (which appears to be the main source of pain) may be treated empirically with an overlay appliance which provides a free sliding occlusion and may also interfere with grinding. In addition, diazepam p. 321, which has muscle relaxant as well as anxiolytic properties, may be helpful but it should only be prescribed on a short-term basis during the acute phase. Analgesics such as aspirin or ibuprofen may also be required.

Dysmenorrhoea
Use of an oral contraceptive prevents the pain of dysmenorrhoea which is generally associated with ovulatory cycles. If treatment is necessary paracetamol or a NSAID will generally provide adequate relief of pain. The vomiting and severe pain associated with dysmenorrhoea in women with endometriosis may call for an antiemetic (in addition to an analgesic). Antispasmodics (such as alverine citrate p. 82) have been advocated for dysmenorrhoea but the antispasmodic action does not generally provide significant relief.

Non-opioid analgesics and compound analgesic preparations
Aspirin is indicated for headache, transient musculoskeletal pain, dysmenorrhoea, and pyrexia. In inflammatory conditions, most physicians prefer anti-inflammatory treatment with another NSAID which may be better tolerated and more convenient for the patient. Aspirin is used increasingly for its antiplatelet properties. Aspirin tablets or dispersible aspirin tablets are adequate for most purposes as they act rapidly.

Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available, but have a slow onset of action and are therefore unsuitable for single-dose analgesic use (though their prolonged action may be useful for night pain).

Aspirin interacts significantly with a number of other drugs and its interaction with warfarin sodium p. 131 is a special hazard.

Paracetamol is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irritant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly. Overdosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days.

Nefopam hydrochloride p. 416 may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics. It causes little or no respiratory depression, but sympathomimetic and antimuscarinic side-effects may be troublesome.

Non-steroidal anti-inflammatory analgesics (NSAIDs) are particularly useful for the treatment of patients with chronic disease accompanied by pain and inflammation. Some of them are also used in the short-term treatment of mild to moderate pain including transient musculoskeletal pain but paracetamol is now often preferred, particularly in the elderly. They are also suitable for the relief of pain in secondary bone tumours, many of which produce lysis of bone and release prostaglandins. Selective inhibitors of cyclo-oxygenase–2 may be used in preference to non-selective NSAIDs for patients at high risk of developing serious gastro-intestinal side-effects. Several NSAIDs are also used for postoperative analgesia.

A non-opioid analgesic administered by intrathecal infusion (ziconotide (Prialt®), available from Eisai) is licensed for the treatment of chronic severe pain; ziconotide can be used by a hospital specialist as an adjunct to opioid analgesics.
Compound analgesic preparations
Compound analgesic preparations that contain a simple analgesic (such as aspirin p. 114 or paracetamol p. 414) with an opioid component reduce the scope for effective titration of the individual components in the management of pain of varying intensity.

Compound analgesic preparations containing paracetamol or aspirin with a low dose of an opioid analgesic (e.g. 8 mg of codeine phosphate p. 421 per compound tablet) are commonly used, but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of overdosage yet may not provide significant additional relief of pain.

A full dose of the opioid component (e.g. 60 mg codeine phosphate) in compound analgesic preparations effectively augments the analgesic activity but is associated with the full range of opioid side-effects including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration.

Important: the elderly are particularly susceptible to opioid side-effects and should receive lower doses.

In general, assessing pain, it is necessary to weigh up carefully whether there is a need for a non-opioid and an opioid analgesic to be taken simultaneously.

Caffeine is a weak stimulant that is often included, in small doses, in analgesic preparations. It is claimed that the addition of caffeine may enhance the analgesic effect, but the alerting effect, mild habit-forming effect and possible provocation of headache may not always be desirable. Moreover, in excessive dosage or on withdrawal caffeine may itself induce headache.

Co-proxamol tablets (dextropropoxyphene in combination with paracetamol) are no longer licensed because of safety concerns, particularly toxicity in overdose. Co-proxamol tablets (unlicensed) may still be prescribed for patients who find it difficult to change, because alternatives are not effective or suitable.

Opioid analgesics
Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is no deterrent in the control of pain in terminal illness. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by a specialist and the patient should be assessed at regular intervals.

Strong opioids
Morphine p. 429 remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of severe pain in palliative care. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations).

Buprenorphine p. 417 has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in patients dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone hydrochloride p. 1214.

Dipipanone hydrochloride used alone is less sedating than morphine but the only preparation available contains an antiemetic and is therefore not suitable for regular regimens in palliative care.

Diamorphine hydrochloride p. 423 (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In palliative care the greater solubility of diamorphine hydrochloride allows effective doses to be injected in smaller volumes and this is important in the emaciated patient.

Allentanil p. 1187, fentanyl p. 424 and remifentanil p. 1188 are used by injection for intra-operative analgesia; fentanyl is available in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

Methadone hydrochloride p. 464 is less sedating than morphine and acts for longer periods. In prolonged use, methadone hydrochloride should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdosage. Methadone hydrochloride may be used instead of morphine in the occasional patient who experiences excitation (or exacerbation of pain) with morphine.

Oxycodone hydrochloride p. 431 has an efficacy and side-effect profile similar to that of morphine. It is used primarily for control of pain in palliative care.

Papaveretum p. 434 is rarely used; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pentazocine p. 434 has both agonist and antagonist properties and precipitates withdrawal symptoms, including pain in patients dependent on other opioids. By injection it is more potent than dihydrocodeine tartrate p. 423 or codeine phosphate, but hallucinations and thought disturbances may occur. It is not recommended and, in particular, should be avoided after myocardial infarction as it may increase pulmonary and aortic blood pressure as well as cardiac work.

Pethidine hydrochloride p. 434 produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesia in labour; however, other opioids, such as morphine or diamorphine hydrochloride, are often preferred for obstetric pain.

Tapentadol p. 435 produces analgesia by two mechanisms. It is an opioid-receptor agonist and it also inhibits noradrenaline reuptake. Nausea, vomiting, and constipation are less likely to occur with tapentadol than with other strong opioid analgesics.

Tramadol hydrochloride p. 435 produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

Weak opioids
Codeine phosphate can be used for the relief of mild to moderate pain where other painkillers such as paracetamol or ibuprofen p. 999 have proved ineffective.

Dihydrocodeine tartrate has an analgesic efficacy similar to that of codeine phosphate. Higher doses may provide some additional pain relief but this may be at the cost of more nausea and vomiting.

Meptazinol p. 428 is claimed to have a low incidence of respiratory depression. It has a reported length of action of 2 to 7 hours with onset within 15 minutes.

Postoperative analgesia
A combination of opioid and non-opioid analgesics is used to treat postoperative pain. The use of intra-operative opioids affects the prescribing of postoperative analgesics. A postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression.

Morphine is used most widely. Tramadol hydrochloride is not as effective in severe pain as other opioid analgesics. Buprenorphine may antagonise the analgesic effect of previously administered opioids and is generally not
recommended. Pethidine hydrochloride is generally not recommended for postoperative pain because it is metabolised to norpethidine which may accumulate, particularly in renal impairment; norpethidine stimulates the central nervous system and may cause convulsions.

Opioids are also given epidurally [unlicensed route] in the postoperative period but are associated with side-effects such as pruritus, urinary retention, nausea and vomiting; respiratory depression can be delayed, particularly with codeine or morphine p. 429.

Patient-controlled analgesia (PCA) can be used to relieve postoperative pain—consult individual hospital protocols.

Pain management and opioid dependence

Although caution is necessary, patients who are dependent on opioids or have a history of drug dependence may be treated with opioid analgesics when there is a clinical need. Treatment with opioid analogesics in this patient group should normally be carried out with the advice of specialists. However, doctors do not require a special licence to prescribe opioid analogesics to patients with opioid dependence for relief of pain due to organic disease or injury.

Other drugs used for Pain

- Diclofenac potassium, p. 992
- Fenoprofen, p. 997
- Levomepromazine, p. 411
- Mefenamic acid, p. 1004

**ANALGESICS**  
**NON-OPIOID**

### Paracetamol

(Paracetamol)

#### INDICATIONS AND DOSE

**Mild to moderate pain | Pyrexia**

- **By mouth**
  - Adult: 0.5–1 g every 4–6 hours; maximum 4 g per day
  - By intravenous infusion
  - Adult (body-weight up to 50 kg): 15 mg/kg every 4–6 hours; dose to be administered over 15 minutes; maximum 60 mg/kg per day
  - Adult (body-weight 50 kg and above): 1 g every 4–6 hours; dose to be administered over 15 minutes; maximum 4 g per day
  - By rectum
  - Adult: 0.5–1 g every 4–6 hours; maximum 4 g per day

**Mild to moderate pain in patients with risk factors for hepatotoxicity | Pyrexia in patients with risk factors for hepatotoxicity**

- By intravenous infusion
  - Adult (body-weight up to 50 kg): 15 mg/kg every 4–6 hours; dose to be administered over 15 minutes; maximum 60 mg/kg per day
  - Adult (body-weight 50 kg and above): 1 g every 4–6 hours; dose to be administered over 15 minutes; maximum 3 g per day

**Pain | Pyrexia with discomfort**

- By mouth
  - Child 3–5 months: 60 mg every 4–6 hours; maximum 4 doses per day
  - Child 6 months–1 year: 120 mg every 4–6 hours; maximum 4 doses per day
  - Child 2–3 years: 180 mg every 4–6 hours; maximum 4 doses per day
  - Child 4–5 years: 240 mg every 4–6 hours; maximum 4 doses per day
  - Child 6–7 years: 240–250 mg every 4–6 hours; maximum 4 doses per day
  - Child 8–9 years: 360–375 mg every 4–6 hours; maximum 4 doses per day

- By rectum
  - Child 2 months: 60 mg after 60 mg every 6 hours; dose to be taken not more often than every 4 hours
  - Child 12–17 years: 500 mg every 4–6 hours

**Post-immunisation pyrexia in infants**

- By mouth
  - Child 2 months: 60 mg, first dose to be given at the time of vaccination, then 60 mg after 4–6 hours, then 60 mg after 4–6 hours
  - Child 4 months: 60 mg, first dose to be given at the time of vaccination, then 60 mg after 4–6 hours, then 60 mg after 4–6 hours

**PANADOL OA™**

Mild to moderate pain | Pyrexia

- By mouth
  - Adult: 1 g up to 4 times a day, dose not to be taken more often than every 4 hours

**UNLICENSED USE**

Paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years. Not licensed for use as prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine.

**CAUTIONS**

Before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours. Body-weight under 50 kg, chronic alcohol consumption, chronic dehydration, chronic malnutrition, hepatocellular insufficiency, long-term use (especially in those who are malnourished)

**INTERACTIONS**

- Appendix 1 (paracetamol).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Rare: Acute generalised exanthematous pustulosis - malaise - skin reactions - Stevens-Johnson syndrome - toxic epidermal necrolysis
- Frequency not known: Blood disorders - leucopenia - neutropenia - thrombocytopenia

**SPECIFIC SIDE-EFFECTS**

- Rare
  - With intravenous use: Flushing - tachycardia
  - Frequency not known:
  - With intravenous use: Hypotension
Overdose

**Important:** Liver damage and less frequently renal damage can occur following overdose.

Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis.

For specific details on the management of poisoning, see Paracetamol, under Emergency treatment of poisoning p. 1204

- **Pregnancy** Not known to be harmful.
- **Breast Feeding** Amount too small to be harmful.
- **Hepatic Impairment** Dose-related toxicity—avoid large doses.
- **Renal Impairment**
  - In adults: Increase infusion dose interval to every 6 hours if eGFR less than 30 mL/minute/1.73 m².
  - In children: Increase infusion dose interval to every 6 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².
- **Directions for Administration**
  - With intravenous use: For *intravenous infusion* (Perfalgan®), give in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of not less than 1 mg/mL and use within an hour; may also be given undiluted. For children under 33 kg, use 50 mL-vial.
- **Prescribing and Dispensing Information** BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed Paracetamol Oral Suspension 120 mg/5 mL should be dispensed.
- **Patient and Carer Advice** Medicines for Children leaflet: Paracetamol for mild-to-moderate pain www.medicinesforchildren.org.uk/paracetamol-for-mildtome moderate-pain
- **Profession Specific Information**
  - Dental practitioners’ formulary: Paracetamol Tablets may be prescribed.
  - Paracetamol Soluble Tablets 500 mg may be prescribed.
  - Paracetamol Oral Suspension may be prescribed.
- ** Exceptions to Legal Category** Paracetamol capsules or tablets can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, suppository.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>29 (does not apply to 1 g tablet), 30</th>
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<tbody>
<tr>
<td><strong>Paracetamol (Non-proprietary)</strong></td>
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<td>Paracetamol 500 mg</td>
<td>Paracetamol 500 mg caplets</td>
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<td>32 tablet P £1.24 DT price = £0.73</td>
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<tr>
<td>Paracetamol 500 mg</td>
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<td>Paracetamol 500 mg caplets</td>
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<td><strong>Paravict</strong> (Ecogen Europe Ltd)</td>
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**Effervescent tablet**

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<td>Paracetamol 500 mg</td>
<td>Paracetamol 500 mg soluble tablets</td>
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**Soluble tablet**

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<tr>
<td><strong>Paracetamol (Non-proprietary)</strong></td>
<td></td>
</tr>
<tr>
<td>Paracetamol 120 mg</td>
<td>Paracetamol 120 mg soluble tablets sugar-free</td>
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</table>
| Brands may include Disprin
| **Orodispersible tablet** | |
| CAUTIONARY AND ADVISORY LABELS | 30 |
| **Calpol Fastmelt** (McNeil Products Ltd) | |
| Paracetamol 250 mg | Calpol Six Plus Fastmelt 250 mg tablets sugar-free | 12 tablet P £2.28 sugar-free | 24 tablet P £3.59 |

**Capsule**

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<tr>
<td>Paracetamol 500 mg</td>
<td>Numark Paracetamol 500 mg capsules</td>
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<td>Paracetamol 500 mg tablets</td>
<td>16 capsule P £0.55</td>
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**Oral suspension**

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<td><strong>Paracetamol (Non-proprietary)</strong></td>
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<td>Paracetamol 24 mg per 1 ml</td>
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<td>Paracetamol 250 mg/5 ml oral suspension sugar-free</td>
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<td>Paracetamol 500 mg/5 ml oral suspension sugar-free</td>
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<td>200 ml P £3.35</td>
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<td>Paracetamol 50 mg per 1 ml</td>
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<td>Mandanol Infant paracetamol 120 mg/5 ml oral suspension</td>
</tr>
<tr>
<td>Mandanol 50 mg per 1 ml</td>
<td>Mandanol + paracetamol 200 mg/5 ml oral suspension sugar-free</td>
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**Oral solution**

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<tr>
<td>Paracetamol 24 mg per 1 ml</td>
<td>Paracetamol 120 mg/5 ml oral solution paediatric sugar-free</td>
</tr>
<tr>
<td>Paracetamol 100 mg per 1 ml</td>
<td>Paracetamol 500 mg/5 ml oral solution sugar-free</td>
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**Solution for infusion**

| **Paracetamol (Non-proprietary)** | |
| Paracetamol 10 mg per 1 ml | Paracetamol 1 g/100 ml solution for infusion | 10 vial POM £12.00 |
| **Perfalgan** (Bristol-Myers Squibb Pharmaceuticals Ltd) | |
| Paracetamol 10 mg per 1 ml | Perfalgan 1 g/100 ml solution for infusion | 12 vial POM £14.96 |
| Perfalgan 500 mg/50 ml solution for infusion | 12 vial POM £13.60 |
**Paracetamol with tramadol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 414, tramadol hydrochloride p. 435.

- **INICATIONS AND DOSE**
  - **Moderate to severe pain**
    - **BY MOUTH**
      - Child 12-17 years: 2 tablets up to every 6 hours; maximum 8 tablets per day
      - Adult: 2 tablets up to every 6 hours; maximum 8 tablets per day

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 2, 25, 29, 30
      - **Paracetamol with tramadol (Non-proprietary)**
        - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg
          - Tramadol 37.5mg / Paracetamol 325mg tablets | 60 tablet [PO] £9.20-£9.68 DT price = £9.22 [CD]
        - **Tramacet** (Grunenthal Ltd)
          - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg
            - Tramacet 37.5mg/325mg tablets | 60 tablet [PO] £9.68 DT price = £9.22 [CD]
  - **Effervescent tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 2, 13, 29, 30
      - **Tramacet** (Grunenthal Ltd)
        - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg
          - Tramacet 37.5mg/325mg effervescent tablets sugar-free | 60 tablet [PO] £9.68 DT price = £9.68 [CD]

**ANALGESICS > NON-OPIOID, CENTRALLY ACTING**

**Nefopam hydrochloride**

- **INDICATIONS AND DOSE**
  - **Moderate pain**
    - **BY MOUTH**
      - Adult: Initially 60 mg 3 times a day, adjusted according to response; usual dose 30–90 mg 3 times a day
      - Elderly: Initially 30 mg 3 times a day, adjusted according to response; usual dose 30–90 mg 3 times a day
  - **CONTRA-INDICATIONS** Convulsive disorders - not indicated for myocardial infarction

**CAUTIONS** Elderly - urinary retention

**INTERACTIONS** → Appendix 1 (nefopam).

**SIDE-EFFECTS**
- **Common or very common** Dry mouth - lightheadedness - nausea - nervousness - urinary retention
- **Uncommon** Blurred vision - confusion - drowsiness - hallucinations - headache - insomnia - sweating - tachycardia - vomiting
- **Frequency not known** May colour urine (pink)

**PREGNANCY** No information available—avoid unless no safer treatment.

**HEPATIC IMPAIRMENT** Caution.

**RENAI IMPAIRMENT** Caution.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 2, 14
  - **Nefopam hydrochloride (Non-proprietary)**
    - Nefopam hydrochloride 30 mg
      - Nefopam 30mg tablets | 90 tablet [PO] £55.00-£69.30 DT price = £66.11

**ANALGESICS > NON-SEROSTED ANTI-INFLAMMATORY DRUGS**

**Aspirin > NON-STERoidal ANTI-INFLAMMATORY DRUGS**

The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 114, codeine phosphate p. 421.

- **INDICATIONS AND DOSE**
  - **Mild to moderate pain** | Pyrexia
    - **BY MOUTH**
      - Adult: 1–2 tablets every 4–6 hours as required, dose to be dispensed in water; maximum 8 tablets per day

**PRESCRIBING AND DISPENSING INFORMATION** When co-codaprin tablets or dispersible tablets are prescribed and no strength is stated, tablets or dispersible tablets, respectively, containing codeine phosphate 8 mg and aspirin 400 mg should be dispensed.

**LESS SUITABLE FOR PRESCRIBING** Aspirin with codeine is less suitable for prescribing.

**EXCEPTIONS TO LEGAL CATEGORY** Aspirin with codeine can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 13, 21, 32
  - **Aspirin with codeine (Non-proprietary)**
    - Codeine phosphate 8 mg, Aspirin 400 mg
      - Boots Aspirin and Codeine tablets | 32 tablet [PO] no price available [CD]

**Dispersible tablet**
- **CAUTIONARY AND ADVISORY LABELS** 13, 21, 32
  - **Aspirin with codeine (Non-proprietary)**
    - Codeine phosphate 8 mg, Aspirin 400 mg
      - Co-codaprin 8mg/400mg dispersible tablets | 100 tablet [PO] £97.55 DT price = £92.18 [CD]

**OPIOIDS**

- **CONTRA-INDICATIONS** Acute respiratory depression - comatose patients - head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment)
Dependence and withdrawal

Respiratory depression

Hyperalgesia

▶

Common or very common

Palliative care

Dependence

▶

CAUTIONS

Use of opioid analgesics.

Respiratory depression and withdrawal can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

HEPATIC IMPAIRMENT

Avoid use or reduce dose; may precipitate coma in patients with hepatic impairment.

TREATMENT CESSATION

Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced. Driving at the start of therapy with opioid analgesics, and following dose changes, should be avoided.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including opioids, see Drugs and driving under Guidance on prescribing p. 1.

Buprenorphine

DRUG ACTION

Buprenorphine is an opioid-receptor partial agonist (it has opioid agonist and antagonist properties).

INDICATIONS AND DOSE

Moderate to severe pain

▶ BY SUBLINGUAL ADMINISTRATION

Child (body-weight 16-25 kg): 100 micrograms every 6–8 hours

Child (body-weight 25-37.5 kg): 100–200 micrograms every 6–8 hours

Child (body-weight 37.5-50 kg): 200–300 micrograms every 6–8 hours

Child (body-weight 50 kg and above): 200–400 micrograms every 6–8 hours

Adult: 200–400 micrograms every 6–8 hours

▶ BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION

Child 6 months-11 years: 3–6 micrograms/kg every 6–8 hours (max. per dose 9 micrograms/kg)

Child 12-17 years: 300–600 micrograms every 6–8 hours

Adult: 300–600 micrograms every 6–8 hours

Premedication

▶ BY SUBLINGUAL ADMINISTRATION

Adult: 400 micrograms

▶ BY INTRAMUSCULAR INJECTION

Adult: 300 micrograms

Intra-operative analgesia

▶ BY SLOW INTRAVENOUS INJECTION

Adult: 300–450 micrograms

Adjunct in the treatment of opioid dependence

▶ BY SUBLINGUAL ADMINISTRATION

Adult: Initially 0.8–4 mg for 1 dose on the first day, adjusted in steps of 2–4 mg daily if required; usual dose 12–24 mg daily; maximum 32 mg per day

DOSE EQUIVALENCE AND CONVERSION

For opioid substitution therapy, in patients taking methadone who want to switch to buprenorphine, the dose of methadone should be reduced to a maximum of 30 mg daily before starting buprenorphine treatment. If the dose of methadone is over 10 mg daily, buprenorphine can be started at a dose of 4 mg daily and titrated according to requirements; if the methadone dose is below 10 mg daily, buprenorphine can be started at a dose of 2 mg daily.

BUTRANS®

Moderate, non-malignant pain unresponsive to non-opioid analgesics

▶ BY TRANSDERMAL APPLICATION USING PATCHES

Adult: Initially 5 micrograms/hour up to every 7 days, dose adjustments—when starting, continued
analgesic effect should not be evaluated until the system has been worn for 72 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of at least 3 days using a patch of the next strength or a combination of 2 patches applied in different places (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time

**HAPOTASIN**

**Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic** | **Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic**

> **BY TRANSDERMAL APPLICATION USING PATCHES**
> **Adult:** Initially 35 micrograms/hour up to every 72 hours, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually

**PHARMACOKINETICS**

For Hapotasin®: It may take approximately 25 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**TRANSTEC®**

**Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic** | **Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic**

> **BY TRANSDERMAL APPLICATION USING PATCHES**
> **Adult:** The initial dose should be based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually

**IMPORTANT SAFETY INFORMATION**

Do not confuse the formulations of transdermal patches which are available as 72-hourly, 96-hourly and 7-day patches, see Prescribing and dispensing information.

**UNLICENSED USE** Sublingual tablets not licensed for use in children under 6 years. Injection not licensed for use in children under 6 months.

**INTERACTIONS** Caution with concomitant use of hepatotoxic drugs.

**SIDE-EFFECTS**

**Common or very common** Abdominal pain · agitation · anorexia · anxiety · asthenia · diarrhoea · dyspepsia · dysphonia · fatigue · mild withdrawal symptoms in patients dependent on opioids · paraesthesia · vasodilatation

**Uncommon** Angina (in adults) · cough · depersonalisation · dry eye · dry skin · dysarthria · flattulence · hypertension · hypoaesthesia · hypoxia · impaired memory · influenza-like symptoms · muscle cramp · myalgia · pyrexia · restlessness · rhinitis · rigors · syncope · taste disturbance · tinnitus · tremor · wheezing

**Rare** Diverticulitis (in children) · dysphagia · impaired concentration · paralytic ileus · psychosis

**Very rare** Hiccups · hyperventilation · muscle fasciculation · retching

**Frequency not known** Hepatic necrosis · hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Fever or external heat**

With transdermal use in adults Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat (may also increase absorption).

**Overdose**

The effects of buprenorphine are only partially reversed by naloxone.
**Methadone and buprenorphine for the management of opioid dependence**

**NATIONAL FUNDING/ACCESS DECISIONS**

**PATIENT AND CARER ADVICE**

*With transdermal use in adults*

**BREAST FEEDING**

Present in low levels in breast milk. Neonates should be monitored for drowsiness, adequate weight gain, and developmental milestones.

**RENAL IMPAIRMENT**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**PRE-TREATMENT SCREENING**

Documentation of viral hepatitis status is recommended before commencing therapy for opioid dependence.

**MONITORING REQUIREMENTS**

Monitor liver function; when used in opioid dependence baseline liver function test is recommended before commencing therapy, and regular liver function tests should be performed throughout treatment.

**DIRECTIONS FOR ADMINISTRATION**

- With sublingual use in children. For administration by mouth, tablets may be halved.

**TRANSTEC®**

Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 96 hours and sitting replacement patch on a different area (avoid same area for at least 6 days).

**BUTRANS®**

Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after 7 days and sitting replacement patch on a different area (avoid same area for at least 7 days).

**HAPOCTASIN®**

Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 72 hours and sitting replacement patch on a different area (avoid same area for at least 3 weeks).

**PRESCRIBING AND DISPENSING INFORMATION**

- With transdermal use in adults. Transdermal buprenorphine patches are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose.

Transdermal patches are available as 72-hourly, 96-hourly and 7-day formulations; prescribers and dispensers must ensure that the correct preparation is prescribed and dispensed. Preparations that should be applied up to every 72 hours include **Hapoctasin®**. Preparations that should be applied up to every 96 hours include **Transtec®**. Preparations that should be applied up to every 7 days include **BuTrans®**.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer buprenorphine transdermal patches.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Methadone and buprenorphine for the management of opioid dependence (January 2007) NICE TA14

Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable.

[www.nice.org.uk/TA114](http://www.nice.org.uk/TA114)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Sublingual tablet**

**CAUTIONARY AND ADVISORY LABELS 2, 26**

- **Buprenorphine (Non-proprietary)**
  - Buprenorphine (as Buprenorphine hydrochloride) 2 mg Buprenorphine 2mg sublingual tablets sugar free sugar-free | 7 tablet [PoM] £8.35 DT price = £1.24 [CD]
  - Buprenorphine (as Buprenorphine hydrochloride) 200 microgram Buprenorphine 200microgram sublingual tablets sugar free sugar-free | 50 tablet [PoM] £6.05 DT price = £0.12 [CD]
  - Buprenorphine (as Buprenorphine hydrochloride) 400 microgram Buprenorphine 400microgram sublingual tablets sugar free sugar-free | 7 tablet [PoM] £1.60 DT price = £0.16 [CD]

- **Buprenorphine (as Buprenorphine hydrochloride)**
  - 8 mg Buprenorphine 8mg sublingual tablets sugar free sugar-free | 7 tablet [PoM] £2.50 DT price = £0.33 [CD]
  - **Natzon (Morningside Healthcare Ltd)**
    - Natzon 2mg sublingual tablets sugar-free | 7 tablet [PoM] £6.35 DT price = £1.24 [CD]
  - **Natzon (Morningside Healthcare Ltd)**
    - Natzon 0.4mg sublingual tablets sugar-free | 7 tablet [PoM] £1.60 DT price = £0.16 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 8 mg Buprenorphine 8mg sublingual tablets sugar-free | 7 tablet [PoM] £19.05 DT price = £1.83 [CD]
  - **Prefibin (Sandoz Ltd)**
    - Prefibin 2mg sublingual tablets sugar-free | 7 tablet [PoM] £5.38 DT price = £0.12 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 400 microgram Prefibin 400microgram sublingual tablets sugar-free | 7 tablet [PoM] £1.60 DT price = £0.16 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 8 mg Prefibin 8mg sublingual tablets sugar-free | 7 tablet [PoM] £16.15 DT price = £1.83 [CD]
  - **Subutex (RB Pharmaceuticals Ltd)**
    - Buprenorphine (as Buprenorphine hydrochloride) 2 mg Subutex 2mg sublingual tablets sugar-free | 7 tablet [PoM] £6.35 DT price = £1.24 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 400 microgram Subutex 400microgram sublingual tablets sugar-free | 7 tablet [PoM] £1.60 DT price = £0.16 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 8 mg Subutex 8mg sublingual tablets sugar-free | 7 tablet [PoM] £19.05 DT price = £1.83 [CD]
  - **Temgesic (RB Pharmaceuticals Ltd)**
    - Buprenorphine (as Buprenorphine hydrochloride) 200 microgram Temgesic 200microgram sublingual tablets sugar-free | 50 tablet [PoM] £5.04 DT price = £0.10 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 400 microgram Temgesic 400microgram sublingual tablets sugar-free | 50 tablet [PoM] £10.07 DT price = £0.20 [CD]
  - **Tephine (Sandoz Ltd)**
    - Buprenorphine (as Buprenorphine hydrochloride) 200 microgram Tephine 200microgram sublingual tablets sugar-free | 50 tablet [PoM] £4.27 DT price = £0.08 [CD]
  - **Buprenorphine (as Buprenorphine hydrochloride)**
    - 400 microgram Tephine 400microgram sublingual tablets sugar-free | 50 tablet [PoM] £8.54 DT price = £0.17 [CD]

**Solution for injection**

- **Temgesic (RB Pharmaceuticals Ltd)**
  - Buprenorphine (as Buprenorphine hydrochloride) 300 microgram per 1 ml Temgesic 300micrograms/1ml solution for injection ampoules | 5 ampoule [PoM] £2.46 [CD]

**Transdermal patch**

**CAUTIONARY AND ADVISORY LABELS 2**

- **BuTrans (Napp Pharmaceuticals Ltd)**
  - Buprenorphine 5 microgram per 1 hour BuTrans 5micromgrams/hour transdermal patches | 4 patch [PoM] £17.60 DT price = £2.46 [CD]
  - **BuTrans (Napp Pharmaceuticals Ltd)**
    - 10 microgram per 1 hour BuTrans 10micrograms/hour transdermal patches | 4 patch [PoM] £31.55 DT price = £4.42 [CD]
  - **Buprenorphine 15 microgram per 1 hour BuTrans 15micrograms/hour transdermal patches | 4 patch [PoM] £49.15 [CD]
**Co-codamol**

**INDICATIONS AND DOSE**

**Mild to moderate pain (using co-codamol 8/500 preparations only)**
- **BY MOUTH**
  - Adult: 8/500–16/1000 mg every 4–6 hours as required; maximum 64/4000 mg per day

**Mild to moderate pain (using co-codamol 15/500 preparations only)**
- **BY MOUTH**
  - Adult: 15/500–30/1000 mg every 4–6 hours as required; maximum 120/4000 mg per day

**Severe pain (using co-codamol 30/500 preparations only)**
- **BY MOUTH**
  - Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day

**KAPAKE® 15/500**
- **Mild to moderate pain**
  - **BY MOUTH**
    - Adult: 2 tablets every 4–6 hours as required; maximum 8 tablets per day

**SOLPADOL® CAPLETS**
- **Severe pain**
  - **BY MOUTH**
    - Adult: 2 tablets every 4–6 hours as required; maximum 8 tablets per day

**SOLPADOL® CAPSULES**
- **Severe pain**
  - **BY MOUTH**
    - Adult: 2 capsules every 4–6 hours as required; maximum 8 capsules per day

**SOLPADOL® EFFERVESCENT TABLETS**
- **Severe pain**
  - **BY MOUTH USING EFFERVESCENT TABLETS**
    - Adult: 2 tablets every 4–6 hours as required, tablets to be dispersed in water; maximum 8 tablets per day

**CONTRA-INDICATIONS**
- Acute ulcerative colitis · antibiotic-associated colitis · conditions where abdominal distention develops · conditions where inhibition of peristalsis should be avoided · known ultra-rapid codeine metabolisers

**CAUTIONS**
- Acute abdomen · alcohol dependence · avoid abrupt withdrawal after long-term treatment · cardiac arrhythmias · chronic alcoholism · chronic dehydration · chronic malnutrition · convulsive disorders · gallstones · hepatocellular insufficiency

**CAUTIONS, FURTHER INFORMATION**
- Variation in metabolism · The capacity to metabolise codeine to morphine can vary considerably between individuals · there is a marked increase in morphine toxicity in patients who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers.

**INTERACTIONS**
- Appendix 1 (paracetamol).

**SIDE-EFFECTS**
- Abdominal pain · anorexia · blood disorders · depression (with larger doses) · hypothermia · leucopenia · malaise · muscle fasciculation · neutropenia · pancreatitis · seizures · thrombocytopenia

**Overdose**
- Important: liver damage (and less frequently renal damage) following overdosage with paracetamol.

**BREAST FEEDING**
- Avoid—although amount of codeine usually too small to be harmful, mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant.

**HEPATIC IMPAIRMENT**
- Dose-related toxicity with paracetamol—avoid large doses.

**RENAL IMPAIRMENT**
- Reduce dose or avoid codeine; increased and prolonged effect; increased cerebral sensitivity.

**PRESCRIBING AND DISPENSING INFORMATION**
- Co-codamol is a mixture of codeine phosphate and paracetamol; the proportions are expressed in the form x:y, where x and y are the strengths in milligrams of codeine phosphate and paracetamol respectively.

  When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and no strength is stated, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate 8 mg and paracetamol 500 mg should be dispensed.

  The Drug Tariff allows tablets of co-codamol labelled ‘dispersible’ to be dispensed against an order for ‘effervescent’ and vice versa.

**LESS SUITABLE FOR PRESCRIBING**
- Co-codamol is less suitable for prescribing.

**EXCEPTIONS TO LEGAL CATEGORY**
- Co-codamol 8/500 can be sold to the public in certain circumstances; for exemptions see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 2 (does not apply to the 8/500 tablet), 29, 30

  - **Co-codamol (Non-proprietary)**
    - Codeine phosphate 8 mg, Paracetamol 500 mg Co-codamol 8mg/500mg tablets | 32 tablet £1.02 | Co-codamol 8mg/500mg tablets | 100 tablet £2.36
    - £4.43 | Co-codamol 8mg/500mg tablets | 1000 tablet £13.15 | Co-codamol 8mg/500mg tablets | 10000 tablet £30.30
    - Codeine phosphate 15 mg, Paracetamol 500 mg Co-codamol 15mg/500mg tablets | 100 tablet £15.00
    - £4.58
    - Codeine phosphate 30 mg, Paracetamol 500 mg Co-codamol 30mg/500mg tablets | 100 tablet £4.03
    - £4.03
    - Co-codamol 30mg/500mg tablets | 30 tablet £1.21
    - £4.03
    - Co-codamol 30mg/500mg tablets | 100 tablet £7.52 | £4.03

  - **Codipar (AMCo)**
    - Codeine phosphate 15 mg, Paracetamol 500 mg Codipar 15mg/500mg tablets | 100 tablet £8.25
    - £9.58
    - Codipar 15mg/500mg tablets | 100 tablet £18.50
    - £18.50
    - Codipar 15mg/500mg tablets | 30 tablet £5.04
    - £5.04
    - Codipar 15mg/500mg tablets | 100 tablet no price available

  - **Kapake (Galen Ltd)**
    - Codeine phosphate 30 mg, Paracetamol 500 mg Kapake 30mg/500mg tablets | 100 tablet £6.50
    - £4.03

  - **Migraleve (McNeil Products Ltd)**
    - Codeine phosphate 8 mg, Paracetamol 500 mg Migraleve Yellow tablets | 16 tablet £0.96
    - £0.96

  - **Paracetamol 500 mg**
    - Codeine phosphate 30 mg, Paracetamol 500 mg Co-codamol 30mg/500mg tablets | 100 tablet £4.63
    - £4.03
    - Co-codamol 30mg/500mg tablets | 30 tablet £1.21
    - £1.21
    - Co-codamol 30mg/500mg tablets | 100 tablet £7.52 | £4.03
### Codeine phosphate

#### INDICATIONS AND DOSE

**Acute diarrhoea**
- **BY MOUTH**
  - Child 12–17 years: 30 mg 3–4 times a day; usual dose 15–60 mg 3–4 times a day
  - Adult: 30 mg 3–4 times a day; usual dose 15–60 mg 3–4 times a day

**Mild to moderate pain**
- **BY MOUTH**
  - Adult: 30–60 mg every 4 hours if required; maximum 240 mg per day
  - **BY INTRAMUSCULAR INJECTION**
  - Adult: 30–60 mg every 4 hours if required

**Short-term treatment of acute moderate pain**
- **BY MOUTH, OR BY INTRAMUSCULAR INJECTION**
  - Child 12–17 years: 30–60 mg every 6 hours if required for maximum 3 days; maximum 240 mg per day

**Dry or painful cough**
- **BY MOUTH USING LINCTUS**
  - Adult: 15–30 mg 3–4 times a day

### IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE (JULY 2013)** CODEINE FOR ANALGESIA: RESTRICTED USE IN CHILDREN DUE TO REPORTS OF MORPHINE TOXICITY

Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone. A significant risk of serious and life-threatening adverse reactions has been identified in children with obstructive sleep apnoea who received codeine after tonsillectomy or adenoidectomy:
- in children aged 12–18 years, the maximum daily dose of codeine should not exceed 240 mg. Doses may be taken up to four times a day at intervals of no less than 6 hours. The lowest effective dose should be used and duration of treatment should be limited to 3 days
- codeine is contra-indicated in all children (under 18 years) who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea
- codeine is not recommended for use in children whose breathing may be compromised, including those with neuromuscular disorders, severe cardiac or respiratory conditions, respiratory infections, multiple trauma or extensive surgical procedures
- codeine is contra-indicated in patients of any age who are known to be ultra-rapid metabolisers of codeine (CYP2D6 ultra-rapid metabolisers)
- codeine should not be used in breast-feeding mothers because it can pass to the baby through breast milk
- parents and carers should be advised on how to recognise signs and symptoms of morphine toxicity, and to stop treatment and seek medical attention if signs or symptoms of toxicity occur (including reduced consciousness, lack of appetite, somnolence, constipation, respiratory depression, ‘pin-point’ pupils, nausea, vomiting)

**MHRA/CHM ADVICE (APRIL 2015)** CODEINE FOR COUGH AND COLD: RESTRICTED USE IN CHILDREN

Do not use codeine in children under 12 years as it is associated with a risk of respiratory side effects. Codeine is not recommended for adolescents (12–18 years) who have problems with breathing. When prescribing or dispensing codeine-containing medicines for cough and cold, consider that codeine is contra-indicated in:
- children younger than 12 years old
patients of any age known to be CYP2D6 ultra-rapid metabolisers
breastfeeding mothers

CONTRA-INDICATIONS  Acute ulcerative colitis - antibiotic-associated colitis - children under 18 years who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea - conditions where abdominal distension develops - conditions where inhibition of peristalsis should be avoided - known ultra-rapid codeine metabolisers

CAUTIONS  Acute abdomen - cardiac arrhythmias - gallstones - not recommended for adolescents aged 12–18 years with breathing problems

SIDE-EFFECTS  Abdominal pain - anorexia - antidiuretic effect - hypothermia - malaise - muscle fasciculation - pancreatitis - seizures

BREAST FEEDING  Avoid—although amount usually too small to be harmful, mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant.

RENAI IMPAIRMENT  Avoid use or reduce dose; opioid effects increased and prolonged, and increased cerebral sensitivity occurs.

PRESCRIBING AND DISPENSING INFORMATION  BP directs

INDICATIONS AND DOSE  Mild to moderate pain (using co-dydramol 10/500 preparations only)

BY MOUTH

Adult: 10/500–20/1000 mg every 4–6 hours as required; maximum 80/4000 mg per day

Severe pain (using co-dydramol 20/500 preparations only)

BY MOUTH

Adult: 20/500–40/1000 mg every 4–6 hours as required; maximum 160/4000 mg per day

Severe pain (using co-dydramol 30/500 preparations only)

BY MOUTH

Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day

DOSE EQUIVALENT AND CONVERSION  A mixture of dihydrocodeine tartrate and paracetamol; the proportions are expressed in the form x/y, where x and y are the strengths in milligrams of dihydrocodeine and paracetamol respectively.

CAUTIONS  Alcohol dependence - before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours - chronic alcoholism - chronic dehydration - chronic malnutrition - hepatocellular insufficiency - pancreatitis - severe cor pulmonale

INTERACTIONS  → Appendix 1 (paracetamol).


Overdose  Important: liver damage (and less frequently renal damage) following overdosage with paracetamol.

CAUTIONS  Alcohol dependence - before administering, check whether paracetamol is prescribed; Codeine Linctus formulated with a vehicle appropriate for administration to diabetics, whether or not labelled ‘Diabetic Codeine Linctus’, shall be dispensed or supplied.

PATIENT AND CARER ADVICE  Medicines for Children leaflet: Codeine phosphate for pain  www.medicinesforchildren.org.uk/codeine-phosphate-pain-0

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection

Tablet  CAUTIONARY AND ADVISORY LABELS  2

Codeine phosphate (Non-proprietary)

| Codeine phosphate 15 mg | Codeine 15mg tablets | 28 tablet [P] | £1.40  DT price = £0.96  CDS | 100 tablet [P] | £3.43  DT price = £3.35  CDS |
| Codeine phosphate 30 mg | Codeine 30mg tablets | 28 tablet [P] | £1.59  DT price = £1.16  CDS | 100 tablet [P] | £5.68  DT price = £5.41  CDS |
| Codeine phosphate 60 mg | Codeine 60mg tablets | 28 tablet [P] | £3.95  DT price = £3.83  CDS |

Oral solution  CAUTIONARY AND ADVISORY LABELS  2

Codeine phosphate (Non-proprietary)

| Codeine phosphate 3 mg per 1 ml | Codeine 15mg/5ml linctus sugar free-sugar-free | 200 ml [P] | £1.87  DT price = £1.63  CDS  sugar-free | 2000 ml [P] | £6.30  CDS |
| Codeine 15mg/5ml linctus | 200 ml [P] | £1.84  DT price = £1.84  CDS | 2000 ml [P] | £6.46  CDS |

Codeine phosphate 5 mg per 1 ml  Codeine 25mg/5ml oral solution | 500 ml [P] | £6.46  DT price = £6.46  CDS |

Galcodine  (Thornton & Ross Ltd)

| Codeine phosphate 3 mg per 1 ml | Galcocodeine 15mg/5ml linctus sugar-free | 2000 ml [P] | £9.90  CDS |

Solution for injection  2

Codeine phosphate 60 mg per 1 ml  Codeine 60mg/1ml solution for injection ampoules | 10 ampoule [P] | £23.70–25.70  CDS |

Combinations available:  Aspirin with codeine, p. 416

Co-dydramol  2

INDICATIONS AND DOSE  Mild to moderate pain (using co-dydramol 10/500 preparations only)

BY MOUTH

Adult: 10/500–20/1000 mg every 4–6 hours as required; maximum 80/4000 mg per day

Severe pain (using co-dydramol 20/500 preparations only)

BY MOUTH

Adult: 20/500–40/1000 mg every 4–6 hours as required; maximum 160/4000 mg per day

Severe pain (using co-dydramol 30/500 preparations only)

BY MOUTH

Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day

DOSE EQUIVALENT AND CONVERSION  A mixture of dihydrocodeine tartrate and paracetamol; the proportions are expressed in the form x/y, where x and y are the strengths in milligrams of dihydrocodeine and paracetamol respectively.

CAUTIONS  Alcohol dependence - before administering, check whether paracetamol is prescribed; Codeine Linctus formulated with a vehicle appropriate for administration to diabetics, whether or not labelled ‘Diabetic Codeine Linctus’, shall be dispensed or supplied.

PATIENT AND CARER ADVICE  Medicines for Children leaflet: Codeine phosphate for pain  www.medicinesforchildren.org.uk/codeine-phosphate-pain-0

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet  CAUTIONARY AND ADVISORY LABELS  2

Co-dydramol (Non-proprietary)

| Dihydrocodeine tartrate 10 mg, Paracetamol 500 mg | Co-dydramol 10mg/500mg tablets | 30 tablet [P] | £1.01  CDS | 100 tablet [P] | £3.37  DT price = £3.37  CDS | 500 tablet [P] | £16.85  CDS |
Diamorphine hydrochloride (Heroin hydrochloride)

**INDICATIONS AND DOSE**

**Acute pain**
- BY INTRAMUSCULAR INJECTION, OR BY SUBCUTANEOUS INJECTION
  - Adult: 5 mg every 4 hours if required
  - BY SLOW INTRAVENOUS INJECTION
  - Adult: 1.25–2.5 mg every 4 hours if required

**Acute pain (heavier, well-muscled patients)**
- BY INTRAMUSCULAR INJECTION, OR BY SUBCUTANEOUS INJECTION
  - Adult: Up to 10 mg every 4 hours if required
  - BY SLOW INTRAVENOUS INJECTION
  - Adult: 2.5–5 mg every 4 hours if required

**Chronic pain not currently treated with a strong opioid analgesic**
- BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
  - Adult: Initially 2.5–5 mg every 4 hours, adjusted according to response
  - BY SUBCUTANEOUS INFUSION
  - Adult: Initially 5–10 mg, adjusted according to response, dose to be administered over 24 hours

**Acute pulmonary oedema**
- BY SLOW INTRAVENOUS INJECTION
  - Adult: 2.5–5 mg, dose to be administered at a rate of 1 mg/minute

**Myocardial infarction**
- BY SLOW INTRAVENOUS INJECTION
  - Adult: 5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute
  - Elderly: 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**Myocardial infarction (frail patients)**
- BY SLOW INTRAVENOUS INJECTION
  - Adult: 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**CONTRA-INDICATIONS**
- Delayed gastric emptying
- Phaeochromocytoma

**CAUTIONS**
- CNS depression
- Severe cor pulmonale
- Severe diarrhoea
- Toxic psychosis

**SIDE-EFFECTS**
- Anorexia
- Asthenia
- Myocardial infarction
- Raised intracranial pressure
- Syncope
- Taste disturbance

**BREAST FEEDING**
- Therapeutic doses unlikely to affect anorexia
- Effects increased and prolonged; increased cerebral sensitivity

**RENAL IMPAIRMENT**
- Avoid use or reduce dose; opioid effects increased and prolonged; increased cerebral sensitivity

**MEDI-cal forms**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Powder for solution for injection**
- Diamorphine hydrochloride (Non-proprietary)
  - Diamorphine hydrochloride 5 mg: Diamorphine 5mg powder for solution for injection vials | 5 vial | £12.00–£15.00 (C02)
  - Diamorphine 5mg powder for solution for injection ampoules | 5 ampoule | £11.36 DT price = £11.36 (C02)

  - Diamorphine hydrochloride 10 mg: Diamorphine 10mg powder for solution for injection ampoules | 5 ampoule | £16.56 DT price = £13.72 (C02)
  - Diamorphine 10mg powder for solution for injection vials | 5 vial | £12.49–£19.00 (C02)

**Dihydrocodeine tartrate**

**INDICATIONS AND DOSE**

**Moderate to severe pain**
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Child 4–11 years: 0.5–1 mg/kg every 4–6 hours (max. per dose 30 mg)
  - Child 12–17 years: 30 mg every 4–6 hours
  - Adult: 30 mg every 4–6 hours as required

  - BY DEEP SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
  - Adult: Up to 50 mg every 4–6 hours if required

**Chronic severe pain**
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Child 12–17 years: 60–120 mg every 12 hours
  - Adult: 60–120 mg every 12 hours

**DF118 FORTE**
- Severe pain
  - BY MOUTH
  - Child 12–17 years: 40–80 mg 3 times a day; maximum 240 mg per day
  - Adult: 40–80 mg 3 times a day; maximum 240 mg per day

**UNLICENSED USE**
- Most preparations not licensed for use in children under 4 years.

**CAUTIONS**
- Pancreatitis
- Severe cor pulmonale

**SIDE-EFFECTS**
- Abdominal pain
- Diarrhoea
- Parasthesia
- Paralytic ileus
- Seizures

**BREAST FEEDING**
- Use only if potential benefit outweighs risk.

**RENA1 IMPAIRMENT**
- Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**PROFESSIONAL INFORMATION**
- Dental practitioners’ formulary

**MEDI-cal forms**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**
- Dihydrocodeine tartrate (Non-proprietary)
  - Dihydrocodeine tartrate 30 mg: Dihydrocodeine 30mg tablets | 28 tablet | £1.33 DT price = £1.15 (C05) | 30 tablet | £1.56 (C05)
  - 100 tablet | £4.75 DT price = £4.11 (C05) | 500 tablet | £20.89 (C05)

  - DF 118 (Martindale Pharmaceuticals Ltd)
  - Dihydrocodeine tartarate 40 mg: DF 118 Forte 40mg tablets | 100 tablet | £9.78 DT price = £9.78 (C05)

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 2**
- DHC Continus (Napp Pharmaceuticals Ltd)
  - Dihydrocodeine tartrate 60 mg: DHC Continus 60mg tablets | 56 tablet | £5.20 DT price = £5.20 (C05)
  - Dihydrocodeine tartrate 90 mg: DHC Continus 90mg tablets | 56 tablet | £8.66 DT price = £8.66 (C05)
Dihydrocodeine tartrate 120 mg  DHC Continus 120mg tablets  |  56 tablet  

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS** 2

- **Dihydrocodeine tartrate (Non-proprietary)**
- **Dihydrocodeine tartrate 2 mg per 1 ml** Dihydrocodeine 10mg/5ml oral solution  |  150 ml  

**Solution for injection**

- **Dihydrocodeine tartrate (Non-proprietary)**
- **Dihydrocodeine tartrate 50 mg per 1 ml** Dihydrocodeine 50mg/1ml solution for injection ampoules  |  10 ampoule  

**INDICATIONS AND DOSE**

**Adult:** Initially 1 tablet every 6 hours, then increased if necessary up to 3 tablets every 6 hours, dose to be increased gradually

- **CAUTIONS**  Diabetes mellitus  •  palliative care (not recommended)  •  phaeochromocytoma
- **SIDE-EFFECTS**  Psychosis  •  raised intracranial pressure  •  restlessness
- **BREAST FEEDING**  No information available.
- **RENAL IMPAIRMENT**  Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Dipipanone hydrochloride with cyclizine (Non-proprietary)**
- **Dipipanone hydrochloride 10 mg**, Cyclizine hydrochloride 30 mg  Dipipanone 10mg / Cyclizine 30mg tablets  |  50 tablet  

**Fentanyl**

**INDICATIONS AND DOSE**

**Chronic intractable pain not currently treated with a strong opioid analgesic**

- **BY TRANSDERMAL APPLICATION**
  - **Child 2-17 years:** Initially based on previous 24-hour opioid requirement (consult product literature), for evaluating analgesic efficacy and dose increments, see under **Chronic intractable pain not currently treated with a strong opioid analgesic**, for conversion from long term oral morphine to transdermal fentanyl, see **Pain management with opioids**  p. 22.
  - **Adult:** Initial dose based on previous 24-hour opioid requirement (consult product literature), for evaluating analgesic efficacy and dose increments, see **Chronic intractable pain not currently treated with a strong opioid analgesic**, for conversion from long term oral morphine to transdermal fentanyl, see **Pain management with opioids**  p. 22.

**Spontaneous respiration: analgesia and enhancement of anaesthesia, during operation**

- **BY SLOW INTRAVENOUS INJECTION**
  - **Adult:** Initially 50–100 micrograms (max. per dose 200 micrograms), dexametadon specialist advice, then 25–50 micrograms as required

**Assisted ventilation: analgesia and enhancement of anaesthesia during operation**

- **BY SLOW INTRAVENOUS INJECTION**
  - **Adult:** Initially 300–3500 micrograms, then 100–200 micrograms as required

**Assisted ventilation: analgesia and respiratory depression in intensive care**

- **BY SLOW INTRAVENOUS INJECTION**
  - **Adult:** Initially 300–3500 micrograms, then 100–200 micrograms as required

**Breakthrough pain in patients receiving opioid therapy for chronic cancer pain**

- **BY BUCAL ADMINISTRATION USING LOZENGES**
  - **Child 16-17 years:** Initially 200 micrograms, dose to be given over 15 minutes, then 200 micrograms after 15 minutes if required, no more than 2 dose units for each pain episode; if adequate pain relief not achieved with 1 dose unit for consecutive breakthrough pain episodes, increase the strength of the dose unit until adequate pain relief achieved with 4 lozenges or less daily, if more than 4 episodes of breakthrough pain at least 15 minutes each day, adjust background analgesia
  - **Adult:** Initially 200 micrograms, dose to be given over 15 minutes, then 200 micrograms after 15 minutes if therapy should be phased out gradually from time of first patch application, dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (important: it takes 12 hours or more for the plasma-fentanyl concentration to decrease by 50%— replacement opioid therapy should be initiated at a low dose and increased gradually)
required, no more than 2 dose units for each pain episode; if adequate pain relief not achieved with 1 dose unit for consecutive breakthrough pain episodes, increase the strength of the dose unit until adequate pain relief achieved with 4 lozenges or less daily, if more than 4 episodes of breakthrough pain each day, adjust background analgesia

BY INTRANASAL ADMINISTRATION
Adult: Fentanyl preparations for the treatment of breakthrough pain in patients receiving opioid therapy are not bioequivalent to other fentanyl preparations. Fentanyl preparations for the treatment of breakthrough pain are not interchangeable; if patients are switched from another fentanyl-containing preparation, a new dose titration is required.

DOSE EQUIVALENCE AND CONVERSION
- Fentanyl films are not bioequivalent to other fentanyl preparations.
- Fentanyl preparations for the treatment of breakthrough pain are not interchangeable; if patients are switched from another fentanyl-containing preparation, a new dose titration is required.

DOSES AT EXTREMES OF BODY-WEIGHT
To avoid excessive dosage in obese patients, weight-based doses may need to be calculated on the basis of ideal bodyweight.

ABSTRAL®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY MOUTH USING SUBLINGUAL TABLETS
- Adult: Initially 100 micrograms, then 100 micrograms after 15–30 minutes if required, dose to be adjusted according to response—consult product literature, no more than 2 dose units 15–30 minutes apart, for each pain episode; max. 800 micrograms per episode of breakthrough pain; leave at least 4 hours between treatment of episodes of breakthrough pain, if more than 4 episodes of breakthrough pain each day, adjust background analgesia

EFFENTORA®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY MOUTH USING SUBLINGUAL TABLETS
- Adult: Initially 100 micrograms, then 100 micrograms after 30 minutes if required, dose to be adjusted according to response—consult product literature, no more than 2 dose units for each pain episode; max. 133 micrograms per episode of breakthrough pain; leave at least 2 hours between treatment of episodes of breakthrough pain, if more than 4 episodes of breakthrough pain each day, adjust background analgesia

INSTANYL®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY INTRANASAL ADMINISTRATION
- Adult: Initially 50 micrograms, dose to be administered into one nostril, then 50 micrograms after 10 minutes if required, dose to be adjusted according to response, maximum 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode, if more than 4 breakthrough pain episodes daily, adjust background analgesia

PECFENT®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY INTRANASAL ADMINISTRATION
- Adult: Initially 200 micrograms, adjusted according to response, dose to be administered into one nostril only, maximum 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode, if more than 4 breakthrough pain episodes daily, adjust background analgesia

RECVIT® SUBLINGUAL TABLETS
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY MOUTH
- Adult: Initially 133 micrograms, then 133 micrograms after 15–30 minutes (max. per dose 800 micrograms), dose to be repeated only if necessary. Consult product literature for dose adjustments, no more than 2 dose units, 15–30 minutes apart, for each pain episode, maximum of 800 micrograms per episode of breakthrough pain, if more than 4 episodes of breakthrough pain each day, adjust background analgesia; maximum 4 doses per day

DOSE EQUIVALENCE AND CONVERSION
- Fentanyl preparations for the treatment of breakthrough pain are not bioequivalent; if patients are switched from another fentanyl-containing preparation, a new dose titration is required.

CAUTIONS
GENERAL CAUTIONS
Cerebral tumour - diabetes mellitus (with Actiq® lozenges) - impaired consciousness

SPECIFIC CAUTIONS
- With buccal use Mucositis—absorption from oral preparations may be increased, caution during dose titration (in adults)

CAUTIONS, FURTHER INFORMATION
- With transdermal use Transdermal fentanyl patches are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic; manufacturer recommends use only in opioid tolerant patients.
- With intravenous use Repeated intra-operative doses should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive.

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
- Common or very common Abdominal pain - aesthesia - anorexia - anxiety - appetite changes - application-site reactions - diarrhoea - dysgeusia - dysphonia - gastrooesophageal reflux disease - hypertension - myoclonus - paraesthesia - pharyngitis - rhinitis - stomatitis - tremor - vasodilation
- Rare Hiccups
- Very rare Appnoea - arrhythmia - ataxia - bladder pain - delusions - haemoptysis

SPECIFIC SIDE-EFFECTS
- Common or very common With intravenous use Myoclonic movements
- Uncommon With intravenous use Laryngospasm
- Rare With intravenous use Asystole - insomnia
**SIDE-EFFECTS, FURTHER INFORMATION**

- **Fever or external heat** Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat, for example a hot bath or sauna (may also increase absorption).

- **Muscle rigidity** Intravenous administration of fentanyl can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

- **BREAST FEEDING** Monitor infant for opioid-induced side-effects.

- **RENAI IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

- **DIRECTIONS FOR ADMINISTRATION**
  - With transdermal use For patches, apply to dry, non-irritated, non-hairy skin on torso or upper arm, removing after 72 hours and siting replacement patch on a different area (avoid using the same area for several days).

- With intravenous use in adults For intravenous infusion (Sublimaze), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%.

- With buccal use in adults For buccal films, moisten mouth, place film on inner lining of cheek (pink side to cheek), hold for at least 5 seconds until it sticks, and leave to dissolve (15–30 minutes); if more than 1 film required do not overlap, but use another area of the mouth. Avoid liquids for 5 minutes after application; avoid food until the film has dissolved.

- With buccal use Patients should be advised to place the lozenge in the mouth against the cheek and move it around the mouth using the applicator; each lozenge should be sucked over a 15 minute period. In patients with a dry mouth, water may be used to moisten the buccal mucosa. Patients with diabetes should be advised each lozenge contains approximately 2 g glucose.

**INSTANYL®** Patient should sit or stand during administration.

**EFFENTORA®** Place tablet between cheek and gum and leave to dissolve; if more than 1 tablet required, place second tablet on the other side of the mouth; tablet may alternatively be placed under the tongue (sublingually).

**PRESCRIBING AND DISPENSING INFORMATION**

- With transdermal use Prescriptions for fentanyl patches can be written to show the strength in terms of the release rate and it is acceptable to write 'Fentanyl 25 patches' to prescribe patches that release fentanyl 25 micrograms per hour. The dosage should be expressed in terms of the interval between applying a patch and replacing it with a new one, e.g. ‘one patch to be applied every 72 hours’. The total quantity of patches to be supplied should be written in words and figures.

**PATIENT AND CARER ADVICE**

- **Medicines for Children leaflet:** Fentanyl lozenges for pain www.medicinesforchildren.org.uk/fentanyl-lozenges-for-pain

- **Medicines for Children leaflet:** Fentanyl patches for pain www.medicinesforchildren.org.uk/fentanyl-patches-for-pain

- With transdermal use Patients and carers should be informed about safe use, including correct administration and disposal, strict adherence to dosage instructions, and the symptoms and signs of opioid overdosage. Patches should be removed immediately in case of breathing difficulties, marked drowsiness, confusion, dizziness, or impaired speech, and patients and carers should seek prompt medical attention.

- In adults Patients or carers should be given advice on how to administer fentanyl nasal spray. Patients or carers should be given advice on how to administer Instanyl® spray.

**INSTANYL®** Avoid concomitant use of other nasal preparations. Patients or carers should be given advice on how to administer Instanyl® spray.

**PECFENT®** Avoid concomitant use of other nasal preparations. Patients or carers should be given advice on how to administer PecFent® spray.

**EFFENTORA®** Patients or carers should be given advice on how to administer Effentora® buccal tablets. Patients should be advised not to eat or drink until the tablet is completely dissolved; after 30 minutes, if any remnants remain, they may be swallowed with a glass of water. Patients with a dry mouth should be advised to drink water to moisten the buccal mucosa before administration of the tablets; if appropriate effervescence does not occur, a switch of therapy may be advised.

**ABSTRAL®** Patients should be advised not to eat or drink until the tablet is completely dissolved; after 30 minutes, if any remnants remain, they may be swallowed. In patients with a dry mouth, the buccal mucosa may be moistened with water before administration of tablet.

**RECVIT® SUBLINGUAL TABLETS** Patients should be advised not to eat or drink until the tablet is completely dissolved; after 30 minutes, if any remnants remain, they may be swallowed. In patients with a dry mouth, the buccal mucosa may be moistened with water before administration of tablet.

**NATIONAL FUNDING/ACCESS DECISIONS**

**INSTANYL®**

**Scottish Medicines Consortium (SMC) Decisions** The Scottish Medicines Consortium has advised that Instanyl® nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**PECFENT®**

**Scottish Medicines Consortium (SMC) Decisions** The Scottish Medicines Consortium has advised (September 2008) that PecFent® nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**EFFENTORA®**

**Scottish Medicines Consortium (SMC) Decisions** The Scottish Medicines Consortium has advised that Effentora® buccal tablets should be restricted for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**ABSTRAL®**

**Scottish Medicines Consortium (SMC) Decisions** The Scottish Medicines Consortium has advised (January 2009) that Abstral® sublingual tablets should be restricted for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**MEDIACIAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion, solution for infusion

**Sublingual tablet**

**CAUTIONARY AND ADVISORY LABELS 2, 26**

- **Abstral** (Kyowa Kirin Ltd)
  - Fentanyl (as Fentanyl citrate) 100 microgram Abstral 100microgram sublingual tablets sugar-free | 10 tablet £49.99 (C2) sugar-free | 30 tablet £149.70 (C2)
  - Fentanyl (as Fentanyl citrate) 200 microgram Abstral 200microgram sublingual tablets sugar-free | 10 tablet £49.99 (C2) sugar-free | 30 tablet £149.70 (C2)
Fentanyl (as Fentanyl citrate) 300 microgram Abstral 300microgram sublingual tablets sugar-free | 10 tablet (P, M) £49.99 (C) sugar-free | 30 tablet (P, M) £149.70 (C)

Fentanyl (as Fentanyl citrate) 400 microgram Abstral 400microgram sublingual tablets sugar-free | 10 tablet (P, M) £49.99 (C) sugar-free | 30 tablet (P, M) £149.70 (C)

Fentanyl (as Fentanyl citrate) 800 microgram Abstral 800microgram sublingual tablets sugar-free | 30 tablet (P, M) £149.70 (C)

Recivit (Grunenthal Ltd)
Fentanyl (as Fentanyl citrate) 133 microgram Recivit 133microgram sublingual tablets sugar-free | 30 tablet (P, M) £127.20 (C)

Fentanyl (as Fentanyl citrate) 267 microgram Recivit 267microgram sublingual tablets sugar-free | 30 tablet (P, M) £127.20 (C)

Fentanyl (as Fentanyl citrate) 400 microgram Recivit 400microgram sublingual tablets sugar-free | 30 tablet (P, M) £127.20 (C)

Fentanyl (as Fentanyl citrate) 533 microgram Recivit 533microgram sublingual tablets sugar-free | 30 tablet (P, M) £127.20 (C)

Fentanyl (as Fentanyl citrate) 800 microgram Recivit 800microgram sublingual tablets sugar-free | 30 tablet (P, M) £127.20 (C)

Buccal tablet
CAUTIONARY AND ADVISORY LABELS. 2 ELECTROLYTES: May contain Sodium

Effentora (Teva UK Ltd)
Fentanyl (as Fentanyl citrate) 10 microgram Effentora 10microgram buccal tablets sugar-free | 4 tablet (P, M) £19.96 (C) sugar-free | 28 tablet (P, M) £139.72 DT price = £139.72 (C)

Fentanyl (as Fentanyl citrate) 200 microgram Effentora 200microgram buccal tablets sugar-free | 4 tablet (P, M) £19.96 (C) sugar-free | 28 tablet (P, M) £139.72 DT price = £139.72 (C)

Fentanyl (as Fentanyl citrate) 400 microgram Effentora 400microgram buccal tablets sugar-free | 4 tablet (P, M) £19.96 (C) sugar-free | 28 tablet (P, M) £139.72 DT price = £139.72 (C)

Fentanyl (as Fentanyl citrate) 600 microgram Effentora 600microgram buccal tablets sugar-free | 4 tablet (P, M) £19.96 (C) sugar-free | 28 tablet (P, M) £139.72 DT price = £139.72 (C)

Fentanyl (as Fentanyl citrate) 800 microgram Effentora 800microgram buccal tablets sugar-free | 4 tablet (P, M) £19.96 (C) sugar-free | 28 tablet (P, M) £139.72 DT price = £139.72 (C)

Fentanyl (as Fentanyl citrate) 1.0 mg Actiq 1.0mg lozenges with integral oromucosal applicator | 3 lozenge (P) £21.05 (C) 30 lozenge (P, M) £210.41 (C)

Fentanyl (as Fentanyl citrate) 1.6 mg Actiq 1.6mg lozenges with integral oromucosal applicator | 3 lozenge (P) £21.05 (C) 30 lozenge (P, M) £210.41 (C)

Solution for infusion
Fentanyl (Non-proprietary)
Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml Fentanyl 50micrograms/ml solution for infusion ampoules | 10 ampoule (P, M) £13.95 (C)

Fentanyl 50micrograms/10ml solution for injection ampoules | 10 ampoule (P, M) £13.95 (C)

Sublimaze (Jansen-Cilag Ltd)
Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml Sublimaze 50micrograms/10ml solution for injection ampoules | 5 ampoule (P, M) £6.53 (C)

Solution for infusion
Fentanyl (Non-proprietary)
Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml Fentanyl 50micrograms/ml solution for infusion ampoules | 1 vial (P, M) £5.00 (C)

Transdermal patch
CAUTIONARY AND ADVISORY LABELS. 2

Fentanyl 12 microgram per 1 hour transdermal patches | 5 patch (P, M) £12.59 DT price = £12.59 (C)

Fentanyl 25 microgram per 1 hour transdermal patches | 5 patch (P, M) £17.99 DT price = £17.99 (C)

Fentanyl 50 microgram per 1 hour transdermal patches | 5 patch (P, M) £35.91 DT price = £33.66 (C)

Fentanyl 75 microgram per 1 hour transdermal patches | 5 patch (P, M) £50.12 DT price = £46.99 (C)

Fentanyl 100 microgram per 1 hour transdermal patches | 5 patch (P, M) £61.72 DT price = £57.86 (C)

Durogesic DTrans (Janssen-Cilag Ltd)
Fentanyl 12 microgram per 1 hour transdermal patches | 5 patch (P, M) £12.59 DT price = £12.59 (C)

Fentanyl 25 microgram per 1 hour transdermal patches | 5 patch (P, M) £17.99 DT price = £17.99 (C)

Fentanyl 50 microgram per 1 hour transdermal patches | 5 patch (P, M) £33.66 DT price = £33.66 (C)

Fentanyl 75 microgram per 1 hour transdermal patches | 5 patch (P, M) £46.99 DT price = £46.99 (C)

Fentanyl 100 microgram per 1 hour transdermal patches | 5 patch (P, M) £57.86 DT price = £57.86 (C)

Recivit (Grunenthal Ltd)
Fentanyl 12 microgram per 1 hour transdermal patches | 5 patch (P, M) £8.46 DT price = £8.46 (C)

Fentanyl 25 microgram per 1 hour transdermal patches | 5 patch (P, M) £12.10 DT price = £12.10 (C)

Fentanyl 50 microgram per 1 hour transdermal patches | 5 patch (P, M) £22.52 DT price = £22.52 (C)

Fentanyl 75 microgram per 1 hour transdermal patches | 5 patch (P, M) £31.54 DT price = £31.54 (C)

Fentanyl 100 microgram per 1 hour transdermal patches | 5 patch (P, M) £38.88 DT price = £38.88 (C)

Fenticis (Sandoz Ltd)
Fentanyl 25 microgram per 1 hour transdermal patches | 5 patch (P, M) £22.89 DT price = £22.89 (C)

Fentanyl 50 microgram per 1 hour transdermal patches | 5 patch (P, M) £42.77 DT price = £42.77 (C)

Fentanyl 75 microgram per 1 hour transdermal patches | 5 patch (P, M) £59.62 DT price = £59.62 (C)

Fentanyl 100 microgram per 1 hour transdermal patches | 5 patch (P, M) £73.49 DT price = £73.49 (C)

Matrifen (Teva UK Ltd)
Fentanyl 12 microgram per 1 hour transdermal patches | 5 patch (P, M) £7.52 DT price = £7.52 (C)

Fentanyl 25 microgram per 1 hour transdermal patches | 5 patch (P, M) £10.76 DT price = £10.76 (C)

Fentanyl 50 microgram per 1 hour transdermal patches | 5 patch (P, M) £20.12 DT price = £20.12 (C)

Fentanyl 75 microgram per 1 hour transdermal patches | 5 patch (P, M) £28.06 DT price = £28.06 (C)

Fentanyl 100 microgram per 1 hour transdermal patches | 5 patch (P, M) £34.59 DT price = £34.59 (C)

Mezolar Matrix (Sandoz Ltd)
Fentanyl 12 microgram per 1 hour transdermal patches | 5 patch (P, M) £7.53 DT price = £7.53 (C)

Fentanyl 25 microgram per 1 hour transdermal patches | 5 patch (P, M) £10.77 DT price = £10.77 (C)

Fentanyl 50 microgram per 1 hour transdermal patches | 5 patch (P, M) £20.13 DT price = £20.13 (C)

Fentanyl 75 microgram per 1 hour transdermal patches | 5 patch (P, M) £28.07 DT price = £28.07 (C)
Hydromorphone hydrochloride

- **INDICATIONS AND DOSE**
  - **Severe pain in cancer**
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Child 12–17 years: 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain
    - Adult: 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Child 12–17 years: 4 mg every 12 hours, dose to be increased if necessary according to severity of pain
    - Adult: 4 mg every 12 hours, dose to be increased if necessary according to severity of pain

- **CONTRA-INDICATIONS** Acute abdomen
- **CAUTIONS** Pancreatitis, toxic psychosis
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain • anorexia • anxiety
  - **Uncommon** Agitation • diarrhoea • dysgeusia • dyskinesia • myoclonus • paraesthesia • paralytic ileus • peripheral oedema • seizures • tremor
- **BREAST FEEDING** Avoid—no information available.
- **RENAI IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.
- **DIRECTIONS FOR ADMINISTRATION** For immediate-release capsules, swallow whole capsule or sprinkle contents on soft food. For modified-release capsules, swallow whole or open capsule and sprinkle contents on soft cold food (swallow the pellets within the capsule whole; do not crush or chew).
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer hydromorphone hydrochloride capsules and modified-release capsules.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Capsole

**CAUTIONARY AND ADVISORY LABELS**

- **Palladone (Napp Pharmaceuticals Ltd)**
  - Hydromorphone hydrochloride 1.3 mg Palladone 1.3mg capsules
    - 56 capsule (Pom) £8.82 (C02)
  - Hydromorphone hydrochloride 2.6 mg Palladone 2.6mg capsules
    - 56 capsule (Pom) £17.64 (C02)

**Modified-release capsule**

**CAUTIONARY AND ADVISORY LABELS**

- **Palladone SR (Napp Pharmaceuticals Ltd)**
  - Hydromorphone hydrochloride 2 mg Palladone SR 2mg capsules
    - 56 capsule (Pom) £20.98 (C02)
  - Hydromorphone hydrochloride 4 mg Palladone SR 4mg capsules
    - 56 capsule (Pom) £28.75 (C02)
  - Hydromorphone hydrochloride 8 mg Palladone SR 8mg capsules
    - 56 capsule (Pom) £56.08 (C02)
  - Hydromorphone hydrochloride 16 mg Palladone SR 16mg capsules
    - 56 capsule (Pom) £106.53 (C02)
  - Hydromorphone hydrochloride 24 mg Palladone SR 24mg capsules
    - 56 capsule (Pom) £159.82 (C02)
● INDICATIONS AND DOSE

Pain

BY SUBCUTANEOUS INJECTION

Adult: Initially 50–100 micrograms/kg every 6 hours, adjusted according to response

Child 1–5 months: Initially 50–100 micrograms/kg every 4 hours, adjusted according to response

Child 6 months–1 year: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response

Child 2–11 years: Initially 200 micrograms/kg every 4 hours, adjusted according to response

Child 12–17 years: Initially 200–300 micrograms/kg every 4 hours, adjusted according to response

BY INTRAMUSCULAR INJECTION

Adult: Initially 50–200 micrograms/kg every 4 hours, adjusted according to response

Child 1–2 months: Initially 50–100 micrograms/kg every 4 hours, adjusted according to response

Child 3–5 months: 100–150 micrograms/kg every 4 hours, adjusted according to response

Child 6–11 months: 200 micrograms/kg every 4 hours, adjusted according to response

Child 1 year: 200–300 micrograms/kg every 4 hours, adjusted according to response

Child 2–11 years: 200–300 micrograms/kg every 4 hours (max. per dose 10 mg), adjusted according to response

Child 12–17 years: Initially 5–10 mg every 4 hours, adjusted according to response

Opioid requirements should be reviewed if the brand is altered.

Pain with modified-release 24-hourly preparations

BY MOUTH, USING MODIFIED-RELEASE MEDICINES

Adult: Every 24 hours, dose adjusted according to daily morphine requirements. Dosage requirements should be reviewed if the brand is altered.

Pain management in palliative care (starting dose for opioid-naïve patients)

BY MOUTH

Adult: 20–30 mg daily in divided doses, using immediate-release preparation 4-hourly or a 12-hourly modified-release preparation, for management of breakthrough pain and other general advice, see Pain management with opioids p. 22.

Pain management in palliative care (starting dose for patients being switched from a regular weak opioid)

BY MOUTH

Adult: 40–60 mg daily in divided doses, using immediate-release preparation 4-hourly or a 12-hourly modified-release preparation, for management of breakthrough pain and other general advice, see Pain management with opioids p. 22. continued →
Pain in palliative care (following initial titration)

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Usual dose 30 mg every 4 hours; up to 200 mg every 4 hours, higher dose may be required for some patients (occasionally more is needed); for management of breakthrough pain and other general advice, see Pain management with opioids p. 22.

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Usual dose 100 mg every 12 hours; up to 600 mg every 12 hours, higher dose may be required for some patients (occasionally more is needed); for management of breakthrough pain and other general advice, see Pain management with opioids p. 22.

Cough in terminal disease

- **BY MOUTH**
  - Adult: Initially 5 mg every 4 hours

Premedication

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: Up to 10 mg, dose to be administered 60–90 minutes before operation

Patient controlled analgesia (PCA)

- **BY INTRAVENOUS INFUSION**
  - Adult: (consult local protocol)

Myocardial infarction

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, followed by 5–10 mg if required, dose to be administered at a rate of 1–2 mg/minute, use dose for elderly in frail patients
  - Elderly: 2.5–5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute

Acute pulmonary oedema

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, dose to be administered at a rate of 2 mg/minute, use dose for elderly in frail patients
  - Elderly: 2.5–5 mg, dose to be administered at a rate of 2 mg/minute

Dyspnoea at rest in palliative care

- **BY MOUTH**
  - Adult: Initially 5 mg every 4 hours, to be given in carefully titrated doses

DOSAGE EQUVALENCE AND CONVERSION

- The doses stated refer equally to morphine hydrochloride and sulfate.

**UNLICENSSED USE**

  - With rectal use in children Suppositories are not licensed for use in children.

**CONTRA-INDICATIONS** Acute abdomen - delayed gastric emptying - heart failure secondary to chronic lung disease - phaeochromocytoma

**CAUTIONS** Cardiac arrhythmias - pancreatitis - severe cor pulmonale


**BREAST FEEDING** Therapeutic doses unlikely to affect infant.

**RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged; increased cerebral sensitivity.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children For *continuous intravenous infusion*, dilute with Glucose 5% or 10% or Sodium Chloride 0.9%.
- With oral use For *modified release capsules*—swallow whole or open capsule and sprinkle contents on soft food.

**PRESCRIBING AND DISPENSING INFORMATION**

- Modified-release preparations are available as 12-hourly or 24-hourly formulations; prescribers must ensure that the correct preparation is prescribed. Preparations that should be given 12-hourly include Filnarine® SR, MST Continus®, Morphgesic® SR and Zomorph®. Prescriptions must specify the ‘form’.

- With rectal use Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber.

**Palliative care**

- In adults For further information on the use of morphine in palliative care, see www.palliativedrugs.com/formulary/en/morphine.html.

**PATIENT AND CARER ADVICE**

- Medicines for Children leaflet: Morphine for pain www.medicinesforchildren.org.uk/morphine-for-pain

- With oral use Patients or carers should be given advice on how to administer morphine modified-release capsules.

**EXCEPTIONS TO LEGAL CATEGORY**

Morphine Oral Solutions Prescription-only medicines or schedule 2 controlled drug. The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 13 mg per 5 mL the solution becomes a schedule 2 controlled drug. It is usual to adjust the strength so that the dose volume is 5 or 10 mL.

Oral solutions of morphine can be prescribed by writing the formula:

- Morphine hydrochloride 5 mg
- Chloroform water to 5 mL

**MEdICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral solution, solution for injection, infusion, solution for infusion, suppository

**Tablet**

CAUTIONARY AND ADVISORY LABELS

- **Sevredol** (Napp Pharmaceuticals Ltd)
  - Morphine sulfate 10 mg Sevredol 10 mg tablets | 56 tablet POM £5.31 DT price = £5.31 CD
  - Morphine sulfate 20 mg Sevredol 20 mg tablets | 56 tablet POM £10.61 DT price = £10.61 CD
  - Morphine sulfate 50 mg Sevredol 50 mg tablets | 56 tablet POM £28.02 DT price = £28.02 CD

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS

- **MST Continus** (Napp Pharmaceuticals Ltd)
  - Morphine sulfate 5 mg MST Continus 5 mg tablets | 60 tablet POM £3.29 DT price = £3.29 CD
  - Morphine sulfate 10 mg MST Continus 10 mg tablets | 60 tablet POM £5.20 DT price = £5.20 CD
  - Morphine sulfate 15 mg MST Continus 15 mg tablets | 60 tablet POM £9.10 DT price = £9.10 CD
  - Morphine sulfate 20 mg MST Continus 20 mg tablets | 60 tablet POM £12.47 DT price = £12.47 CD
  - Morphine sulfate 60 mg MST Continus 60 mg tablets | 60 tablet POM £24.32 DT price = £24.32 CD
  - Morphine sulfate 100 mg MST Continus 100 mg tablets | 60 tablet POM £38.50 DT price = £38.50 CD
  - Morphine sulfate 200 mg MST Continus 200 mg tablets | 60 tablet POM £81.34 DT price = £81.34 CD
**Morphine with cyclizine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, morphine p. 429, cyclizine p. 401.

### INDICATIONS AND DOSE

#### CYCLIMORPH-10®

**Moderate to severe pain (short-term use only)**

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
- **Adult:** 1 mL, do not repeat dose more often than every 4 hours; maximum 3 doses per day

#### CYCLIMORPH-15®

**Moderate to severe pain (short-term use only)**

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
- **Adult:** 1 mL, do not repeat dose more often than every 4 hours; maximum 3 doses per day

### CAUTIONS

Myocardial infarction (cyclizine may aggravate severe heart failure and counteract the haemodynamic benefits of opioids) - not recommended in palliative care

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

### Solution for injection

#### Morphine (Non-proprietary)

| Morphine sulfate 1 mg per 1 mL | Morphine sulfate 5mg/5mL solution for injection ampoules | 10 ampoule (PoM) £135.50 (CD2) |
| Morphine sulfate 3 mg per 1 mL | Morphine sulfate 1mg/1mL solution for injection ampoules | 10 ampoule (PoM) £61.10 (CD2) |
| Morphine sulfate 10 mg per 1 mL | Morphine sulfate 10mg/10ml solution for injection ampoules | 10 ampoule (PoM) £15.00-38.00 (CD2) |
| Morphine sulfate 20 mg per 1 mL | Morphine sulfate 10mg/10ml solution for injection ampoules | 10 ampoule (PoM) £9.36 DT price = £9.36 (CD2) |
| Morphine sulfate 25 mg per 1 mL | Morphine sulfate 15mg/1ml solution for injection ampoules | 10 ampoule (PoM) £8.95 DT price = £8.95 (CD2) |
| Morphine sulfate 30 mg per 1 mL | Morphine sulfate 20mg/1ml solution for injection ampoules | 10 ampoule (PoM) £51.69 (CD2) |

### Oxycodeone hydrochloride

#### INDICATIONS AND DOSE

**Postoperative pain | Severe pain | Moderate to severe pain in palliative care**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult:** Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - **Adult:** Initially 10 mg every 12 hours (max. per dose 200 mg every 12 hours), dose to be increased if necessary according to severity of pain, some patients might require higher doses than the maximum daily dose

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**BNF 73**

**Pain 431**

**Nervous System**

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**Oxycodeone hydrochloride**

12-Dec-2016

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**Morphine sulfate 30 mg per 1 mL**

Morphine sulfate 30mg/1mL solution for injection ampoules | 10 ampoule (PoM) £9.04 DT price = £8.84 (CD2)

Morphine sulfate 60mg/2mL solution for injection ampoules | 5 ampoule (PoM) £10.07 (CD2)

### Solution for infusion

#### Morphine (Non-proprietary)

| Morphine sulfate 1 mg per 1 mL | Morphine sulfate 50mg/50ml solution for infusion vials | 1 vial (PoM) £5.78 DT price = £5.78 (CD2) |
| Morphine sulfate 2 mg per 1 mL | Morphine sulfate 100mg/50ml solution for infusion vials | 1 vial (PoM) £6.48 (CD2) |

### Suppository

#### Morphine (Non-proprietary)

| Morphine sulfate 10 mg | Morphine sulfate 10mg suppositories | 12 suppository (PoM) £16.34-19.45 DT price = £18.90 (CD2) |
| Morphine sulfate 15 mg | Morphine sulfate 15mg suppositories | 12 suppository (PoM) £16.48 DT price = £16.48 (CD2) |

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**BNF 73**

**Pain 431**

**Nervous System**

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**Morphine sulfate 20 mg per 1 mL**

Morphine sulfate 20mg/1ml solution for injection ampoules | 10 ampoule (PoM) £9.04 DT price = £8.84 (CD2)

Morphine sulfate 60mg/2mL solution for injection ampoules | 5 ampoule (PoM) £10.07 (CD2)
CONTRA-INDICATIONS Acute abdomen · chronic constipation · cor pulmonale · delayed gastric emptying

CAUTIONS Pancreatitis · toxicty psychosis

SIDE-EFFECTS

Common or very common Abdominal pain · anoxemia · anxiety · asthenia · bronchospasm · chills · diarrhoea · dyspepsia · dysphoae · impaired cough reflex

Uncommon Agitation · amnorrhoea · amnesia · belching · cholestasis · dehydration · disorientation · dry skin · dysphagia · flatulence · gastritis · hiccups · hypoaesthesia · hypotonia · malaise · muscle fasciculation · paraesthesia · paralytic ileus · pyrexia · restlessness · seizures · speech disorder · supraventricular tachycardia · syncope · taste disturbance · thirst · tremor · vasodilatation

BREAST FEEDING Present in milk—avoid.

HEPATIC IMPAIRMENT Max. initial dose 2.5 mg every 6 hours in patients not currently treated with an opioid with mild impairment. Avoid in moderate to severe impairment.

RENAL IMPAIRMENT Max. initial dose 2.5 mg every 6 hours in patients not currently treated with an opioid with mild to moderate impairment. Opioid effects increased and prolonged and increased cerebral sensitivity occurs. Avoid if eGFR less than 10 mL/min/1.73 m².

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Oxynorm®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to a concentration of 1 mg/mL.

PRESCRIBING AND DISPENSING INFORMATION

Palliative care

For further information on the use of oxycodone in palliative care, see www.palliativedrugs.com/formulary/en/oxycodone.html.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2004 and November 2010) that OxNorm® injection is restricted for use within NHS Scotland for patients with cancer who have difficulty in tolerating morphine or diamorphine.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, solution for infusion

Modified-release tablet

OXOCODONE HYDROCHLORIDE (Non-proprietary)

Oxycodone hydrochloride 4 mg Oxycodone 40 mg modified-release tablets | 56 tablet (Pom) $100.19 DT price = $100.19 (CD)

Oxycodone hydrochloride 8 mg Oxycodone 80 mg modified-release tablets | 56 tablet (Pom) $200.39 DT price = $200.39 (CD)

Abtard (Ethlypharm UK Ltd)

Oxycodone hydrochloride 5 mg Abtard 5 mg modified-release tablets | 28 tablet (Pom) $16.26 DT price = $12.52 (CD)

Oxycodone hydrochloride 10 mg Abtard 10 mg modified-release tablets | 56 tablet (Pom) $12.52 DT price = $25.04 (CD)

Oxycodone hydrochloride 15 mg Abtard 15 mg modified-release tablets | 56 tablet (Pom) $9.08 DT price = $38.12 (CD)

Oxycodone hydrochloride 20 mg Abtard 20 mg modified-release tablets | 56 tablet (Pom) $5.08 DT price = $50.08 (CD)

Oxycodone hydrochloride 30 mg Abtard 30 mg modified-release tablets | 56 tablet (Pom) $3.11 DT price = $76.23 (CD)

Oxycodone hydrochloride 40 mg Abtard 40 mg modified-release tablets | 56 tablet (Pom) $2.19 DT price = $150.19 (CD)

Oxycodone hydrochloride 60 mg Abtard 50 mg modified-release tablets | 56 tablet (Pom) $2.49 DT price = $152.49 (CD)

Oxycodone hydrochloride 80 mg Abtard 80 mg modified-release tablets | 56 tablet (Pom) $2.39 DT price = $200.39 (CD)

Carexil (Sandoz Ltd)

Oxycodone hydrochloride 5 mg Carexil 5 mg modified-release tablets | 28 tablet (Pom) $16.26 DT price = $12.52 (CD)

Oxycodone hydrochloride 10 mg Carexil 10 mg modified-release tablets | 56 tablet (Pom) $12.52 DT price = $25.04 (CD)

Oxycodone hydrochloride 20 mg Carexil 20 mg modified-release tablets | 56 tablet (Pom) $5.08 DT price = $50.08 (CD)

Oxycodone hydrochloride 30 mg Carexil 30 mg modified-release tablets | 56 tablet (Pom) $3.11 DT price = $76.23 (CD)

Oxycodone hydrochloride 40 mg Carexil 40 mg modified-release tablets | 56 tablet (Pom) $2.19 DT price = $150.19 (CD)

Longtec (Qdem Pharmaceuticals Ltd)

Oxycodone hydrochloride 5 mg Longtec 5 mg modified-release tablets | 28 tablet (Pom) $5.26 DT price = $12.52 (CD)

Oxycodone hydrochloride 10 mg Longtec 10 mg modified-release tablets | 56 tablet (Pom) $12.52 DT price = $25.04 (CD)

Oxycodone hydrochloride 15 mg Longtec 15 mg modified-release tablets | 56 tablet (Pom) $9.08 DT price = $38.12 (CD)

Oxycodone hydrochloride 20 mg Longtec 20 mg modified-release tablets | 56 tablet (Pom) $5.08 DT price = $50.08 (CD)

Oxycodone hydrochloride 30 mg Longtec 30 mg modified-release tablets | 56 tablet (Pom) $3.11 DT price = $76.23 (CD)

Oxycodone hydrochloride 40 mg Longtec 40 mg modified-release tablets | 56 tablet (Pom) $2.19 DT price = $150.19 (CD)

Oxycodone hydrochloride 60 mg Longtec 60 mg modified-release tablets | 56 tablet (Pom) $5.09 DT price = $100.19 (CD)

Oxycodone hydrochloride 80 mg Longtec 80 mg modified-release tablets | 56 tablet (Pom) $3.02 DT price = $150.19 (CD)

Oxycodone hydrochloride 120 mg Longtec 120 mg modified-release tablets | 56 tablet (Pom) $1.19 DT price = $200.39 (CD)

Oxela (Wockhardt UK Ltd)

Oxycodone hydrochloride 5 mg Oxela 5 mg modified-release tablets | 28 tablet (Pom) $1.27 DT price = $12.52 (CD)

Oxycodone hydrochloride 10 mg Oxela 10 mg modified-release tablets | 56 tablet (Pom) $2.54 DT price = $25.04 (CD)

Oxycodone hydrochloride 15 mg Oxela 15 mg modified-release tablets | 56 tablet (Pom) $3.31 DT price = $38.12 (CD)

Oxycodone hydrochloride 20 mg Oxela 20 mg modified-release tablets | 56 tablet (Pom) $4.07 DT price = $50.08 (CD)

Oxycodone hydrochloride 30 mg Oxela 30 mg modified-release tablets | 56 tablet (Pom) $6.11 DT price = $76.23 (CD)

Oxycodone hydrochloride 40 mg Oxela 40 mg modified-release tablets | 56 tablet (Pom) $9.17 DT price = $150.19 (CD)

Oxycodone hydrochloride 60 mg Oxela 60 mg modified-release tablets | 56 tablet (Pom) $17.24 DT price = $150.19 (CD)

Oxycodone hydrochloride 80 mg Oxela 80 mg modified-release tablets | 56 tablet (Pom) $18.35 DT price = $200.39 (CD)

OxyContin (Napp Pharmaceuticals Ltd)

Oxycodone hydrochloride 5 mg OxyContin 5 mg modified-release tablets | 28 tablet (Pom) $12.52 DT price = $12.52 (CD)

Oxycodone hydrochloride 10 mg OxyContin 10 mg modified-release tablets | 56 tablet (Pom) $25.04 DT price = $25.04 (CD)

Oxycodone hydrochloride 15 mg OxyContin 15 mg modified-release tablets | 56 tablet (Pom) $38.12 DT price = $38.12 (CD)

Oxycodone hydrochloride 20 mg OxyContin 20 mg modified-release tablets | 56 tablet (Pom) $50.08 DT price = $50.08 (CD)

Oxycodone hydrochloride 30 mg OxyContin 30 mg modified-release tablets | 56 tablet (Pom) $76.23 DT price = $76.23 (CD)
Oxycodone hydrochloride 40 mg OxyContin 40mg modified-release tablets | 56 tablet £100.19 DT price = £100.19 (C02)
Oxycodone hydrochloride 60 mg OxyContin 60mg modified-release tablets | 56 tablet £152.49 DT price = £152.49 (C02)
Oxycodone hydrochloride 80 mg OxyContin 80mg modified-release tablets | 56 tablet £200.39 DT price = £200.39 (C02)
Oxycodone hydrochloride 120 mg OxyContin 120mg modified-release tablets | 56 tablet £305.02 DT price = £305.02 (C02)

Oxycodone hydrochloride 5 mg | 28 tablet £12.50 DT price = £12.52 (C02)
Oxycodone hydrochloride 10 mg | 28 tablet £24.99 DT price = £25.04 (C02)
Oxycodone hydrochloride 20 mg | 28 tablet £49.98 DT price = £50.08 (C02)
Oxycodone hydrochloride 40 mg | 28 tablet £98.97 DT price = £100.00 (C02)
Oxycodone hydrochloride 80 mg | 28 tablet £199.97 DT price = £200.39 (C02)

Oxycodone hydrochloride 5 mg | 28 tablet £6.26 DT price = £12.52 (C02)
Oxycodone hydrochloride 10 mg | 28 tablet £12.52 DT price = £25.04 (C02)
Oxycodone hydrochloride 15 mg | 28 tablet £19.06 DT price = £38.12 (C02)
Oxycodone hydrochloride 20 mg | 28 tablet £25.04 DT price = £50.08 (C02)
Oxycodone hydrochloride 30 mg | 28 tablet £38.11 DT price = £76.23 (C02)
Oxycodone hydrochloride 40 mg | 28 tablet £50.09 DT price = £100.19 (C02)
Oxycodone hydrochloride 60 mg | 28 tablet £76.24 DT price = £152.49 (C02)
Oxycodone hydrochloride 80 mg | 28 tablet £100.19 DT price = £200.39 (C02)

Zomestine (Accord Healthcare Ltd)
Oxycodone hydrochloride 5 mg | 28 tablet £3.01 DT price = £12.52 (C02)
Oxycodone hydrochloride 10 mg | 28 tablet £5.02 DT price = £25.04 (C02)
Oxycodone hydrochloride 20 mg | 28 tablet £10.02 DT price = £50.08 (C02)
Oxycodone hydrochloride 40 mg | 28 tablet £20.03 DT price = £100.19 (C02)
Oxycodone hydrochloride 80 mg | 28 tablet £40.08 DT price = £100.19 (C02)

OxyNorm (Napp Pharmaceuticals Ltd)
Oxycodone hydrochloride 5 mg | 50 ampoule £84.00 DT price = £84.00 (C02)
Oxycodone hydrochloride 10 mg | 50 ampoule £100.19 DT price = £200.39 (C02)

Calcium carbonate modified-release tablets | 56 tablet £46.63 DT price = £46.63 (C02)

Oxycodone hydrochloride 1 mg per 1 ml OxyNorm liquid 5mg/5ml oral solution sugar-free | 250 ml £9.71 DT price = £9.71 (C02)
Oxycodone hydrochloride 10 mg per 1 ml OxyNorm 10mg/ml concentrate oral solution sugar-free | 120 ml £46.63 DT price = £46.63 (C02)

Solution for injection

Oxycodone hydrochloride (Non-proprietary)
Oxycodone hydrochloride 10 mg per 1 ml Oxycodone 20mg/2ml solution for injection ampoules | 5 ampoule £16.00 DT price = £16.00 (C02)
Oxycodone hydrochloride 20 mg per 1 ml Oxycodone 40mg/4ml solution for injection ampoules | 5 ampoule £8.00 DT price = £8.00 (C02)
Oxycodone hydrochloride 50 mg per 1 ml Oxycodone 100mg/10ml solution for injection ampoules | 5 ampoule £70.10 DT price = £70.10 (C02)

OxyNorm (Napp Pharmaceuticals Ltd)
Oxycodone hydrochloride 10 mg per 1 ml Oxycodone 20mg/2ml solution for injection ampoules | 5 ampoule £16.00 DT price = £16.00 (C02)
Oxycodone hydrochloride 50 mg per 1 ml Oxycodone 100mg/10ml solution for injection ampoules | 5 ampoule £70.10 DT price = £70.10 (C02)

Oxycodone with naloxone

The properties listed below are those particular to the combination only. For the properties of the components please consider, oxycodone hydrochloride p. 431, naloxone hydrochloride p. 1214.

- INDICATIONS AND DOSE
  - Severe pain requiring opioid analgesia in patients not currently treated with opioid analgesics
    - BY MOUTH
    - Adult: Initially 10/5 mg every 12 hours (max. per dose 40/20 mg every 12 hours), dose to be increased according to response; patients already receiving opioid analgesics can start with a higher dose
    - Second-line treatment of symptomatic severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy
    - BY MOUTH
    - Adult: Initially 5/2.5 mg every 12 hours, adjusted weekly according to response, usual dose 10/5 mg every 12 hours; maximum 60/30 mg per day
  - DOSE EQUIVALENCE AND CONVERSION
    - Dose quantities are expressed in the form x/y where x and y are the strengths in milligrams of oxycodone and naloxone respectively.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
  - Modified-release tablets
    - CAUTIONARY AND ADVISORY LABELS. 2
    - Targan (Napp Pharmaceuticals Ltd)
      - Naloxone hydrochloride 2.5 mg, Oxycodone hydrochloride 5 mg Targan 5mg/2.5mg modified-release tablets | 28 tablet £21.16 DT price = £21.16 (C02)
      - Naloxone hydrochloride 5 mg, Oxycodone hydrochloride 10 mg Targan 10mg/5mg modified-release tablets | 28 tablet £42.32 DT price = £42.32 (C02)
      - Naloxone hydrochloride 10 mg, Oxycodone hydrochloride 20 mg Targan 20mg/10mg modified-release tablets | 56 tablet £84.62 DT price = £84.62 (C02)
      - Naloxone hydrochloride 20 mg, Oxycodone hydrochloride 40 mg Targan 40mg/20mg modified-release tablets | 56 tablet £169.28 (C02)
  - Oral solution
    - CAUTIONARY AND ADVISORY LABELS. 2
    - Oxycodone hydrochloride (Non-proprietary)
      - Oxycodone hydrochloride 1 mg per 1 ml Oxycodone 5mg/5ml oral solution sugar-free | 250 ml £9.71 DT price = £9.71 (C02)
      - Oxycodone hydrochloride 10 mg per 1 ml Oxycodone 10mg/ml oral solution sugar-free | 120 ml £46.63 DT price = £46.63 (C02)
**Papaveretum**

- **INDICATIONS AND DOSE**
  - Postoperative analgesia | Severe chronic pain
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 7.7–15.4 mg every 4 hours if required
  - Elderly: Initially 7.7 mg every 4 hours if required
  - **BY INTRAVENOUS INJECTION**
  - Adult: Use 25 to 50% of the corresponding subcutaneous/intramuscular dose

**Premedication**
- **BY INTRAVENOUS INJECTION**
- Adult: Use 25 to 50% of the corresponding subcutaneous/intramuscular dose

**IMPORTANT SAFETY INFORMATION**
Do not confuse with papaverine.

- **CONTRA-INDICATIONS** Heart failure secondary to chronic lung disease • phaeochromocytoma
- **CAUTIONS** Supraventricular tachycardia
- **SIDE-EFFECTS** Hypothermia
- **BREAST FEEDING** Therapeutic doses unlikely to affect infant.
- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.
- **PRESCRIBING AND DISPENSING INFORMATION** The name Omnopon® was formerly used for papaveretum preparations.
- Papaveretum is a mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride and 20 parts of codeine hydrochloride.
- **LESS SUITABLE FOR PRESCRIBING** Papaveretum is less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 2, 21
    - **Pentazocine (Non-proprietary)**
      - Pentazocine hydrochloride 25 mg | 28 tablet [PO] £24.27 DT price = £24.27 [CD3]
    - **Capsule**
      - **CAUTIONARY AND ADVISORY LABELS** 2, 21
      - **Pentazocine (Non-proprietary)**
        - Pentazocine hydrochloride 50 mg | 28 capsule [PO] £28.50 DT price = £28.50 [CD3]
    - **Solution for injection**
      - **Pentazocine (Non-proprietary)**
        - Pentazocine (as Pentazocine lactate) 30 mg per 1 ml | Pentazocine 60mg/2ml solution for injection ampoules | 10 ampoule [PO] £32.14 DT price = £32.14 [CD3]

**Pentazocine**

- **INDICATIONS AND DOSE**
  - Moderate to severe pain
    - **BY MOUTH**
      - Adult: 50 mg every 3–4 hours, dose to be taken preferably after food, usual dose 25–100 mg every 3–4 hours; maximum 600 mg per day
  - Moderate pain
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 30 mg every 3–4 hours as required; maximum 360 mg per day
  - Severe pain
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 45–60 mg every 3–4 hours as required; maximum 360 mg per day

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 • heart failure secondary to chronic lung disease • patients dependent on opioids (can precipitate withdrawal)

- **CAUTIONS** Arterial hypertension • cardiac arrhythmias • myocardial infarction • pancreatitis • phaeochromocytoma • pulmonary hypertension
- **SIDE-EFFECTS** Abdominal pain • blood disorders • chills • disorientation • hypertension • hypothermia • myalgia • paraesthesia • raised intracranial pressure • seizures • syncope • toxic epidermal necrolysis • tremor
- **Overdose** Effects only partially reversed by naloxone.
- **BREAST FEEDING** Use with caution—limited information available.
- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.
- **LESS SUITABLE FOR PRESCRIBING** Pentazocine is less suitable for prescribing.

**Pethidine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Acute pain**
    - **BY MOUTH**
      - Adult: 50–150 mg every 4 hours
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
      - Adult: 25–100 mg, then 25–100 mg after 4 hours, for debilitated patients use dose described for elderly patients
      - Elderly: Initially 25 mg, then 25–100 mg after 4 hours
    - **BY SLOW INTRAVENOUS INJECTION**
      - Adult: 25–50 mg, then 25–50 mg after 4 hours, for debilitated patients use dose described for elderly patients
      - Elderly: Initially 25 mg, then 25–50 mg after 4 hours
  - **Obstetric analgesia**
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
      - Adult: 50–100 mg, then 50–100 mg after 1–3 hours if required; maximum 400 mg per day
  - **Premedication**
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: 25–100 mg, dose to be given 1 hour before operation, for debilitated patients use dose described for elderly patients
      - Elderly: 25 mg, dose to be given 1 hour before operation
Postoperative pain
▶ BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
▶ Adult: 25–100 mg every 2–3 hours if required, for debilitated patients use dose described for elderly patients
▶ Elderly: Initially 25 mg every 2–3 hours if required

- **CONTRA-INDICATIONS** Phaeochromocytoma
- **CAUTIONS** Accumulation of metabolites may result in neurotoxicity - cardiac arrhythmias - not suitable for severe continuing pain - severe cor pulmonale
- **SIDE-EFFECTS** Hypothermia - restlessness - tremor
- **OVERDOSE** Convulsions reported in overdosage.
- **BREAST FEEDING** Present in milk but not known to be harmful.
- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral solution, solution for injection

**Tablet**
- **Pethidine hydrochloride** (Non-proprietary)
  - Pethidine hydrochloride 50 mg

**Solution for injection**
- **Pethidine hydrochloride** (Non-proprietary)
  - Pethidine hydrochloride 10 mg per 1 ml

**INSTRUCTIONS FOR USE**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 50 mg every 4–6 hours, adjusted according to response, maximum 700 mg in the first 24 hours, during the first 24 hours of treatment, an additional dose of 50 mg may be taken 1 hour after the initial dose, if pain control not achieved; maximum 600 mg per day

**Severe chronic pain**
▶ BY MOUTH USING MODIFIED-RELEASE MEDICINES
▶ Adult: Initially 50 mg every 12 hours, adjusted according to response; maximum 500 mg per day

**SIDE-EFFECTS** Abdominal discomfort - anxiety - ataxia - decreased appetite - diarrhoea - dysarthria - dyspepsia - hypoaesthesia - malaise - muscle spasms - paraesthesia - seizures - tremor - weight loss

**BREAST FEEDING** Avoid - no information available.

**HEPATIC IMPAIRMENT** For immediate-release tablets, initial max. daily dose 150 mg; for modified-release tablets, initial max. daily dose 50 mg.

**RENAL IMPAIRMENT** Manufacturer advises no dose adjustment needed in mild or moderate impairment. Avoid in severe impairment; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (May 2011) that tapentadol (Palexia® SR) is accepted for restricted use within NHS Scotland for the management of severe chronic pain in adult patients, which can be adequately managed only with opioid analgesics, when morphine sulfate modified-release has failed to provide adequate pain control or is not tolerated.

**MEDICINAL FORMS**

**INDICATIONS AND DOSE**

**Moderate to severe pain**
▶ BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
▶ Adult: 50–100 mg every 4–6 hours, intravenous injection to be given over 2–3 minutes

**Moderate to severe acute pain**
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12–17 years: Initially 100 mg, then 50–100 mg every 4–6 hours; Usual maximum 400 mg/24 hours
▶ Adult: Initially 100 mg, then 50–100 mg every 4–6 hours; Usual maximum 400 mg/24 hours

**Moderate to severe chronic pain**
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12–17 years: Initially 50 mg, then, adjusted according to response; Usual maximum 400 mg/24 hours
▶ Adult: Initially 50 mg, then, adjusted according to response; Usual maximum 400 mg/24 hours

**Postoperative pain**
▶ BY INTRAVENOUS INJECTION
▶ Adult: Initially 100 mg, then 50 mg every 10–20 minutes if required up to total maximum 250 mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours, intravenous injection to be given over 2–3 minutes; maximum 600 mg per day
DIRECTIONS FOR ADMINISTRATION

- **HEPATIC IMPAIRMENT**
- **BREAST FEEDING**

Rare

- **Embryotoxic in**
- **speech disorders**
- **hypertension**
- **bronchospasm**
- **Abnormal coordination**
- **Diarrhoea**

Excessive bronchial secretions

**Child 12-17 years**: Initially 100–150 mg once daily; increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours

**Adult**: Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours

**ZYDOL® XL**

Moderate to severe pain

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - **Child 12-17 years**: 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, doses exceeding the usual maximum not generally required; Usual maximum 400 mg/24 hours
  - **Adult**: 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, doses exceeding the usual maximum not generally required; Usual maximum 400 mg/24 hours

**Moderate to severe pain (with modified-release 24-hour preparations)**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - **Child 12-17 years**: Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours
  - **Adult**: Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours

**ZYDOL® XL**

Moderate to severe pain

- **BY MOUTH USING MODIFIED-RELEASE TABLETS**
  - **Child 12-17 years**: Initially 150 mg once daily, increased if necessary up to 400 mg once daily
  - **Adult**: Initially 150 mg once daily, increased if necessary up to 400 mg once daily

IMMPORTANT SAFETY INFORMATION

Do not confuse modified-release 12-hourly preparations with 24-hourly preparations, see Prescribing and dispensing information.

- **CONTRA-INDICATIONS** Acute intoxication with alcohol • acute intoxication with analgesics • acute intoxication with hypnotics • acute intoxication with opioids • not suitable for narcotic withdrawal treatment • uncontrolled epilepsy

- **CAUTIONS** Excessive bronchial secretions • history of epilepsy—use tramadol only if compelling reasons • impaired consciousness • not suitable as a substitute in opioid-dependent patients • not suitable in some types of general anaesthesia • susceptibility to seizures—use tramadol only if compelling reasons

CAUTIONS, FURTHER INFORMATION

- **General anaesthesia** Not recommended for analgesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported).

- **SIDE-EFFECTS**
  - **Common or very common** Malaise
  - **Uncommon** Diarrhoea • flatulence • gastritis • retching
  - **Rare** Abnormal coordination • anorexia • anxiety • bronchospasm • changes in appetite • delirium • dypsnoea • hypertension • muscle weakness • nightmares • paraesthesia • seizures • syncope • tremor • wheezing
  - **Frequency not known** Blood disorders • hypoglycaemia • speech disorders

- **PREGNANCY** Embryotoxic in animal studies—manufacturers advise avoid.

- **BREAST FEEDING** Amount probably too small to be harmful, but manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Caution (avoid for oral drops) in severe impairment.

- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs. Caution (avoid for oral drops) in severe impairment.

- **DIRECTIONS FOR ADMINISTRATION** Tramadol hydrochloride orodispersible tablets should be sucked and then swallowed. May also be dispersed in water. Some tramadol hydrochloride modified-release capsule preparations may be opened and the contents swallowed immediately without chewing—check individual preparations.

- **For intravenous infusion**, dilute in Glucose 5% or Sodium Chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION** Modified-release preparations are available as 12-hourly or 24-hourly formulations. Non-proprietary preparations of modified-release tramadol may be available as either 12-hourly or 24-hourly formulations; prescribers and dispensers must ensure that the correct formulation is prescribed and dispensed. Branded preparations that should be given 12-hourly include Invodol® SR, Mabron®, Maneo®, Marol®, Maxitran®, SR, Oldaram®, Tilodol® SR, Tramquel® SR, Tramulief® SR, Zamadol® SR, Zeridame® SR and Zydol SR®. Preparations that should be given 24-hourly include Tradacril® SR, Zamadol® 24hr, and Zydol XL®.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer tramadol hydrochloride orodispersible tablets.

| Manufacturers include: oral suspension |

Soluble tablet

CAUTIONARY AND ADVISORY LABELS 2, 13

- **Zydol** (Grunenthal Ltd)
  - **Tramadol hydrochloride 50 mg** Zydol 50mg soluble tablets sugar-free • 20 tablet [PO] £2.79 Schedule 3 (CD No Register Exempt Safe Custody) sugar-free | 100 tablet [PO] £13.33 DT price = £13.33 [CD]

Orodispensible tablet

CAUTIONARY AND ADVISORY LABELS 2

- **Tramadol hydrochloride (Non-proprietary)**
  - **Tramadol hydrochloride 50 mg** Tramadol 50mg orodispersible tablets sugar free sugar-free | 60 tablet [PO] no price available [CD]
  - **Zamadol Melt** (Meda Pharmaceuticals Ltd)
  - **Tramadol hydrochloride 50 mg** Zamadol Melt 50mg tablets sugar-free | 60 tablet [PO] £7.12 [CD]

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 2, 25

- **Tramadol hydrochloride (Non-proprietary)**
  - **Tramadol hydrochloride 50 mg** Tramadol 50mg modified-release tablets | 60 tablet [PO] no price available DT price = £4.60 [CD]
  - **Tramadol hydrochloride 100 mg** Tramadol 100mg modified-release tablets | 60 tablet [PO] £4.40 [CD]
  - **Tramadol hydrochloride 150 mg** Tramadol 150mg modified-release tablets | 60 tablet [PO] £5.75 [CD]
  - **Tramadol hydrochloride 200 mg** Tramadol 200mg modified-release tablets | 30 tablet [PO] no price available | 60 tablet [PO] £69.60 [CD]
  - **Tramadol hydrochloride 300 mg** Tramadol 300mg modified-release tablets | 30 tablet [PO] no price available | 60 tablet [PO] £69.60 [CD]
  - **Tramadol hydrochloride 400 mg** Tramadol 400mg modified-release tablets | 28 tablet [PO] no price available | 30 tablet [PO] no price available [CD]
  - **Invodol SR** (Ennogen Healthcare Ltd)
  - **Tramadol hydrochloride 100 mg** Invodol SR 100mg tablets | 60 tablet [PO] £14.61 [CD]
  - **Tramadol hydrochloride 150 mg** Invodol SR 150mg tablets | 60 tablet [PO] £21.91 [CD]
  - **Tramadol hydrochloride 200 mg** Invodol SR 200mg tablets | 60 tablet [PO] £25.22 [CD]
  - **Mabron** (Morningside Healthcare Ltd)
  - **Tramadol hydrochloride 100 mg** Mabron 100mg modified-release tablets | 60 tablet [PO] £18.26 [CD]
  - **Tramadol hydrochloride 150 mg** Mabron 150mg modified-release tablets | 60 tablet [PO] £27.39 [CD]
  - **Tramadol hydrochloride 200 mg** Mabron 200mg modified-release tablets | 60 tablet [PO] £36.52 [CD]
  - **Maneo** (Mylan Ltd)
  - **Tramadol hydrochloride 100 mg** Maneo 100mg modified-release tablets | 60 tablet [PO] £6.95 [CD]
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**Capsule**

*CAUTIONARY AND ADVISORY LABELS 2 13*

- **Tramadol hydrochloride (Non-proprietary)**
  - Tramadol hydrochloride 50 mg | Tramadol 50mg capsules | 30 capsule (Pom) | £4.71 DT price = £0.85 (C3) |
  - 100 capsule (Pom) | £14.40 DT price = £2.83 (C3) |

**Modified-release capsule**

- **Tramadol hydrochloride (Non-proprietary)**
  - Tramadol hydrochloride 50 mg | Tramadol 50mg modified-release capsules | 60 capsule (Pom) | £7.24 DT price = £7.24 (C3) |
  - Tramadol hydrochloride 100 mg | Tramadol 100mg modified-release capsules | 60 capsule (Pom) | £14.47 DT price = £14.47 (C3) |
  - Tramadol hydrochloride 150 mg | Tramadol 150mg modified-release capsules | 60 capsule (Pom) | £21.71 DT price = £21.71 (C3) |

**Oral drops**

*CAUTIONARY AND ADVISORY LABELS 2 13*

- **Tramadol hydrochloride (Non-proprietary)**
  - Tramadol (as Tramadol hydrochloride) 100 mg per 1 ml | Tramadol 100mg/ml oral drops | 10 ml (Pom) | £3.50 DT price = £3.50 (C3) |

**Solution for injection**

- **Tramadol hydrochloride (Non-proprietary)**
  - Tramadol hydrochloride 50 mg per 1 ml | Tramadol 50mg/2ml solution for injection ampoules | 5 ampoule (Pom) | £4.90-£5.15 (C3) |
  - 10 ampoule (Pom) | £10.00 (C3) |

- **Zamadol (Meda Pharmaceuticals Ltd)**
  - Tramadol hydrochloride 50 mg per 1 ml | Tramadol 50mg/2ml solution for injection ampoules | 5 ampoule (Pom) | £5.49 (C3) |

- **Zydol (Grunenthal Ltd)**
  - Tramadol hydrochloride 50 mg per 1 ml | Tramadol 50mg/2ml solution for injection ampoules | 5 ampoule (Pom) | £4.00 (C3) |

**Combinations available:** Paracetamol with tramadol, p. 416

### 6.1 Headache

Other drugs used for Headache

- Clonidine hydrochloride, p. 136
- Sumatriptan, p. 444
- Verapamil hydrochloride, p. 155
Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A simple analgesic such as aspirin p. 114, paracetamol p. 414 (preferably in a soluble or dispersible form) or a NSAID is often effective; concomitant antiemetic treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as a 5HT1-receptor agonist (‘triptan’). Ergot alkaloids are rarely required now; oral preparations are associated with many side-effects and should be avoided in cerebrovascular or cardiovascular disease.

Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT1-receptor agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, decreasing consumption of these medicines needs careful management.

Analgesics
Most migraine headaches respond to analgesics such as aspirin or paracetamol but because peristalsis is often reduced during migraine attacks the medication may not be sufficiently well absorbed to be effective; dispersible or effervescent preparations are therefore preferred. Compound preparations containing analgesics and antiemetics are available.

The NSAID tolfenamic acid p. 440 is licensed specifically for the treatment of an acute attack of migraine; diclofenac potassium p. 992, flurbiprofen p. 998, and ibuprofen p. 999 are also licensed for use in migraine.

5HT1-receptor agonists
A 5HT1-receptor agonist is of considerable value in the treatment of an acute migraine attack. The 5HT1-receptor agonists (‘triptans’) act on the 5HT (serotonin) 1B/1D receptors and they are therefore sometimes referred to as 5HT1B/1D-receptor agonists. A 5HT1-receptor agonist may be used during the established headache phase of an attack and is the preferred treatment in those who fail to respond to conventional analgesics. 5HT1-receptor agonists are not indicated for the treatment of hemiplegic, basilar, or ophthalmoplegic migraine.

The 5HT1-receptor agonists available for treating migraine are almogreltriptan p. 441, eleetrotriptan p. 442, frovatriptan p. 442, naratriptan p. 443, rizatriptan p. 443, sumatriptan p. 444, and zolmitriptan p. 445. If a patient does not respond to one 5HT1-receptor agonist, an alternative 5HT1-receptor agonist should be tried. For patients who have prolonged attacks that frequently recur despite treatment with a 5HT1-receptor agonist, combination therapy with a NSAID such as naproxen can be considered. Sumatriptan or zolmitriptan are also used to treat cluster headache.

Ergot Alkaloids
The value of ergotamine tartrate p. 441 for migraine is limited by difficulties in absorption and by its side-effects, particularly nausea, vomiting, abdominal pain, and muscular cramps; it is best avoided. The recommended doses of ergotamine tartrate preparations should not be exceeded and treatment should not be repeated at intervals of less than 4 days.

To avoid habituation the frequency of administration of ergotamine tartrate should be limited to no more than twice a month. It should never be prescribed prophylactically but in the management of cluster headache a low dose is occasionally given for 1 to 2 weeks [unlicensed indication].

Antiemetics
Antiemetics, such as metoclopramide hydrochloride p. 403 or domperidone p. 402, or phenothiazine and antihistamine antiemetics, relieve the nausea associated with migraine attacks. Antiemetics may be given by intramuscular injection or rectally if vomiting is a problem. Metoclopramide hydrochloride and domperidone have the added advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms. Oral analgesic preparations containing metoclopramide hydrochloride are a convenient alternative.
**Prophylaxis of migraine**

Where migraine attacks are frequent, possible provoking factors such as stress, irregular life-style (e.g. lack of sleep), or chemical triggers (e.g. alcohol and nitrates) should be sought; combined oral contraceptives may also provoke migraine.

Preventive treatment for migraine should be considered for patients who:

- suffer at least two attacks a month;
- suffer an increasing frequency of headaches;
- suffer significant disability despite suitable treatment for migraine attacks;
- cannot take suitable treatment for migraine.

Prophylaxis is also necessary in some rare migraine subtypes and those at risk of migrainous infarction.

The beta-blockers propranolol hydrochloride p. 142, atenolol p. 143, metoprolol tartrate p. 145, nadolol p. 141, and timolol maleate p. 142 are all effective. Propranolol hydrochloride is the most commonly used.

Tricyclic antidepressants [unlicensed indication], valproic acid p. 331 [unlicensed indication], and gabapentin p. 295 [unlicensed indication] are also effective for preventing migraine.

Botulinum toxin type A is licensed for the prophylaxis of headaches in adults with chronic migraine.

**Cluster headache and the trigeminal autonomic cephalalgias**

Cluster headache rarely responds to standard analgesics. Sumatriptan given by subcutaneous injection is the drug of choice for the treatment of cluster headache. If an injection is unsuitable, sumatriptan nasal spray or zolmitriptan nasal spray [both unlicensed use] may be used. Alternatively, 100% oxygen at a rate of 10–15 litres/minute for 10–20 minutes is useful in aborting an attack.

Prophylaxis of cluster headache is considered if the attacks are frequent, last over 3 weeks, or if they cannot be treated effectively. Verapamil hydrochloride p. 155 or lithium [both unlicensed use] are used for prophylaxis.

Prednisolone p. 622 can be used for short-term prophylaxis of episodic cluster headache [unlicensed use] either as monotherapy, or in combination with verapamil hydrochloride during verapamil titration.

Ergotamine tartrate, used on an intermittent basis is an alternative for patients with short bouts, but it should not be used for prolonged periods.

The other trigeminal autonomic cephalalgias, paroxysmal hemicrania (sensitive to indometacin p. 1001), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, are seen rarely and are best managed by a specialist.

### Other drugs used for Migraine

- Amitriptyline hydrochloride, p. 349
- Botulinum toxin type A, p. 380
- Clonidine hydrochloride, p. 136
- Trifluoperazine, p. 366

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### ANALGESICS > NON-OPIOID

#### Paracetamol with isometheptene

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 414.

**INDICATIONS AND DOSE**

**Treatment of acute attacks of migraine**

- **BY MOUTH**
  - Adult: 2 capsules, dose to be taken at onset of attack, followed by 1 capsule every 1 hour if required, maximum of 5 capsules in 12 hours

**PATIENT AND CARER ADVICE**

Patient counselling is advised (dosage).

**LESS SUITABLE FOR PRESCRIBING**

Isometheptene with paracetamol is less suitable for prescribing (more effective treatments available).

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midrid (DHP Healthcare Ltd)</td>
<td></td>
</tr>
</tbody>
</table>

*Isometheptene muate 65 mg, Paracetamol 325 mg* Midrid

325mg/65mg capsules | 30 capsule | £7.50

#### Paracetamol with metoclopramide

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 414, metoclopramide hydrochloride p. 403.

**INDICATIONS AND DOSE**

**Acute migraine**

- **BY MOUTH USING TABLETS**
  - Adult: 2 tablets, to be taken at the onset of attack, followed by 2 tablets every 4 hours if required; maximum 6 tablets per day
  - **BY MOUTH USING EFFERVESCENT POWDER SACHETS**
    - Adult: 2 sachets, to be taken at the onset of attack, followed by 2 sachets every 4 hours if required, sachets to be dissolved in a quarter tumblerful of water; maximum 6 sachets per day

**IMPORTANT SAFETY INFORMATION**

Metoclopramide can cause severe extrapyramidal effects, particularly in young adults.

**CAUTIONS**

Treatment should not exceed 3 months due to risk of tardive dyskinesia.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>17, 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paramax (Zentiva)</td>
<td></td>
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</table>

*Metoclopramide hydrochloride 5 mg, Paracetamol*

500 mg Paramax tablets | 42 tablet | £9.64 DT price = £9.64

*Effervescent powder*

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>13, 17, 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paramax (Zentiva)</td>
<td></td>
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</tbody>
</table>

*Metoclopramide hydrochloride 5 mg, Paracetamol*

500 mg Paramax sachets sugar-free | 42 sachet | £12.52 DT price = £12.52
ANALGESICS > NON-STERoidal ANTI-INFLAMMATORY DRUGS

Aspirin with metoclopramide

The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 114, metoclopramide hydrochloride p. 403.

INDICATIONS AND DOSE

Acute migraine

Adult: 1 sachet, sachet to be mixed in water, and dose to be taken at the start of the attack, then 1 sachet after 2 hours if required; maximum 3 sachets per day

IMPORTANT SAFETY INFORMATION

Metoclopramide can cause severe extrapyramidal effects, particularly in children and young adults.

CAUTIONS

Treatment should not exceed 3 months due to risk of tardive dyskinesia

PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral powder formulations may include lemon.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Powder

CAUTIONARY AND ADVISORY LABELS 13, 21, 32

EXCIPIENTS: May contain Aspartame

Metoclopramide hydrochloride 10 mg, Aspirin DL-Lysine

900 mg MigraMax oral powder sachets sugar-free | 6 sachet POM

DT price = £6.61

Tolfenamic acid

INDICATIONS AND DOSE

Treatment of acute migraine

BY MOUTH

Adult: 200 mg, dose to be taken at onset, then 200 mg after 1–2 hours if required

CONTRA-INDICATIONS

Active gastro-intestinal bleeding • active gastro-intestinal ulceration • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal haemorrhage (two or more distinct episodes) • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • severe heart failure

CAUTIONS

Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease • coagulation defects • connective-tissue disorders • Crohn's disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • heart failure • ischaemic heart disease • peripheral arterial disease • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated) • uncontrolled hypertension

INTER ACTIONS → Appendix 1 (NSAIDs).

SIDE-EFFECTS

Rare: Alveolitis • aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • hepatic damage • interstitial fibrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis

Frequency not known: Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • confusion • Crohn's disease (induction of or exacerbation of) • depression • diarrhea • dizziness • drowsiness • dysuria (most commonly in men) • euphoria • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • hallucination • headache • hearing disturbances • hypersensitivity reactions • insomnia • malaise • nausea • nervousness • paraesthesia • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • tremor • vertigo • visual disturbances

SIDE-EFFECTS, FURTHER INFORMATION

Serious side-effects. For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

BREAST FEEDING

Amount too small to be harmful. Use with caution during breast-feeding.

HEPATIC IMPAIRMENT

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

RENAL IMPAIRMENT

The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

Tolfenamic acid 200 mg Tolfenamic acid 200mg tablets | 10 tablet POM £19.25 DT price = £19.25

Clotam Rapid (Galen Ltd)

Tolfenamic acid 200 mg Clotam Rapid 200mg tablets | 10 tablet POM £12.75 DT price = £19.25

ANTIHISTAMINES > SEDATING ANTIHISTAMINES

Paracetamol with buclizine hydrochloride and codeine phosphate

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 414, codeine phosphate p. 421.

INDICATIONS AND DOSE

MIGRALEVE®

Acute migraine

BY MOUTH

Child 12–14 years: Initially 1 tablet, (pink tablet) to be taken at onset of attack, or if it is imminent, followed
ERGOT ALKALOIDS

Ergotamine tartrate

- **INDICATIONS AND DOSE**
  - **Management of cluster headache**
    - **BY MOUTH USING TABLETS**
    - Adult: 1 mg once daily for 6 nights in 7; occasionally given for 1–2 weeks, dose to be taken at night

- **UNLICENSED USE** Not licensed for the management of cluster headache.
- **CONTRA-INDICATIONS** Acute porphyrias p. 930 - coronary heart disease - hyperthyroidism - inadequately controlled hypertension - obliterative vascular disease - peripheral vascular disease - Raynaud’s syndrome - spondylosis - severe hypertension - temporal arteritis
- **CAUTIONS** Anaemia - cardiac disease - dependence - elderly - risk of peripheral vasospasm
- **INTERACTIONS** → Appendix 1 (ergot alkaloids).
- **SIDE-EFFECTS**
  - Common or very common Abdominal pain - dizziness - nausea - vomiting
  - Uncommon Cyanosis - diarrhoea - hypoaesthesia - pain in extremities - paraesthesia - peripheral vasocnstriction - weakness in extremities
  - Rare Arrhythmias - bradycardia - dyspnoea - ergotism (including absence of pulse and numbness in extremities) - increased blood pressure - intestinal ischaemia - myalgia - rash - tachycardia - urticaria
  - Very rare Gangrene - heart-valve fibrosis - myocardial infarction - myocardial ischaemia
- **Frequency not known** Anxiety - arthralgia - blood disorders - blurred vision - cerebral ischaemia - confusion - constipation - depression - drowsiness - dry mouth - extrapyramidal effects - hallucinations - renal artery spasm - seizures - sleep disturbances - thrombosis - tremor - urinary retention
- **PREGNANCY** Avoid; ocytotic effect on the uterus.
- **BREAST FEEDING** Avoid; ergotism may occur in infant; repeated doses may inhibit lactation.
- **HEPATIC IMPAIRMENT** Avoid in severe impairment — risk of toxicity increased.

- **RENAL IMPAIRMENT** Avoid; risk of renal vasocnstriction.
- **PATIENT AND CARER ADVICE** Peripheral vasospasm Warn patient to stop treatment immediately if numbness or tingling of extremities develops and to contact doctor.
- **LESS SUITABLE FOR PRESCRIBING** Ergotamine tartrate is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. 

**Tablet** 

| CAUTIONARY AND ADVISORY LABELS | 2, 17, 30 |
| Migraine Pink (McNeil Products Ltd) | Buclizine hydrochloride 6.25 mg, Codeine phosphate 8 mg, Paracetamol 500 mg |
| Migraine Pink tablets | 32 tablet (POM) no price available | £3.97 (ED) |
| Migraine (McNeil Products Ltd) | Migraine tablets | 48 tablet (POM) £3.64 (ED) |

**Ergotamine tartrate with caffeine hydrate and cyclizine hydrochloride**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergotamine tartrate above, cyclizine p. 401.

- **INDICATIONS AND DOSE** Treatment of acute migraine and migraine variants unresponsive to analgesics
  - **BY MOUTH**
  - Adult: 1 tablet, to be taken at onset, followed by 0.5–1 tablet after 30 minutes, then 0.5–1 tablet every 30 minutes if required, max. 3 tablets in 24 hours, max. 4 tablets per attack, max. 6 tablets in one week

- **PATIENT AND CARER ADVICE** Patient counselling is advised for cyclizine hydrochloride with caffeine hydrate and ergotamine tartrate tablets (dosage).
- **LESS SUITABLE FOR PRESCRIBING** Cyclizine hydrochloride with caffeine hydrate and ergotamine tartrate (Migril®) is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

| CAUTIONARY AND ADVISORY LABELS | 2, 18 |
| Migril (Wockhardt UK Ltd) | Ergotamine tartrate 2 mg, Cyclizine hydrochloride 50 mg, Caffeine hydrate 100 mg |
| Migril tablets | 100 tablet (POM) £1.00 |

**TRIPTANS**

Almotriptan

- **INDICATIONS AND DOSE** Treatment of acute migraine
  - **BY MOUTH**
  - Adult: 12.5 mg, dose to be taken as soon as possible after onset, followed by 12.5 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 25 mg per day

- **UNLICENSED USE** Not licensed for use in elderly.
- **CONTRA-INDICATIONS** Coronary vasospasm - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension
- **CAUTIONS** Conditions which predispose to coronary artery disease - elderly
- **INTERACTIONS** → Appendix 1 (SHT, agonists).
- **SIDE-EFFECTS**
  - Common or very common Drowsiness - transient increase in blood pressure
Uncommon
Bone pain · chest pain · diarrhoea · dry mouth · dyspepsia · headache · myalgia · palpitation · paraesthesia · tinnitus

Very rare
Myocardial infarction · tachycardia

Frequency not known
Dizziness · fatigue · feeling of weakness · flushing · hypertension · ischaemic colitis · nausea · vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

ALLERGY AND CROSS-SENSITIVITY
Caution in patients with sensitivity to sulfonamides.

PREGNANCY
There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

BREAST FEEDING
Present in milk—avoid breast-feeding for 24 hours.

HEPATIC IMPAIRMENT
Caution in mild to moderate impairment. Avoid in severe impairment.

RENAI IMPAIRMENT
Max. 12.5 mg in 24 hours if eGFR less than 30 mL/minute/1.73 m².

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS

Almotriptan (Non-proprietary)

Almotriptan (as Almotriptan hydrogel male) 12.5 mg

Tablet 12.5 mg 3 tablet 6 tablet (POM) £18.14 6 tablet (POM) £18.14 9 tablet (POM) £27.21

Almogran (Almirall Ltd)

Almotriptan (as Almotriptan hydrogel male) 12.5 mg

Tablet 12.5 mg tablets 3 tablet (POM) £9.07 6 tablet (POM) £18.14 9 tablet (POM) £27.20

Frovatriptan

INDICATIONS AND DOSE
Treatment of acute migraine

BY MOUTH
Adult: 2.5 mg, dose to be taken as soon as possible after onset, followed by 2.5 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 5 mg per day

UNLICENSED USE
Not licensed for use in elderly.

CONTRA-INDICATIONS
Coronary vasospasm · ischaemic heart disease · peripheral vascular disease · previous cerebrovascular accident · previous myocardial infarction · previous transient ischaemic attack · Prinzmetal’s angina · severe hypertension · uncontrolled hypertension

CAUTIONS
Conditions which predispose to coronary artery disease · elderly

INTERACTIONS
Appendix 1 (5HT1 agonists).

SIDE-EFFECTS
Abdominal pain · chills · drowsiness · dry mouth · dyspepsia · headache · myalgia · myasthenia · palpitation · pharyngitis · rhinitis · sweating · tachycardia

Uncommon
Agitation · anorexia · arthralgia · confusion · depersonalisation · depression · diarrhoea · dysarthria · dyspnoea · euphoria · glossitis · hypertension · insomnia · movement disorders · oedema · photophobia · pruritus · rash · stupor · taste disturbance · thirst · tinnitus · tremor · urinary frequency · visual disturbances · yawning

Rare
Asthma · bradycardia · constipation · hypophagia · hypomagnesaemia · hypomagnesaemia · hypokalaemia · hypothyroidism · irritable bowel syndrome · peptic ulcer · purpura · pyrexia · stomatitis · uticaria

Frequency not known
Dizziness · fatigue · feeling of weakness · flushing · nausea · vomiting

SIDE-EFFECTS, FURTHER INFORMATION

CONTRA-INDICATIONS
Coronary vasospasm · cerebrovascular attack · previous myocardial infarction · previous transient ischaemic attack · Prinzmetal’s angina · severe hypertension · uncontrolled hypertension

CAUTIONS
Conditions which predispose to coronary artery disease · elderly

INTERACTIONS
Appendix 1 (5HT1 agonists).

SIDE-EFFECTS
Abdominal pain · chills · drowsiness · dry mouth · dyspepsia · headache · paraesthesia · sweating · visual disturbances

Uncommon
Agitation · anxiety · arthralgia · asthenia · confusion · dehydration · depersonalisation · depression · diarrhoea · dysphagia · flatulence · hypertension · impaired concentration · insomnia · laryngitis · micturition disorders · muscle stiffness · nervousness · palpititation · pharyngitis · pruritus · rhinitis · sinusitis · tachycardia · taste disturbances · thirst · tinnitus · tremor · vertigo

Rare
Abnormal dreams · amnesia · bilirubinaemia · bradycardia · breast tenderness · constipation · epistaxis · gastro-esophageal reflux · hiccup · hypertension · hyperventilation · hypocalcaemia · hypoglycaemia · hypotonia · irritable bowel syndrome · peptic ulcer · purpura · pyrexia · stomatitis · uticaria

Frequency not known
Dizziness · fatigue · feeling of weakness · flushing · nausea · vomiting
SIDE-EFFECTS, FURTHER INFORMATION

Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

- **PREGNANCY** There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.
- **BREAST FEEDING** Present in milk in animal studies— withhold breast-feeding for 24 hours.
- **HEPATIC IMPAIRMENT** Avoid in severe impairment.
- **INTERACTIONS** Conditions which predispose to coronary artery disease - elderly.
- **SIDE-EFFECTS** Bradycardia - palpitation - tachycardia - visual disturbance
- **FURTHER INFORMATION** Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Naratriptan (as Naratriptan hydrochloride) 2.5 mg | Naratriptan 2.5mg tablets | 6 tablet [Pack] | £25.00 DT price = £2.03 |
| Naratriptan (as Naratriptan succinate monohydrate) 2.5 mg | Mylatrip 2.5mg tablets | 6 tablet [Pack] | £16.50 DT price = £11.60 |
| Naratriptan (as Naratriptan hydrochloride) 2.5 mg | Naramig (GlaxoSmithKline UK Ltd) 2.5mg tablets | 6 tablet [Pack] | £24.55 DT price = £2.03 |

**Rizatriptan**

**INDICATIONS AND DOSE**

Treatment of acute migraine

- **BY MOUTH**
  - Adult: 2.5 mg, followed by 2.5 mg after 2 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 20 mg per day

- **INDICATIONS**
  - Coronary vasospasm - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal's angina - severe hypertension - uncontrolled hypertension

- **CAUTIONS**
  - Conditions which predispose to coronary artery disease - elderly

- **INTERACTIONS**
  - Appendix 1 (5HT1 agonists)

- **SIDE-EFFECTS**
  - Common or very common: Decreased alertness - diarrhoea - drowsiness - dry mouth - dysphoria - headache - palpitation - paraesthesia - pharyngeal discomfort - sweating - tachycardia - tremor
  - Rare: Bradycardia - syncope

- **FREQUENCY NOT KNOWN:** Dizziness - fatigue - feeling of weakness - flushing - nausea - seizures - toxic epidermal necrolysis - vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION** Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

- **PREGNANCY** There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

- **BREAST FEEDING** Present in milk in animal studies— withhold breast-feeding for 24 hours.

- **HEPATIC IMPAIRMENT** Reduce dose to 5 mg in mild to moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Reduce dose to 5 mg in mild to moderate impairment. Avoid in severe impairment.

- **DIRECTIONS FOR ADMINISTRATION** Rizatriptan orodispersible tablets should be placed on the tongue, allowed to disperse and swallowed. Rizatriptan oral
Nervous system

**Sumatriptan**

### INDICATIONS AND DOSE

**Treatment of acute migraine**

- **BY MOUTH**
  - Adult: Initially 50–100 mg for 1 dose, followed by 50–100 mg after at least 2 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 300 mg per day
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 6 mg for 1 dose, followed by 6 mg after at least 1 hour if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack), dose to be administered using an auto-injector; not for intravenous injection which may cause coronary vasospasm and angina; maximum 12 mg per day
  - **BY INTRANASAL ADMINISTRATION**
  - Adult 18–65 years: Initially 10–20 mg, dose to be administered into one nostril, followed by 10–20 mg after at least 2 hours if required, to be taken only if headache recurs (patient not responding to initial dose should not take second dose for same attack); maximum 40 mg per day

**Treatment of acute cluster headache**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 6 mg for 1 dose, followed by 6 mg after at least 1 hour if required, to be taken only if headache recurs (patient not responding to initial dose should not take second dose for same attack), dose to be administered using an auto-injector; not for intravenous injection which may cause coronary vasospasm and angina; maximum 12 mg per day

- **BY INTRANASAL ADMINISTRATION**
  - Adult 18–65 years: Initially 10–20 mg, to be administered into one nostril, followed by 10–20 mg after at least 2 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 40 mg per day

- **UNLICENSED USE** Not licensed for use in elderly.

- **CONTRA-INDICATIONS** Coronary vasospasm · ischaemic heart disease · mild uncontrolled hypertension · moderate and severe hypertension · peripheral vascular disease · previous cerebrovascular accident · previous myocardial infarction · previous transient ischaemic attack · Prinzmetal’s angina

- **CAUTIONS** Conditions which predispose to coronary artery disease · elderly · history of seizures · mild, controlled hypertension · pre-existing cardiac disease · risk factors for seizures

- **INTERACTIONS** → Appendix 1 (5HT₁ agonists).

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
  - **SPECIFIC SIDE-EFFECTS**
  - **INTERACTIONS**
  - **SIDE-EFFECTS, FURTHER INFORMATION**
  - Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

- **ALLERGY AND CROSS-SENSITIVITY** Caution in patients with sensitivity to sulfonamides.

- **PREGNANCY** There is limited experience of using 5HT₁ receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

- **BREAST FEEDING** Present in milk but amount probably too small to be harmful; withhold breast-feeding for 12 hours after treatment.

- **HEPATIC IMPAIRMENT** Reduce oral dose to 25–50 mg. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Use with caution.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - Drowsiness may affect performance of skilled tasks (e.g. driving).

- **EXCEPTIONS TO LEGAL CATEGORY**
  - With oral use Sumatriptan 50 mg tablets can be sold to the public to treat previously diagnosed migraine; max. daily dose 100 mg.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 3 |
| RizatRIPTAN (Non-proprietary) |
| RizatRIPTAN (as RizatRIPTAN benzoate) 5 mg RizatRIPTAN 5mg tablets | 3 tablet (PO) £13.37 | 6 tablet (PO) £26.74 DT price + £26.74 |
| RizatRIPTAN (as RizatRIPTAN benzoate) 10 mg RizatRIPTAN 10mg tablets | 3 tablet (PO) £13.37 DT price + £1.40 | 6 tablet (PO) £26.74 |
| MaxALT (Merck Sharp & Dohme Ltd) |
| RizatRIPTAN (as RizatRIPTAN benzoate) 5 mg MaxALT 5mg tablets | 6 tablet (PO) £26.74 DT price + £26.74 |
| RizatRIPTAN (as RizatRIPTAN benzoate) 10 mg MaxALT 10mg tablets | 3 tablet (PO) £13.37 DT price + £1.40 | 6 tablet (PO) £26.74 |

**Oral lyophilisate**

| CAUTIONARY AND ADVISORY LABELS | 3 |
| EXCIPIENTS: May contain Aspartame |
| RizatRIPTAN (Non-proprietary) |
| RizatRIPTAN (as RizatRIPTAN benzoate) 10 mg RizatRIPTAN 10mg oral lyophilisates sugar-free | 3 tablet (PO) £13.37 DT price + £2.24 sugar-free | 6 tablet (PO) £26.74 |
| MaxALT Melt (Merck Sharp & Dohme Ltd) |
| RizatRIPTAN (as RizatRIPTAN benzoate) 10 mg MaxALT Melt 10mg oral lyophilisates sugar-free | 3 tablet (PO) £13.37 DT price + £1.37 sugar-free | 6 tablet (PO) £26.74 DT price + £26.74 sugar-free | 12 tablet (PO) £53.48 |

**Nervous system**

**Patient and carer advice**

Patients or carers should be given advice on how to administer rizatRIPTAN orodispersible tablets and oral lyophilisates.

**Driving and skilled tasks**

Drowsiness may affect performance of skilled tasks (e.g. driving).

Lyophilisates should be placed on the tongue and allowed to dissolve.

**SIDE-EFFECTS**

- **COMMON OR VERY COMMON**
  - Fatigue · head nausea · nasal congestion · vomiting · visual disturbances
  - **COMMON**
  - Nausea · visual disturbances · palpitations · chest discomfort 
  - **SUGGESTED SIDE-EFFECTS**
  - An increased blood pressure (safety signal).
  - **SIDE-EFFECTS, FURTHER INFORMATION**
  - Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or anaphylaxis).

- **ALLERGY AND CROSS-SENSITIVITY** Caution in patients with sensitivity to sulfonamides.

- **PREGNANCY** There is limited experience of using 5HT₁ receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

- **BREAST FEEDING** Present in milk but amount probably too small to be harmful; withhold breast-feeding for 12 hours after treatment.

- **HEPATIC IMPAIRMENT** Reduce oral dose to 25–50 mg. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Use with caution.

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
  - **SPECIFIC SIDE-EFFECTS**
  - **INTERACTIONS**
  - **SIDE-EFFECTS, FURTHER INFORMATION**
  - Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or anaphylaxis).

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- **RENAL IMPAIRMENT** Use with caution.

- **SIDE-EFFECTS**
  - **COMMON OR VERY COMMON**
  - Dizziness · drowsiness · dysphonia · fatigue · flushing · myalgia · nausea · sensory disturbances · transient increase in blood pressure · vomiting · weakness
  - **COMMON**
  - Nausea · visual disturbances · palpitations · Raynaud’s syndrome · seizures · sweating · tachycardia · transient ischaemic ECG changes · tremor · visual disturbances
  - **SIDE-EFFECTS, FURTHER INFORMATION**
  - Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or anaphylaxis).
Zolmitriptan

- **INDICATIONS AND DOSE**

  Treatment of acute migraine

  **BY MOUTH**

  Adult: 2.5 mg, followed by 2.5 mg after at least 2 hours if required, dose to be taken only if migraine recurs; then increased if necessary to 5 mg, dose to be taken only for subsequent attacks in patients not achieving satisfactory relief with 2.5 mg dose; maximum 10 mg per day.

  **BY INTRanasAL ADMINISTRATION**

  Adult: 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs; maximum 10 mg per day.

  **TREATMENT OF ACUTE CLUSTER HEADACHE**

  **BY INTRanasAL ADMINISTRATION**

  Adult: 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs; maximum 10 mg per day.

  **DOSE ADJUSTMENTS DUE TO INTERACTIONS**

  Max. 5 mg in 24 hours with concomitant cimetidine, fluvoxamine, moclobemide, or quinolone antibiotics.

  **DOSE EQUIVALENCe AND CONVERSION**

  1 spray of Zomig™ nasal spray = 5 mg zolmitriptan.

- **UNLICENSED USE** Not licensed for use in elderly. Not licensed for treatment of cluster headaches.

**CONTRA-INDICATIONS** Arrhythmias associated with accessory cardiac conduction pathways - coronary vasospasm - ischaemic heart disease - previous cerebrovascular accident - previous myocardial infarction - Prinzmetal’s angina - severe hypertension - transient ischaemic attack - uncontrolled hypertension - Wolff-Parkinson-White syndrome

- **CAUTIONS** Conditions which predispose to coronary artery disease - elderly - should not be taken within 24 hours of any other 5HT1-receptor agonist

- **INTERACTIONS** → Appendix 1 (5HT1 agonists).

- **SIDE-EFFECTS**

  - **GENERAL SIDE-EFFECTS**
    - Common or very common Abdominal pain - drowsiness - dry mouth - dysphagia - headache - muscle weakness - myalgia - palpitation - paraesthesia
    - Uncommon Polyuria - tachycardia - transient increase in blood pressure
    - Rare: Urticaria
    - Very rare Angina - gastrointestinal infarction - ischaemic colitis - myocardial infarction - splenic infarction
    - Frequency not known Dizziness - fatigue - feeling of weakness - flushing

  **SPECIFIC SIDE-EFFECTS**

  - With intranasal use Epistaxis - taste disturbance

  **SIDE-EFFECTS, FURTHER INFORMATION**

  Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

- **PREGNANCY**

  There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

- **BREAST FEEDING**

  Use with caution—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**

  Max. 5 mg in 24 hours in moderate or severe impairment.

- **DIRECTIONS FOR ADMINISTRATION**

  Zolmitriptan orodispersible tablets should be placed on the tongue, allowed to disperse and swallowed.

- **PATIENT AND CARER ADVICE**

  Patients or carers should be given advice on how to administer zolmitriptan orodispersible tablets.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Zolmitriptan (Non-proprietary) Zolmitriptan 2.5 mg** Zolmitriptan 2.5mg tablets | 6 tablet £1.41 DT price = £1.38 | 12 tablet £2.82
- **Zolmitriptan 5 mg** Zolmitriptan 5mg tablets | 6 tablet £3.60 | 12 tablet £7.20
- **Zomig** (AstraZeneca UK Ltd) Zolmitriptan 2.5 mg Zomig 2.5mg tablets | 6 tablet £3.94 DT price = £1.38

**Orodispensible tablet**

EXCIPIENTS: May contain Aspartame

- **Zolmitriptan (Non-proprietary) Zolmitriptan 2.5 mg orodispersible tablets** sugar free-sugar-free | 6 tablet £0.35 DT price = £1.42
- **Zolmitriptan 5 mg orodispersible tablets** sugar free-sugar-free | 6 tablet £0.35 DT price = £1.11
- **Zomig Rapimelt** (AstraZeneca UK Ltd) Zolmitriptan 2.5 mg Zomig Rapimelt 2.5mg orodispersible tablets sugar-free | 6 tablet £2.99 DT price = £1.42

**Spray**

- **Zomig** (AstraZeneca UK Ltd) Zolmitriptan 50 mg per 1 ml Zomig 50mg/0.1ml nasal spray 0.1ml unit dose | 6 unit dose £36.50 DT price = £36.50
6.2 Neuropathic pain

Neuropathic pain

Overview and management

Neuropathic pain, which occurs as a result of damage to neural tissue, includes phantom limb pain, compression neuropathies, peripheral neuropathies (e.g. due to diabetes p. 625, chronic excessive alcohol intake, HIV infection p. 590, chemotherapy, idiopathic neuropathy), trauma, central pain (e.g. pain following stroke, spinal cord injury, and syringomyelia), and postherpetic neuralgia (peripheral nerve damage following acute herpes zoster infection (shingles)). The pain may occur in an area of sensory deficit and is sometimes accompanied by pain that is evoked by a non-noxious stimulus (allodynia).

Trigeminal neuralgia is also caused by dysfunction of neural tissue, but its management is distinct from other forms of neuropathic pain.

Neuropathic pain is generally managed with a tricyclic antidepressant or with certain antiepileptic drugs.

Amitriptyline hydrochloride p. 349 [unlicensed indication] and pregabalin p. 304 are effective treatments for neuropathic pain. Amitriptyline hydrochloride and pregabalin can be used in combination if the patient has an inadequate response to either drug at the maximum tolerated dose.

Nortriptyline p. 355 [unlicensed indication] may be better tolerated than amitriptyline hydrochloride.

Gabapentin p. 295 is also effective for the treatment of neuropathic pain.

Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for tramadol hydrochloride p. 435, morphine p. 429, and oxycodone hydrochloride p. 431; however, treatment with morphine or oxycodone hydrochloride should be initiated only under specialist supervision. Tramadol hydrochloride can be prescribed when other treatments have been unsuccessful, while the patient is waiting for assessment by a specialist.

Patients with localised pain who are unable to take oral medicines may benefit from topical local anaesthetic preparations, such as lidocaine hydrochloride p. 97 medicated plasters, while awaiting specialist review.

Capsaicin below is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use). Capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia. A self-adhesive patch containing capsaicin 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients. It should be used under specialist supervision. A corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain.

Neuromodulation by spinal cord stimulation may be of benefit in some patients. Many patients with chronic neuropathic pain require multidisciplinary management, including physiotherapy and psychological support.

Trigeminal neuralgia

Surgery may be the treatment of choice in many patients; a neurological assessment will identify those who stand to benefit. Carbamazepine p. 291 taken during the acute stages of trigeminal neuralgia, reduces the frequency and severity of attacks. It is very effective for the severe pain associated with trigeminal neuralgia and (less commonly) glossopharyngeal neuralgia. Blood counts and electrolytes should be monitored when high doses are given. Small doses should be used initially to reduce the incidence of side-effects e.g. dizziness. Some cases respond to phenytoin p. 302; the drug may be given by intravenous infusion (possibly as fosphenytoin sodium p. 294) in a crisis (specialist use only).

Chronic facial pain

Chronic oral and facial pain including persistent idiopathic facial pain (also termed ‘atypical facial pain’) and temporomandibular dysfunction (previously termed temporomandibular joint pain dysfunction syndrome) may call for prolonged use of analgesics or for other drugs. Tricyclic antidepressants may be useful for facial pain [unlicensed indication], but are not on the Dental Practitioners’ List. Disorders of this type require specialist referral and psychological support to accompany drug treatment. Patients on long-term therapy need to be monitored both for progress and for side-effects.

Other drugs used for Neuropathic pain

Amanadine hydrochloride, p. 390

ANALGESICS > PLANT ALKALOIDS

Capsaicin

- INDICATIONS AND DOSE

AXSAIN®

Post-herpetic neuralgia

- TO THE SKIN
  - Adult: Apply 3–4 times a day, dose to be applied sparingly; important; after lesions have healed, not more often than every 4 hours

PAINFUL DIABETIC NEUROPATHY (UNDER EXPERT SUPERVISION)

- TO THE SKIN
  - Adult: Apply 3–4 times a day for 8 weeks then review, dose to be applied sparingly, not more often than every 4 hours

OUTENZA®

Peripheral neuropathic pain in non-diabetic patients (under the supervision of a physician)

- BY TRANSDERMAL APPLICATION USING PATCHES
  - Adult: (consult product literature)

ZACIN®

Symptomatic relief in osteoarthritis

- TO THE SKIN
  - Adult: Apply 4 times a day, dose to be applied sparingly, not more often than every 4 hours

- CAUTIONS

GENERAL CAUTIONS

Avoid contact with broken skin • avoid contact with inflamed skin

SPECIFIC CAUTIONS

- With topical use • Avoid contact with eyes • avoid hot shower or bath just before or after application (burning sensation enhanced) • avoid inhalation of vapours • not to be used under tight bandages
- With transdermal use • avoid contact with the face, scalp or in proximity to mucous membranes • avoid holding near eyes or mucous membranes • recent cardiovascular events • uncontrolled hypertension

- SIDE-EFFECTS

- Common or very common
  - With topical use • Transient burning sensation during initial treatment (particularly if too much used or if administered less than 3–4 times daily)
  - With transdermal use • Application site reactions • erythema • pruritus • transient burning
  - Uncommon
  - With transdermal use • Burning sensation • cough • dysgeusia • eye irritation • first degree AV block • hypertension • hypoaesthesia • muscle spasm • nausea • pain in extremities
Hypnotics and anxiolytics

Overview
Most anxiolytics (‘sedatives’) will induce sleep when given at night and most hypnotics will sedate when given during the day. Prescribing of these drugs is widespread but dependence (both physical and psychological) and tolerance occur. This may lead to difficulty in withdrawing the drug after the patient has been taking it regularly for more than a few weeks. Hypnotics and anxiolytics should therefore be reserved for short courses to alleviate acute conditions after causal factors have been established.

Benzodiazepines are the most commonly used anxiolytics and hypnotics; they act at benzodiazepine receptors which are associated with gamma-aminobutyric acid (GABA) receptors. Older drugs such as meprobamate p. 324 and barbiturates are not recommended—they have more side-effects and interactions than benzodiazepines and are much more dangerous in overdose.

Benzodiazepine indications
- Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.
- The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate.
- Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress.

Dependence and withdrawal
Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one. It is characterised by insomnia, anxiety, loss of appetite and of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines.

Benzodiazepine withdrawal should be flexible and carried out at a reduction rate that is tolerable for the patient. The rate should depend on the initial dose of benzodiazepine, duration of use, and the patient’s clinical response. Short-term users of benzodiazepines (2–4 weeks only) can usually taper off within 2–4 weeks. However, long-term users should be withdrawn over a much longer period of several months or more.

A suggested protocol for withdrawal for prescribed long-term benzodiazepine patients is as follows:
- Transfer patient stepwise, one dose at a time over about a week, to an equivalent daily dose of diazepam preferably taken at night.
- Reduce diazepam dose, usually by 1–2 mg every 2–4 weeks (in patients taking high doses of benzodiazepines, initially it may be appropriate to reduce the dose by up to one-tenth every 1–2 weeks). If uncomfortable withdrawal symptoms occur, maintain this dose until symptoms lessen.
- Reduce diazepam dose further, if necessary in smaller steps; steps of 500 micrograms may be appropriate towards the end of withdrawal. Then stop completely.
- For long-term patients, the period needed for complete withdrawal may vary from several months to a year or more.

Approximate equivalent doses, diazepam 5 mg
- alprazolam 250 micrograms
- clobazam 10 mg
- clonazepam 250 micrograms
- flurazepam 7.5–15 mg
- clordiazepoxide 12.5 mg
- loprazolam 0.5–1 mg
- lorazepam 500 micrograms
- lormetazepam 0.5–1 mg
- nitrazepam 5 mg
- oxazepam 10 mg
- temazepam 10 mg

Withdrawal symptoms for long-term benzodiazepine patients usually resolve within 6–18 months of the last dose. Some patients will recover more quickly, others may take longer. The addition of beta-blockers, antidepressants and antipsychotics should be avoided where possible.

Counselling can be of considerable help both during and after the taper.
Hypnotics
Before a hypnotic is prescribed the cause of the insomnia should be established and, where possible, underlying factors should be treated. However, it should be noted that some patients have unrealistic sleep expectations, and others underestimate their alcohol consumption which is often the cause of the insomnia. Short-acting hypnotics are preferable in patients with sleep onset insomnia, when sedation the following day is undesirable, or when prescribing for elderly patients. Long-acting hypnotics are indicated in patients with poor sleep maintenance (e.g. early morning waking) that causes daytime effects, when an anxiolytic effect is needed during the day, or when sedation the following day is acceptable.
Transient insomnia may occur in those who normally sleep well and may be due to extraneous factors such as noise, shift work, and jet lag. If a hypnotic is indicated one that is rapidly eliminated should be chosen, and only one or two doses should be given.
Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than three weeks (preferably only one week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.
Chronic insomnia is rarely benefited by hypnotics and is sometimes due to mild dependence caused by injudicious prescribing of hypnotics. Psychiatric disorders such as anxiety, depression, and abuse of drugs and alcohol are common causes. Sleep disturbance is very common in depressive illness and early wakening is often a useful pointer. The underlying psychiatric complaint should be treated, adapting the drug regimen to alleviate insomnia. For example, clomipramine hydrochloride p. 351 or mirtazapine p. 349 prescribed for depression will also help to promote sleep if taken at night. Other causes of insomnia include daytime cat-napping and physical causes such as pain, pruritus, and dyspnoea.
Hypnotics should not be prescribed indiscriminately and routine prescribing is undesirable. They should be reserved for short courses in the acutely distressed. Tolerance to their effects develops within 3 to 14 days of continuous use and long-term efficacy cannot be assured. A major drawback of long-term use is that withdrawal can cause rebound insomnia and a withdrawal syndrome.
Where prolonged administration is unavoidable hypnotics should be discontinued as soon as feasible and the patient warned that sleep may be disturbed for a few days before normal rhythm is re-established; broken sleep with vivid dreams may persist for several weeks.
Elderly
Benzodiazepines and the Z–drugs should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.
Dental patients
Some anxious patients may benefit from the use of hypnotics during dental procedures such as temazepam p. 451 or diazepam p. 321. Temazepam is preferred when it is important to minimise any residual effect the following day.
Benzodiazepines
Benzodiazepines used as hypnotics include nitrazepam p. 450 and flurazepam p. 449 which have a prolonged action and may give rise to residual effects on the following day; repeated doses tend to be cumulative.
Lorazepam p. 449, lormetazepam p. 450, and temazepam act for a shorter time and they have little or no hangover effect. Withdrawal phenomena are more common with the short-acting benzodiazepines.
If insomnia is associated with daytime anxiety then the use of a long-acting benzodiazepine anxiolytic such as diazepam given as a single dose at night may effectively treat both symptoms.
Zaleplon, zolpidem, and zopiclone
Zaleplon p. 453, zolpidem tartrate p. 454 and zopiclone p. 454 are non-benzodiazepine hypnotics (sometimes referred to as Z-drugs), but they act at the benzodiazepine receptor. They are not licensed for long-term use; dependence has been reported in a small number of patients. Zolpidem tartrate and zopiclone have a short duration of action; zaleplon is very short acting.
Chloral and derivatives
There is no convincing evidence that they are particularly useful in the elderly and their role as hypnotics is now very limited.
Clomethiazole
Clomethiazole p. 452 may be a useful hypnotic for elderly patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and dependence occurs.
Antihistamines
Some antihistamines such as promethazine hydrochloride p. 269 are on sale to the public for occasional insomnia; their prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.
Alcohol
Alcohol is a poor hypnotic because the diuretic action interferes with sleep during the latter part of the night. Alcohol also disturbs sleep patterns, and so can worsen sleep disorders.
Melatonin
Melatonin p. 453 is a pineal hormone; it is licensed for the short-term treatment of insomnia in adults over 55 years.
Anxiolytics
Benzodiazepine anxiolytics can be effective in alleviating anxiety states. Although these drugs are sometimes prescribed for stress-related symptoms, unhappiness, or minor physical disease, their use in such conditions is inappropriate. Benzodiazepine anxiolytics should not be used as sole treatment for chronic anxiety, and they are not appropriate for treating depression or chronic psychosis. In bereavement, psychological adjustment may be inhibited by benzodiazepines.
Anxiolytic benzodiazepine treatment should be limited to the lowest possible dose for the shortest possible time. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with marked personality disorders.
Some antidepressant drugs are licensed for use in anxiety and related disorders. Some antipsychotic drugs, in low doses, are also sometimes used in severe anxiety for their sedative action, but long-term use should be avoided because of the risk of adverse effects. The use of antihistamines (e.g. hydroxyzine hydrochloride p. 268) for their sedative effect in anxiety is not appropriate.
Beta-adrenoceptor blocking drugs do not affect psychological symptoms of anxiety, such as worry, tension, and fear, but they do reduce autonomic symptoms, such as palpitation and tremor; they do not reduce non-autonomic symptoms, such as muscle tension. Beta-blockers are therefore indicated for patients with predominantly somatic symptoms; this, in turn, may prevent the onset of worry and fear.
Benzodiazepines

Benzodiazepines are indicated for the short-term relief of severe anxiety; long-term use should be avoided. Diazepam, alprazolam p. 320, chlordiazepoxide hydrochloride p. 321, and clozazepam p. 314 have a sustained action. Shorter-acting compounds such as lorazepam p. 317 and oxazepam p. 324 may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms. In panic disorders (with or without agoraphobia) resistant to antidepressant therapy, a benzodiazepine may be used; alternatively, a benzodiazepine may be used as short-term adjunctive therapy at the start of antidepressant treatment to prevent the initial worsening of symptoms.

Diazepam or lorazepam are very occasionally administered intravenously for the control of panic attacks. This route is the most rapid but the procedure is not without risk and should be used only when alternative measures have failed. The intramuscular route has no advantage over the oral route.

Buspirone

Buspirone hydrochloride p. 320 is thought to act at specific serotonin (5HT1A) receptors. Response to treatment may take up to 2 weeks. It does not alleviate the symptoms of benzodiazepine withdrawal. Therefore a patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone hydrochloride. The dependence and abuse potential of buspirone hydrochloride is low; it is, however, licensed for short-term use only (but specialists occasionally use it for several months).

Meprobamate

Meprobamate p. 324 is less effective than the benzodiazepines, more hazardous in overdosage, and can also induce dependence. It is not recommended.

Barbiturates

The intermediate-acting barbiturates have a place only in the treatment of severe intractable insomnia in patients already taking barbiturates; they should be avoided in the elderly. Intermediate-acting barbiturate preparations containing amobarbital sodium, butobarbital, and secobarbital sodium are available on a named patient basis.

The long-acting barbiturate phenobarbital is still sometimes of value in epilepsy but its use as a sedative is unjustified.

The very short-acting barbiturate thiopental sodium p. 316 is used in anaesthesia. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

Hypnotics, Sedatives and Anxiolytics > Benzodiazepines

Flurazepam

- INDICATIONS AND DOSE

Insomnia (short-term use)

- BY MOUTH

- Adult: 15–30 mg once daily, dose to be taken at bedtime, for debilitated patients, use elderly dose

- Elderly: 15 mg once daily, dose to be taken at bedtime

- CONTRA-INDICATIONS

Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

- CAUTIONS

Acute porphyrias p. 930 - hypoalbuninaemia - marked personality disorder - muscle weakness

CAUTIONS, FURTHER INFORMATION

Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the

IDANTS-EFFECTS

- Common or very common Amnesia - ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness - muscle weakness - paradoxical increase in aggression


- Rare Apnoea - blood disorders - jaundice - respiratory depression - skin reactions

- BREAST FEEDING

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

- HEPATIC IMPAIRMENT

Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer.

- AVOID in severe impairment.

- PATIENT AND CARER ADVICE

Driving and skilled tasks May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

- NATIONAL FUNDING/ACCESS DECISIONS

NHS restrictions Flurazepam capsules are not prescribable under the NHS.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 19

- Dalmane (Meda Pharmaceuticals Ltd)

Flurazepam (as Flurazepam hydrochloride) 15 mg Dalmane 15mg capsules 30 capsule [POM] £6.73 [Q2-3]

Flurazepam (as Flurazepam hydrochloride) 30 mg Dalmane 30mg capsules 30 capsule [POM] £8.63 [Q4-1]

Loprazolam

- INDICATIONS AND DOSE

Insomnia (short-term use)

- BY MOUTH

- Adult: 1 mg once daily, then increased to 1.5–2 mg once daily if required, dose to be taken at bedtime, for debilitated patients, use elderly dose

- Elderly: 0.5–1 mg once daily, dose to be taken at bedtime

- CONTRA-INDICATIONS

Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

- CAUTIONS

Acute porphyrias p. 930 - hypoalbuninaemia - marked personality disorder - muscle weakness

CAUTIONS, FURTHER INFORMATION

Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the
impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**SIDE-EFFECTS**
- **Common or very common** Amnesia - ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression
- **Uncommon** Changes in libido - dizziness - dysarthria - gastro-intestinal disturbances - gynaecostasia - headache - hypotension - incontinence - salivation changes - slurred speech - tremor - urinary retention - vertigo - visual disturbances
- **Rare** Apnoea - blood disorders - jaundice - respiratory depression - skin reactions

**BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**HEPATIC IMPAIRMENT** Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer. Avoid in severe impairment.

**RENAL IMPAIRMENT** Start with small doses in severe impairment.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**
May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Lormetazepam (Non-proprietary)</td>
<td>Lormetazepam (as Lormetazepam mesilate) 1 mg Lormetazepam 1mg tablets</td>
</tr>
</tbody>
</table>

**Nitrazepam**

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**

- **BY MOUTH**
  - Adult: 5–10 mg daily, dose to be taken at bedtime, for debilitated patients, use elderly dose
  - Elderly: 2.5–5 mg daily, dose to be taken at bedtime

**CONTRA-INDICATIONS**
Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

**CAUTIONS**
Acute porphyrias p. 930 - hypoalbuminaemia - marked personality disorder - muscle weakness

**CAUTIONS, FURTHER INFORMATION**
Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**SIDE-EFFECTS**
- **Common or very common** Amnesia - ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression
- **Uncommon** Changes in libido - dizziness - dysarthria - gastro-intestinal disturbances - gynaecostasia - headache - hypotension - incontinence - salivation changes - slurred speech - tremor - urinary retention - vertigo - visual disturbances
- **Rare** Apnoea - blood disorders - jaundice - respiratory depression - skin reactions

**BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.
**Hepatic Impairment**  Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer.  Avoid in severe impairment.

**Renal Impairment**  Start with small doses in severe impairment.

**Patient and Carer Advice**

**Driving and skilled tasks**  May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 19**

- Temazepam (Non-proprietary)
- Nitrazepam 5 mg Nitrazepam 5mg tablets  | 28 tablet  | £5.00  
- Mogadon (Meda Pharmaceuticals Ltd)  
- Nitrazepam 5 mg Mogadon 5mg tablets  | 30 tablet  | £5.76

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS 19**

- Temazepam (Non-proprietary)
- Nitrazepam 500 microgram per 1 ml Nitrazepam 2.5mg/5ml oral suspension  | 70 ml  | £114.00  DT price = £114.00

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**Temazepam**

**Indications and Use**

**Insomnia (short-term use)**

- **By mouth**
  - Adult: 10–20 mg once daily, alternatively 30–40 mg once daily, higher dose range only to be administered in exceptional circumstances, dose to be taken at bedtime, for debilitated patients, use elderly dose.
  - Elderly: 10 mg once daily, alternatively 20 mg once daily, higher dose only to be administered in exceptional circumstances, dose to be taken at bedtime.

**Conscious sedation for dental procedures**

- **By mouth**
  - Adult: 15–30 mg, to be administered 30–60 minutes before procedure.

**Premedication before surgery or investigatory procedures**

- **By mouth**
  - Adult: 10–20 mg, to be taken 1–2 hours before procedure, alternatively 30 mg, to be taken 1–2 hours before procedure, higher alternate dose only administered in exceptional circumstances.
  - Elderly: 10 mg, to be taken 1–2 hours before procedure, alternatively 20 mg, to be taken 1–2 hours before procedure, higher alternate dose only administered in exceptional circumstances.

**Unlicensed Use**  Temazepam doses in BNF may differ from those in product literature.  Not licensed for conscious sedation for dental procedures.

**Contra-Indications**  CNS depression • compromised airway • hyperkinesia • not for use alone to treat chronic psychosis • not for use alone to treat depression (or anxiety associated with depression) • obsessional state • phobic states • respiratory depression

**Caution**  Hypoalbuninaemia • muscle weakness • organic brain changes • personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive)—may increase risk of dependence

**Cautions, Further Information**

- Paradoxical effects  A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**Side-Effects**

- Common or very common  Amnesia • ataxia (especially in the elderly) • confusion (especially in the elderly) • dependence • drowsiness the next day • lightheadedness the next day • muscle weakness • paradoxical increase in aggression

- Uncommon  Changes in libido • dizziness • dysarthria • gastrointestinal disturbances • gynaecomastia • headache • hypotension • incontinence • salivation changes • slurred speech • tremor • urinary retention • vertigo • visual disturbances

- Rare  Apnoea • blood disorders • jaundice • skin reactions

- Frequency not known  Respiratory depression (may be marked when used for sedation; facilities for its treatment are essential)

**Breast Feeding**  Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**Hepatic Impairment**  Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

 If treatment is necessary, benzodiazepines with shorter half-lives are safer.

**Renal Impairment**  Start with small doses in severe impairment.

**Patient and Carer Advice**

**Driving and skilled tasks**  May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

 Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of undertaking skilled tasks (e.g. driving) afterwards. Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

**Profession Specific Information**

Dental practitioners’ formulary

Temazepam Tablets and Oral Solution may be prescribed.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 19**

- Temazepam (Non-proprietary)
  - Temazepam 10 mg Temazepam 10mg tablets  | 28 tablet  | £35.00  DT price = £2.32
  - Temazepam 20 mg Temazepam 20mg tablets  | 28 tablet  | £35.00  DT price = £2.32

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 19**

- Temazepam (Non-proprietary)
  - Temazepam 2 mg per 1 ml  | 300 ml  | £121.08  DT price = £121.03
**HYPNOTICS, SEDATIVES AND ANXIOLYTICS > NON-BENZODIAZEPINE HYPNOTICS AND SEDATIVES**

### Chloral hydrate

- **INDICATIONS AND DOSE**
  - **Insomnia (short-term use) using Chloral Mixture, BP 2000**
    - **BY MOUTH USING ORAL SOLUTION**
      - Adult: 0.5–2 g daily, dose to be taken at bedtime
  - **Insomnia (short-term use), using chloral hydrate 143.3 mg/5 ml oral solution**
    - **BY MOUTH USING ORAL SOLUTION**
      - Adult: 15–30 mL, alternatively 430–860 mg once daily, dose to be taken with water or milk at bedtime; maximum 70 mL per day; maximum 2 g per day
  - **Insomnia (short-term use), using chloral betaine 707 mg (= 414 mg chloral hydrate) tablets**
    - **BY MOUTH USING TABLETS**
      - Adult: 1–2 tablets, alternatively 414–828 mg once daily, dose to be taken with water or milk at bedtime; maximum 4 tablets per day; maximum 2 g per day

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 · gastritis · severe cardiac disease
- **CAUTIONS** Avoid contact with mucous membranes · avoid contact with skin · avoid prolonged use (and abrupt withdrawal thereafter) · reduce dose in debilitated · reduce dose in elderly
- **INTERACTIONS** → Appendix 1 (anxiolytics and hypnotics).
- **SIDE-EFFECTS** Abdominal distention · delirium (especially on abrupt withdrawal) · dependence · excitement · flatulence · gastric irritation · headache · ketonuria · nausea · rash · tolerance · vomiting
- **PREGNANCY** Avoid.
- **BREAST FEEDING** Risk of sedation in infant—avoid.
- **HEPATIC IMPAIRMENT** Reduce dose in mild to moderate impairment. Can precipitate coma. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Avoid in severe impairment.
- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use For administration **by mouth** dilute liquid with plenty of water or juice to mask unpleasant taste.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include black currant.
  - When prepared extemporaneously, the BP states Chloral Mixture, BP 2000 consists of chloral hydrate 500 mg/5 mL in a suitable vehicle.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.
  - **LESS SUITABLE FOR PRESCRIBING** Chloral hydrate is less suitable for prescribing in insomnia.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

#### Tablet

**CAUTIONARY AND ADVISORY LABELS** 19, 27
- **Chloral hydrate (Non-proprietary)**

  - Cloral betaine 707 mg Cloral betaine 707mg tablets | 30 tablet [Pot] £68.00–£138.59 DT price = £138.59

### Clomethiazole

(Chlormethiazole)

- **INDICATIONS AND DOSE**
  - **Severe insomnia (short-term use)**
    - **BY MOUTH USING CAPSULES**
      - Elderly: 192–384 mg once daily, dose to be taken at bedtime
    - **BY MOUTH USING ORAL SOLUTION**
      - Elderly: 5–10 mL once daily, dose to be taken at bedtime
  - **Restlessness and agitation**
    - **BY MOUTH USING CAPSULES**
      - Elderly: 192 mg 3 times a day
    - **BY MOUTH USING ORAL SOLUTION**
      - Elderly: 5 mL 3 times a day
  - **Alcohol withdrawal**
    - **BY MOUTH USING CAPSULES**
      - Adult: Initially 2–4 capsules, to be repeated if necessary after some hours. 9–12 capsules daily in 3–4 divided doses on day 1 (first 24 hours), then 6–8 capsules daily in 3–4 divided doses on day 2, then 4–6 capsules daily in 3–4 divided doses on day 3, dose then to be gradually reduced over days 4–6, total duration of treatment for no more than 9 days
    - **BY MOUTH USING ORAL SOLUTION**
      - Adult: Initially 10–20 mL, to be repeated if necessary after some hours, then 45–60 mL daily in 3–4 divided doses on day 1 (first 24 hours), then 30–40 mL daily in 3–4 divided doses on day 2, then 20–30 mL daily in 3–4 divided doses on day 3, dose then to be gradually reduced over days 4–6, total duration of treatment for no more than 9 days

- **CONTRA-INDICATIONS** Acute pulmonary insufficiency · alcohol-dependent patients who continue to drink
- **CAUTIONS** Avoid prolonged use (and abrupt withdrawal thereafter) · cardiac disease (confusional state may indicate hypoxia) · chronic pulmonary insufficiency · elderly · excessive sedation may occur (particularly with higher doses) · history of drug abuse · marked personality disorder · respiratory disease (confusional state may indicate hypoxia) · sleep apnoea syndrome
- **INTERACTIONS** → Appendix 1 (anxiolytics and hypnotics).
- **SIDE-EFFECTS**
  - **Common or very common** Conjunctival irritation · headache · increased bronchial secretions · increased nasopharyngeal secretions · nasal congestion · nasal irritation
  - **Rare** Alterations in liver enzymes · anaphylaxis · bullous eruption · confusion · dependence · gastro-intestinal disturbances · paradoxical excitement · rash · urticaria
- **PREGNANCY** Avoid if possible—especially during the first and third trimesters.
- **BREAST FEEDING** Use only if benefit outweighs risk—present in breast milk but effects unknown.
- **HEPATIC IMPAIRMENT** Reduce dose. Can precipitate coma.
- **RENAL IMPAIRMENT** Start with small doses in severe impairment. Increased cerebral sensitivity.
**Melatonin**

### INDICATIONS AND DOSE

**Insomnia (short-term use)**

- **BY MOUTH USING MODIFIED-RELEASE TABLETS**
  - Adult 55 years and over: 2 mg once daily for up to 2 weeks, dose to be taken 1–2 hours before bedtime

### CAUTIONS

Autoimmune disease (manufacturer advises avoid—no information available)

### INTERACTIONS

→ Appendix 1 (melatonin).

### SIDE-EFFECTS

- **Uncommon** Abdominal pain · abnormal dreams · anxiety · chest pain · dizziness · dry mouth · dry skin · dyspnea · dysuria · headache · hypertension · irritability · malaise · mouth ulceration · nausea · nervousness · proteinuria · pruritus · rash · restlessness · weight gain

- **Rare** Aggression · angina · arthritis · electrolyte disturbances · flatulence · gastritis · haematuria · halitosis · hot flushes · hypervigilidemia · impaired memory · increased libido · lacrimation · leucopenia · mood changes · muscle spasm · nail disorder · palpitation · paraesthesia · polyuria · priapism · prostatitis · restless legs syndrome · salivation · syncope · thirst · thrombocytopenia · visual disturbances · vomiting

- **Frequency not known** Galactorrhoea · mouth oedema · tongue oedema

### PREGNANCY

No information available—avoid.

### BREAST FEEDING

Present in milk—avoid.

### HEPATIC IMPAIRMENT

Clearance reduced—avoid.

### RENAL IMPAIRMENT

No information available—use with caution.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- **Modified-release tablet**
  - Melatonin 3 mg Melatonin 3mg modified-release tablets | 120 tablet (PoD) no price available
  - Circadin (Flynn Pharma Ltd)
  - Melatonin 2 mg Circadin 2mg modified-release tablets | 30 tablet (PoD) £15.39 DT price = £15.39

**Zaleplon**

### INDICATIONS AND DOSE

**Insomnia (short-term use)**

- **BY MOUTH**
  - Adult: 10 mg daily for up to 2 weeks, dose to be taken at bedtime or after going to bed if difficulty falling asleep
  - Elderly: 5 mg daily for up to 2 weeks, dose to be taken at bedtime or after going to bed if difficulty falling asleep

### CONTRA-INDICATIONS

Marked neuromuscular respiratory weakness · sleep apnoea syndrome · unstable myasthenia gravis

### CAUTIONS

Avoid prolonged use (risk of tolerance and withdrawal symptoms) · depression (risk of suicidal ideation) · history of alcohol abuse · history of drug abuse · muscle weakness · myasthenia gravis · respiratory insufficiency (avoid if severe)

### INTERACTIONS

→ Appendix 1 (anxiolytics and hypnotics).

### SIDE-EFFECTS

- **Common or very common** Amnesia · drowsiness · dysmenorrhea · paraesthesia

- **Uncommon** Anorexia · asthenia · confusion · depersonalisation · depression · disturbances of hearing · disturbances of smell · disturbances of speech · disturbances of vision · dizziness · hallucinations · impaired concentration · incoordination · nausea · photosensitivity

- **Frequency not known** Paradoxical effects · sleep-walking

**SIDE-EFFECTS, FURTHER INFORMATION**

Paradoxical effects A paradoxical increase in hostility and aggression may be reported. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

### PREGNANCY

Use only if necessary and restrict to occasional short-term use. Risk of withdrawal symptoms in neonate if used in late pregnancy.

### BREAST FEEDING

Present in milk but amount probably too small to be harmful.

### HEPATIC IMPAIRMENT

Reduce dose to 5 mg. Can precipitate coma. Avoid if severe impairment.

### RENAL IMPAIRMENT

Avoid in severe impairment.

### PATIENT AND CARER ADVICE

Patients should be advised not to take a second dose during a single night.

### NATIONAL FUNDING/ACCESS DECISIONS

**NICE technology appraisals (TAs)**

- Zaleplon, zolpidem, and zopiclone for the short-term management of insomnia (April 2004) NICE TA77

Zaleplon is recommended for the short-term management of severe insomnia that interferes with normal daily life, and should be prescribed for short periods of time only. [www.nice.org.uk/TA77](http://www.nice.org.uk/TA77)

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.
### Zolpidem tartrate

#### INDICATIONS AND DOSE

**Insomnia (short-term use)**

- **BY MOUTH**
  - Adult: 10 mg daily for up to 4 weeks, dose to be taken at bedtime, for debilitated patients, use elderly dose
  - Elderly: 5 mg daily for up to 4 weeks, dose to be taken at bedtime

- **CONTRA-INDICATIONS**
  - Acute respiratory depression
  - Marked neuromuscular respiratory weakness
  - Obstructive sleep apnoea
  - Psychotic illness
  - Severe respiratory depression
  - Unstable myasthenia gravis

- **CAUTIONS**
  - Avoid prolonged use (and abrupt withdrawal thereafter)
  - Depression
  - History of drug abuse
  - History of alcohol abuse
  - Muscle weakness
  - Myasthenia gravis

- **INTERACTIONS**
  - Paradoxical effects
  - Antihistamines
  - Atopy
  - CNS depressants
  - Opioids
  - Barbiturates
  - Alcohol

#### SIDE-EFFECTS

- Paradoxical effects
  - A paradoxical increase in hostility and aggression may be reported. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

- **PREGNANCY**
  - Avoid regular use (risk of neonatal withdrawal symptoms); high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

- **BREAST FEEDING**
  - Present in milk—avoid.

- **HEPATIC IMPAIRMENT**
  - Reduce dose to 5 mg. Can precipitate coma. Avoid if severe impairment.

- **RENAL IMPAIRMENT**
  - Use with caution.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Drowsiness may persist the next day—leave at least 8 hours between taking zolpidem and performing skilled tasks (e.g., driving, or operating machinery); effects of alcohol and other CNS depressants enhanced.
  - **NATIONAL FUNDING/ACCESS DECISIONS**

#### NICE technology appraisals (TAs)

- Zaleplon, zolpidem, and zopiclone for the short-term management of insomnia (April 2004) NICE TA77
  - Zolpidem is recommended for the short-term management of severe insomnia that interferes with normal daily life, and should be prescribed for short periods of time only.
  - www.nice.org.uk/TA77

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **CAUTIONARY AND ADVISORY LABELS**
  - Zolpidem tartrate (Non-proprietary)

- **Zolpidem tartrate 5 mg**
  - Zolpidem 5mg tablets | 28 tablet [PoM]
  - £3.08 DT price = £1.25 [CD4-1]

- **Zolpidem tartrate 10 mg**
  - Zolpidem 10mg tablets | 28 tablet [PoM]
  - £4.48 DT price = £1.19 [CD4-1]

### Zopiclone

#### INDICATIONS AND DOSE

**Insomnia (short-term use)**

- **BY MOUTH**
  - Adult: 7.5 mg once daily for up to 4 weeks, dose to be taken at bedtime
  - Elderly: Initially 3.75 mg once daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 7.5 mg daily

- **CONTRA-INDICATIONS**
  - Marked neuromuscular respiratory weakness
  - Respiratory failure
  - Severe sleep apnoea syndrome
  - Unstable myasthenia gravis

- **CAUTIONS**
  - Avoid prolonged use (risk of tolerance and withdrawal symptoms)
  - Chronic pulmonary insufficiency (increased risk of respiratory depression)
  - Elderly
  - History of drug abuse
  - Muscle weakness
  - Myasthenia gravis (avoid if unstable)
  - Psychiatric illness

- **INTERACTIONS**
  - Paradoxical effects
  - Antihistamines
  - Atopy
  - CNS depressants
  - Opioids
  - Barbiturates
  - Alcohol

#### SIDE-EFFECTS

- **CONTRA-INDICATIONS**
  - Marked neuromuscular respiratory weakness
  - Respiratory failure
  - Severe sleep apnoea syndrome
  - Unstable myasthenia gravis

- **CAUTIONS**
  - Avoid prolonged use (risk of tolerance and withdrawal symptoms)
  - Chronic pulmonary insufficiency (increased risk of respiratory depression)
  - Elderly
  - History of drug abuse
  - Muscle weakness
  - Myasthenia gravis (avoid if unstable)
  - Psychiatric illness

- **INTERACTIONS**
  - Paradoxical effects
  - Antihistamines
  - Atopy
  - CNS depressants
  - Opioids
  - Barbiturates
  - Alcohol

- **SIDE-EFFECTS**
  - Common or very common
    - Taste disturbance
  - Uncommon
    - Dizziness
    - Drowsiness
    - Dry mouth
    - Headache
    - Nausea
    - Vomiting
  - Rare
    - Amnesia
    - Confusion
    - Depression
    - Hallucinations
    - Nightmares
  - Very rare
    - Incoordination
    - Light headedness

- **SIDE-EFFECTS, FURTHER INFORMATION**

- **Frequency not known**
  - Incoordination
  - Light headedness

- **SIDE-EFFECTS**

- **FURTHER INFORMATION**

- **Paradoxical effects**
  - A paradoxical increase in hostility and aggression may be reported. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

- **PREGNANCY**
  - Not recommended (risk of neonatal withdrawal symptoms). Use during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

- **BREAST FEEDING**
  - Present in milk—avoid.

- **HEPATIC IMPAIRMENT**
  - Reduce dose to 3.75 mg in mild to moderate impairment, dose can be increased with caution if necessary. Avoid in severe impairment—can precipitate encephalopathy.

- **RENAL IMPAIRMENT**
  - Start with reduced dose of 3.75 mg. Increased cerebral sensitivity.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Drowsiness may persist the next day and affect performance of skilled tasks (e.g., driving); effects of alcohol enhanced.
Narcolepsy 455

7.2 Narcolepsy

Other drugs used for Narcolepsy Dexamfetamine sulfate, p. 328 - Methylphenidate hydrochloride, p. 326

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Sodium oxybate

- **DRUG ACTION** A central nervous system depressant.

- **INDICATIONS AND DOSE**
  
  **Narcolepsy with cataplexy (under expert supervision)**
  
  **BY MOUTH**
  
  **Adult:** Initially 2.25 g daily, dose to be taken on retiring and 2.25 g after 2.5–4 hours, then increased in steps of 1.5 g daily in 2 divided doses, dose adjusted according to response at intervals of 1–2 weeks; dose titration should be repeated if restarting after interval of more than 14 days, maximum 9 g daily in 2 divided doses

- **CONTRA-INDICATIONS** Major depression · succinic semialdehyde dehydrogenase deficiency

- **CAUTIONS** Body mass index of 40 kg/m² or greater (higher risk of sleep apnoea) · elderly · epilepsy · heart failure (high sodium content) · history of depression · history of drug abuse · hypertension (high sodium content) · respiratory disorders · risk of discontinuation effects including rebound cataplexy and withdrawal symptoms

- **INTERACTIONS** → Appendix 1 (sodium oxybate). If sodium oxybate and sodium valproate or valproic acid used concomitantly, reduce initial dose of sodium oxybate to 1.8 g on retiring and repeat 2.5–4 hours later.

- **SIDE-EFFECTS**
  
  Common or very common Abdominal pain · anorexia · anxiety · arthralgia · asthenia · back pain · blurred vision · confusion · depression · diarrhoea · disorientation · dizziness · drowsiness · dyspnoea · headache · hypertension · hypoaesthesia · impaired attention · muscle spasm · nasal congestion · nausea · nocturnal enuresis · palpitation · paraesthesia · peripheral oedema · rash · sleep disorders · sleep paralysis · sleep walking · sweating · taste disturbance · tremor · urinary incontinence · vertigo · vomiting

- **Uncommon** Agitation · amnesia · faecal incontinence · hallucination · myoclonus · paranoia · psychosis · restless legs syndrome · suicidal behaviour

- **Frequency not known** Dependence · euphoria · respiratory depression · seizures · sleep apnoea · suicidal ideation · urticaria

- **PREGNANCY** Avoid.

- **BREAST FEEDING** No information available.

- **HEPATIC IMPAIRMENT** Halve initial dose.

- **RENAL IMPAIRMENT** Caution—contains 3.96 mmol Na⁺ per mL.

- **DIRECTIONS FOR ADMINISTRATION** Dilute each dose with 60 mL water; prepare both doses before retiring. Observe the same time interval (2–3 hours) each night between the last meal and the first dose.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer sodium oxybate oral solution.

- **Driving and skilled tasks** Leave at least 6 hours between taking sodium oxybate and performing skilled tasks (e.g. driving or operating machinery); effects of alcohol and other CNS depressants enhanced.

MEdICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution and tablets.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>19, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zopiclone (Non-proprietary)</td>
<td></td>
</tr>
<tr>
<td>Zopiclone 3.75 mg</td>
<td>28 tablet</td>
</tr>
<tr>
<td>Zopiclone 7.5 mg</td>
<td>28 tablet</td>
</tr>
<tr>
<td>Zimovane (Sanofi)</td>
<td></td>
</tr>
<tr>
<td>Zimovane 3.75 mg</td>
<td>28 tablet</td>
</tr>
<tr>
<td>Zimovane 7.5 mg</td>
<td>28 tablet</td>
</tr>
</tbody>
</table>

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

| CAUTIONARY AND ADVISORY LABELS | 13, 19 |
| ELECTROLYTES: May contain Sodium |
| Xyrem (UCB Pharma Ltd)         |        |
| Sodium oxybate 500 mg per 1 ml  |        |

| DT price = £ | Sugar-free | 180 ml | £360.00 DT price = £360.00 (CD2) |

**CNS STIMULANTS**

**Centrally Acting Sympathomimetics**

Modafinil

- **INDICATIONS AND DOSE**
  
  **Excessive sleepiness associated with narcolepsy with or without cataplexy**
  
  **BY MOUTH**
  
  **Adult:** Initially 200 mg daily in 2 divided doses, dose to be taken in the morning and at noon, alternatively initially 200 mg once daily, dose to be taken in the morning, adjusted according to response to 200–400 mg daily in 2 divided doses, alternatively adjusted according to response to 200–400 mg once daily
  
  **Elderly:** Initially 100 mg daily

- **CONTRA-INDICATIONS** Arrhythmia · history of clinically significant signs of CNS stimulant–induced mitral valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias) · history of cor pulmonale · history of left ventricular hypertrophy · moderate uncontrolled hypertension · severe uncontrolled hypertension

- **CAUTIONS** History of alcohol abuse · history of depression · history of drug abuse · history of mania · history of psychosis · possibility of dependence

- **INTERACTIONS** → Appendix 1 (modafinil).

- **SIDE-EFFECTS**
  
  Common or very common Abdominal pain · anxiety · appetite changes · asthenia · chest pain · confusion · constipation · depression · diarrhoea · dizziness · dry mouth · dyspepsia · gastrointestinal disturbances · headache · nausea · palpitation · paraesthesia · sleep disturbances · tachycardia · vasodilatation · visual disturbances
Uncommon Abnormal dreams, acne, aggression, agitation, amnesia, arrhythmia, arthralgia, bradycardia, decreased libido, dry eye, dyskinesia, dysphagia, dyspnoea, emotional lability, eosinophilia, epistaxis, flatulence, glossitis, hypercholesterolaemia, hyperglycaemia, hypertension, hypertonia, hypotension, leucopenia, menstrual disturbances, migraine, mouth ulcers, muscle cramps, myalgia, myasthenia, peripheral oedema, pruritus, rash, reflux, rhinitis, sinusitis, suicidal ideation, sweating, taste disturbance, thirst, tremor, urinary frequency, vomiting, weight changes

Rare Hallucinations, mania, psychosis

Frequency not known Multi-organ hypersensitivity reaction, psychiatric symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

Rash Discontinue treatment if rash develops.

Psychiatric symptoms Discontinue treatment if psychiatric symptoms develop.

PREGNANCY Avoid.

BREAST FEEDING Avoid — present in milk in animal studies.

HEPATIC IMPAIRMENT Halve dose in severe impairment.

RENAL IMPAIRMENT Use with caution — limited information available.

PRE-TREATMENT SCREENING ECG required before initiation.

MONITORING REQUIREMENTS Monitor blood pressure and heart rate in hypertensive patients.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include:

- oral suspension, oral solution

Tablet

- Modafinil (Non-proprietary)
  - Modafinil 100 mg Modafinil 100mg tablets 30 tablet £52.60
    - DT price = £6.83
  - Modafinil 200 mg Modafinil 200mg tablets 30 tablet £105.21
    - DT price = £13.87

- Provigil (Teva UK Ltd)
  - Modafinil 100 mg Provigil 100mg tablets 30 tablet £52.60
    - DT price = £6.83
  - Modafinil 200 mg Provigil 200mg tablets 30 tablet £105.21
    - DT price = £13.87

8 Substance dependence

Substance dependence

Guidance on treatment of drug misuse


Alcohol dependence

Excessive drinking of alcoholic beverages over a prolonged period of time can result in an alcohol withdrawal syndrome on abrupt cessation of, or marked reduction in, drinking. The presence and severity of alcohol dependence can be assessed by the Severity of Alcohol Dependence Questionnaire (SADQ); other assessment questionnaires are also available.

Acute alcohol withdrawal

People with moderate dependence can generally be treated in a community setting unless they are under 18 years of age, or are at high-risk of severe reactions or treatment failure. People with severe dependence should undergo withdrawal in an inpatient setting; withdrawal in severely dependent patients without medical support may lead to seizures, delirium tremens, and death. Long-acting benzodiazepines, usually clorazepoxide hydrochloride p. 321, are used to attenuate alcohol withdrawal symptoms. In primary care, fixed-dose reducing regimens are usually used, whilst a symptom-triggered flexible regimen is used in hospital or other settings where continued assessment and monitoring is carried out for 24–48 hours, usually followed by a fixed 5-day reducing dose schedule (sometimes it may be necessary to continue treatment for up to 10 days). Patients with decompensated liver disease should be treated under specialist supervision.

Carbamazepine p. 291 [unlicensed indication] is sometimes used as an alternative treatment in acute alcohol withdrawal when benzodiazepines are contra-indicated or not tolerated. Clomethiazole p. 452 is licensed for use in acute alcohol withdrawal, but benzodiazepines are preferred. It should only be used in an inpatient setting and should not be prescribed if the patient is liable to continue drinking alcohol.

Patients with marked agitation or hallucinations and those at risk of delirium tremens (characterised by delirium, hallucinations, tremor, and disorientation) may be prescribed antipsychotic drugs, such as haloperidol p. 363 or olanzapine p. 373 [unlicensed indication], as adjunctive therapy to benzodiazepines; antipsychotics should not be used alone because they do not treat alcohol withdrawal and may lower the seizure threshold. Delirium tremens is a medical emergency that requires specialist inpatient care.

If a patient taking a benzodiazepine as part of a withdrawal regimen develops alcohol withdrawal seizures, a fast-acting benzodiazepine (such as intravenous lorazepam p. 317 [unlicensed indication] or rectal diazepam p. 321) should be prescribed; thereafter an increase in the dose of oral benzodiazepine should be considered to prevent further seizures from occurring.

Alcohol dependence

Acamprosate calcium p. 459 and naltrexone hydrochloride p. 460 are effective treatments for relapse prevention in patients with alcohol dependence; disulfiram p. 459 is an alternative. Disulfiram should only be used in patients in whom acamprosate calcium and naltrexone hydrochloride are not suitable, or if the patient prefers disulfiram. Nalmefene p. 460 is licensed for the reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms, and who do not require immediate detoxification.

Patients with alcohol dependence are at risk of developing Wernicke’s encephalopathy; patients at high-risk are those who are malnourished, at risk of malnourishment, or have uncompensated liver disease. Parenteral thiamine p. 950 (as Pabrinex®) should be prescribed for treatment of suspected or confirmed Wernicke’s encephalopathy, and for prophylaxis in alcohol dependent patients attending hospital for acute treatment (including treatment unrelated to alcohol dependence); parenteral prophylaxis may also be considered for high-risk patients being treated in primary care. High-dose oral thiamine should be prescribed following parenteral treatment until cognitive function is maximised. In primary care, prophylactic high-dose oral thiamine should be prescribed during acute withdrawal of alcohol, before planned withdrawal, and for patients not undergoing withdrawal but who are at high-risk of developing Wernicke’s encephalopathy.

Patients with chronic alcohol-related pancreatitis who have symptoms of steatorrhoea or who have poor nutritional status due to exocrine pancreatic insufficiency should be prescribed pancreatic enzyme supplements; supplements are not indicated when pain is the only symptom.

Corticosteroids are used in patients with severe acute alcohol-related hepatitis.
Drugs used in alcohol dependence

Acamprosate
Acamprosate calcium, in combination with counselling, may be helpful for maintaining abstinence in alcohol-dependent patients. It is useful for patients who are concerned that strong cravings will result in relapse. It should be initiated as soon as possible after abstinence has been achieved and continued for 1 year; treatment should be maintained if the patient has a temporary relapse but stopped if the patient returns to regular or excessive drinking that persists 4–6 weeks after starting treatment. Acamprosate calcium is not effective in all patients, so efficacy should be regularly assessed.

Disulfiram
Disulfiram gives rise to an extremely unpleasant systemic reaction after the ingestion of even a small amount of alcohol because it causes accumulation of acetaldehyde in the body; it is only effective if taken daily. Symptoms can occur within 10 minutes of ingesting alcohol and include flushing of the face, throbbing headache, palpitation, tachycardia, nausea, vomiting, and, with large doses of alcohol, arrhythmias, hypotension, and collapse; these reactions can last several hours. Small amounts of alcohol such as those included in many oral medicines may be sufficient to precipitate a reaction—even toiletries and mouthwashes that contain alcohol should be avoided.

Nalmefene
Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene is not recommended for patients aiming to achieve immediate abstinence.

Naltrexone
Naltrexone hydrochloride is an opioid-receptor antagonist, but is useful as an adjunct in the treatment of alcohol dependence after a successful withdrawal. Treatment should be initiated by a specialist and continued under specialist supervision. Naltrexone hydrochloride should be stopped if drinking continues for 4–6 weeks after starting treatment.

Nicotine dependence
Smoking cessation interventions are a cost–effective way of reducing ill health and prolonging life. Smokers should be advised to stop and offered help with follow-up when appropriate. If possible, smokers should have access to smoking cessation services for behavioural support.

Therapy to aid smoking cessation is chosen according to the smoker’s likely adherence, availability of counselling and support, previous experience of smoking-cessation aids, contra-indications and adverse effects of the preparations, and the smoker’s preferences. Nicotine replacement therapy, bupropion hydrochloride p. 461, and varenicline p. 464 are effective aids to smoking cessation. The use of nicotine replacement therapy in an individual who is already accustomed to nicotine introduces few new risks and it is widely accepted that there are no circumstances in which it is safer to smoke than to use nicotine replacement therapy.

Some patients benefit from having more than one type of nicotine replacement therapy prescribed, such as a combination of transdermal and oral preparations. The combination of nicotine replacement therapy with varenicline or bupropion hydrochloride is not recommended.

Concomitant medication
Cigarette smoking increases the metabolism of some medicines by stimulating the hepatic enzyme CYP1A2. When smoking is discontinued, the dose of these drugs, in particular theophylline p. 256, cinacalcet p. 918, ropinirole p. 396, and some antipsychotics (including clozapine p. 371, olanzapine p. 373, chlorpromazine hydrochloride p. 361, and haloperidol p. 363, may need to be reduced. Regular monitoring for adverse effects is advised.

Drugs used in nicotine dependence
Bupropion hydrochloride has been used as an antidepressant. Its mode of action in smoking cessation is not clear and may involve an effect on noradrenaline and dopamine neurotransmission.

Nicotine replacement therapy
Nicotine replacement therapy can be used in place of cigarettes after abrupt cessation of smoking, or alternatively to reduce the amount of cigarettes used in advance of making a quit attempt. Nicotine replacement therapy can also be used to minimise passive smoking, and to treat cravings and reduce compensatory smoking after enforced abstinence in smoke-free environments. Smokers who find it difficult to achieve abstinence should consult a healthcare professional for advice.

Choice
Nicotine p. 462 patches are a prolonged-release formulation and are applied for 16 hours (with the patch removed overnight) or for 24 hours. If patients experience strong cravings for cigarettes on waking, a 24-hour patch may be more suitable. Immediate-release nicotine preparations (gum, lozenges, sublingual tablets, inhalator, nasal spray, and oral spray) are used whenever the urge to smoke occurs or to prevent cravings.

The choice of nicotine replacement preparation depends largely on patient preference, and should take into account what preparations, if any, have been tried before. Patients with a high level of nicotine dependence, or who have failed with nicotine replacement therapy previously, may benefit from using a combination of an immediate-release preparation and patches to achieve abstinence.

Side-effects of specific nicotine preparations
Mild local reactions at the beginning of treatment are common because of the irritant effect of nicotine. Oral preparations and inhalation cartridges can cause irritation of the throat, gum, lozenges, and oral spray can cause increased salivation, and patches can cause minor skin irritation. The nasal spray commonly causes coughing, nasal irritation, epistaxis, sneezing, and watery eyes; the oral spray can cause watery eyes and blurred vision.

Gastro-intestinal disturbances are common and may be caused by swallowed nicotine. Nausea, vomiting, dyspepsia, and hiccup occur most frequently. Ulcerative stomatitis has also been reported. Dry mouth is a common side-effect of lozenges, patches, oral spray, and sublingual tablets. Lozenges cause diarrhoea, constipation, dysphagia, oesophagitis, gastritis, mouth ulcers, bloating, flatulence, and less commonly, taste disturbance, thirst, gingival bleeding, and halitosis. The oral spray may also cause abdominal pain, flatulence, and taste disturbance.

Palpitations may occur with nicotine replacement therapy and rarely patches and oral spray can cause arrhythmia. Patches, lozenges, and oral spray can cause chest pain. The inhalator can very rarely cause reversible atrial fibrillation.

Paraesthesia is a common side-effect of oral spray. Abnormal dreams may occur with patches; removal of the patch before bed may help. Lozenges and oral spray may cause rash and hot flushes. Sweating and myalgia can occur with patches and oral spray; the patches can also cause arthralgia.

Opioid dependence
The management of opioid dependence requires medical, social, and psychological treatment; access to a multidisciplinary team is recommended. Treatment for opioid dependence should be initiated under the supervision of an appropriately qualified prescriber.

Untreated heroin dependence shows early withdrawal symptoms within 8 hours, with peak symptoms at...
Nervous system

usually takes up to of loss of tolerance. Complete withdrawal from opioids ineffective for sustained abstinence, and it increases the risk after careful consideration. Enforced withdrawal is hydrochloride or buprenorphine should be attempted only and during titration. be told to be aware of warning signs of toxicity on initiation should monitor for signs of toxicity, and the patient should

starts within circulation. Precipitated opioid withdrawal, if it occurs, is administered when other opioid agonist drugs are in

are milder, and patients generally require fewer adjunctive are used in conjunction with other sedating drugs, and has fewer reductions made every weeks. If illicit drug use occurs, the patient should be re-stabilised at the optimal maintenance dose and consideration should be given to stopping the withdrawal regimen.

Further withdrawal of methadone hydrochloride or buprenorphine in the third trimester is not recommended because maternal withdrawal, even if mild, is associated with fetal distress, stillbirth, and the risk of neonatal mortality. Drug metabolism can be increased in the third trimester; it may be necessary to either increase the dose of methadone hydrochloride or change to twice-daily consumption (or a combination of both strategies) to prevent withdrawal symptoms from developing.

The neonate should be monitored for respiratory depression and signs of withdrawal if the mother is prescribed high doses of opioid substitute. Signs of neonatal withdrawal from opioids usually develop 

36–72 hours; symptoms subside substantially after 5 days. Methadone hydrochloride p. 464 or buprenorphine p. 417 withdrawal occurs later, with longer-lasting symptoms.

Opioid substitution therapy

Methadone hydrochloride and buprenorphine are used as substitution therapy in opioid dependence. Substitute medication should be commenced with a short period of stabilisation, followed by either a withdrawal regimen or by maintenance treatment. Maintenance treatment enables patients to achieve stability, reduces drug use and crime, and improves health; it should be regularly reviewed to ensure the patient continues to derive benefit. The prescriber should monitor for signs of toxicity, and the patient should be told to be aware of warning signs of toxicity on initiation and during titration. A withdrawal regimen after stabilisation with methadone hydrochloride or buprenorphine should be attempted only after careful consideration. Enforced withdrawal is ineffective for sustained abstinence, and it increases the risk of patients relapsing and subsequently overdosing because of loss of tolerance. Complete withdrawal from opioids usually takes up to 4 weeks in an inpatient or residential setting, and up to 12 weeks in a community setting. If abstinence is not achieved, illicit drug use is resumed, or the patient cannot tolerate withdrawal, the withdrawal regimen should be stopped and maintenance therapy should be resumed at the optimal dose. Following successful withdrawal treatment, further support and monitoring to maintain abstinence should be provided for a period of at least 6 months.

Missed doses

Patients who miss 3 days or more of their regular prescribed dose of opioid maintenance therapy are at risk of overdose because of loss of tolerance. Consider reducing the dose in these patients. If the patient misses 5 or more days of treatment, an assessment of illicit drug use is also recommended before restarting substitution therapy; this is particularly important for patients taking buprenorphine because of the risk of precipitated withdrawal.

Buprenorphine

Buprenorphine is preferred by some patients because it is less sedating than methadone hydrochloride; for this reason it may be more suitable for employed patients or those undertaking other skilled tasks such as driving. Buprenorphine is safer than methadone hydrochloride when used in conjunction with other sedating drugs, and has fewer drug interactions. Dose reductions may be easier than with methadone hydrochloride because the withdrawal symptoms are milder, and patients generally require fewer adjunctive medications; there is also a lower risk of overdose. Buprenorphine can be given on alternate days in higher doses and it requires a shorter drug-free period than methadone hydrochloride before induction with naltrexone hydrochloride p. 460 for prevention of relapse. Patients dependent on high doses of opioids may be at increased risk of precipitated withdrawal. Precipitated withdrawal can occur in any patient if buprenorphine p. 417 is administered when other opioid agonist drugs are in circulation. Precipitated opioid withdrawal, if it occurs, starts within 1–3 hours of the first buprenorphine dose and peaks at around 6 hours. Non-opioid adjunctive therapy, such as lofexidine hydrochloride p. 466, may be required if symptoms are severe.

To reduce the risk of precipitated withdrawal, the first dose of buprenorphine should be given when the patient is exhibiting signs of withdrawal, or 6–12 hours after the last use of heroin (or other short-acting opioid), or 24–48 hours after the last dose of methadone hydrochloride p. 464. It is possible to titrate the dose of buprenorphine within one week—more rapidly than with methadone hydrochloride therapy—but care is still needed to avoid toxicity or precipitated withdrawal; dividing the dose on the first day may be useful. A combination preparation containing buprenorphine with naloxone p. 466 (Suboxone®) can be prescribed for patients when there is a risk of dose diversion for parenteral administration; the naloxone hydrochloride p. 1214 component precipitates withdrawal if the preparation is injected, but it has little effect when the preparation is taken sublingually.

Methadone

Methadone hydrochloride, a long-acting opioid agonist, is usually administered in a single daily dose as methadone hydrochloride oral solution 1 mg/mL. Patients with a long history of opioid misuse, those who typically abuse a variety of sedative drugs and alcohol, and those who experience increased anxiety during withdrawal of opioids may prefer methadone hydrochloride to buprenorphine because it has a more pronounced sedative effect.

Methadone hydrochloride is initiated at least 8 hours after the last heroin dose, provided that there is objective evidence of withdrawal symptoms. A supplementary dose on the first day may be considered if there is evidence of persistent opioid withdrawal symptoms. Because of the long half-life, plasma concentrations progressively rise during initial treatment even if the patient remains on the same daily dose (it takes 3–10 days for plasma concentrations to reach steady-state in patients on a stable dose); a dose tolerated on the first day of treatment may become a toxic dose on the third day as cumulative toxicity develops. Thus, titration to the optimal dose in methadone hydrochloride maintenance treatment may take several weeks.

Opioid substitution during pregnancy

Acute withdrawal of opioids should be avoided in pregnancy because it can cause fetal death. Opioid substitution therapy is recommended during pregnancy because it carries a lower risk to the fetus than continued use of illicit drugs. If a woman who is stabilised on methadone hydrochloride or buprenorphine for treatment of opioid dependence becomes pregnant, therapy should be continued [buprenorphine is not licensed for use in pregnancy]. Many pregnant patients choose a withdrawal regimen, but withdrawal during the first trimester should be avoided because it is associated with an increased risk of spontaneous miscarriage. Withdrawal of methadone hydrochloride or buprenorphine should be undertaken gradually during the second trimester, with dose reductions made every 3–5 days. If illicit drug use occurs, the patient should be re-stabilised at the optimal maintenance dose and consideration should be given to stopping the withdrawal regimen.

Further withdrawal of methadone hydrochloride or buprenorphine in the third trimester is not recommended because maternal withdrawal, even if mild, is associated with fetal distress, stillbirth, and the risk of neonatal mortality. Drug metabolism can be increased in the third trimester; it may be necessary to either increase the dose of methadone hydrochloride or change to twice-daily consumption (or a combination of both strategies) to prevent withdrawal symptoms from developing.

The neonate should be monitored for respiratory depression and signs of withdrawal if the mother is prescribed high doses of opioid substitute. Signs of neonatal withdrawal from opioids usually develop 24–72 hours after delivery but symptoms may be delayed for up to 14 days, so monitoring may be required for several weeks. Symptoms include a high-pitched cry, rapid breathing, hungry but ineffective suckling, and excessive wakefulness; severe, but rare symptoms include hypertonicity and convulsions.

Opioid substitution during breastfeeding

Doses of methadone and buprenorphine should be kept as low as possible in breast-feeding mothers. Increased sleepiness, breathing difficulties, or limpness in breast-fed
babies of mothers taking opioid substitutes should be reported urgently to a healthcare professional.

**Adjunctive therapy and symptomatic treatment**
Adjunctive therapy may be required for the management of opioid withdrawal symptoms. Loperamide hydrochloride p. 63 may be used for the control of diarrhoea; mebeverine hydrochloride p. 82 for controlling stomach cramps; paracetamol p. 414 and non-steroidal anti-inflammatory drugs for muscular pains and headaches; metoclopramide hydrochloride p. 403 or prochlorperazine p. 365 may be useful for nausea or vomiting. Topical rubefacients can be helpful for relieving muscle pain associated with methadone hydrochloride withdrawal. If a patient is suffering from insomnia, short-acting benzodiazepines or zopiclone p. 454 may be prescribed, but because of the potential for abuse, prescriptions should be limited to a short course of a few days only. If anxiety or agitation is severe, specialist advice should be sought.

**Lofexidine**
Lofexidine hydrochloride may alleviate some of the physical symptoms of opioid withdrawal by attenuating the increase in adrenergic neurotransmission that occurs during opioid withdrawal. Lofexidine hydrochloride can be prescribed as an adjuvant to opioid substitution therapy, initiated either at the same time as the opioid substitute or during withdrawal of the opioid substitute. Alternatively, lofexidine hydrochloride may be prescribed instead of an opioid substitute in patients who have mild or uncertain dependence (including young people), and those with a short history of illicit drug use.

**Opioid-receptor antagonists**
Patients dependent on opioids can be given a supply of naloxone hydrochloride to be used in case of accidental overdose.

Naltrexone hydrochloride p. 460 precipitates withdrawal symptoms in opioid-dependent subjects. Because the effects of opioid-receptor agonists are blocked by naltrexone hydrochloride, it is prescribed as an aid to prevent relapse in formerly opioid-dependent patients.

**Opioid dependence in children**
In younger patients (under 18 years), the harmful effects of drug misuse are more often related to acute intoxication than to dependence, so substitution therapy is usually inappropriate. Maintenance treatment with opioid substitution therapy is therefore controversial in young people; however, it may be useful for the older adolescent who has a history of opioid use to undergo a period of stabilisation with buprenorphine or methadone hydrochloride before starting a withdrawal regimen.

### 8.1 Alcohol dependence

**Other drugs used for Alcohol dependence**
Carbamazepine, p. 291 • Chlordiazepoxide hydrochloride, p. 321 • Clomethiazole, p. 452 • Diazepam, p. 321

#### ALDEHYDE DEHYDROGENASE INHIBITORS

**Disulfiram**

- **INDICATIONS AND DOSE**
  Adjunct in the treatment of alcohol dependence (under expert supervision)

  - **BY MOUTH**
  - Adult: 200 mg daily, increased if necessary up to 500 mg daily

  - **UNLICENSED USE**
    Disulfiram doses in BNF may differ from those in product literature.

  - **CONTRA-INDICATIONS**
    Cardiac failure • coronary artery disease • history of cerebrovascular accident • hypertension • psychosis • severe personality disorder • suicide risk

  - **CAUTIONS**
    Alcohol challenge not recommended on routine basis (if considered essential—specialist units only with resuscitation facilities) • avoid in Acute porphyrias p. 930 • diabetes mellitus • epilepsy • respiratory disease

  - **INTERACTIONS**
    → Appendix 1 (disulfiram).

  Disulfiram gives rise to an extremely unpleasant systemic reaction after the ingestion of even a small amount of alcohol. Ensure that alcohol is not consumed for at least 24 hours before initiating treatment and should be avoided for at least 1 week after stopping treatment.

  - **SIDE-EFFECTS**

    - Common or very common
      Drowsiness • fatigue • halitosis • nausea • reduced libido • vomiting

    - Rare
      Allergic dermatitis • depression • hepatic cell damage • mania • paranoia • peripheral neuritis • psychotic reactions • schizophrenia

  - **PREGNANCY**
    High concentrations of acetaldehyde which occur in presence of alcohol may be teratogenic; avoid in first trimester.

  - **BREAST FEEDING**
    Avoid—no information available.

  - **HEPATIC IMPAIRMENT**
    Use with caution.

  - **RENAL IMPAIRMENT**
    Use with caution.

  - **PRE-TREATMENT SCREENING**
    Before initiating disulfiram, prescribers should evaluate the patient’s suitability for treatment, because some patient factors, for example memory impairment or social circumstances, make compliance to treatment or abstinence from alcohol difficult.

  - **MONITORING REQUIREMENTS**
    During treatment with disulfiram, patients should be monitored at least every 2 weeks for the first 2 months, then each month for the following 4 months, and at least every 6 months thereafter.

  - **PATIENT AND CARER ADVICE**
    Patient counselling is advised (alcohol reaction).

  - **MEDICINAL FORMS**
    There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - **CAUTIONARY AND ADVISORY LABELS**
    2

  - **Disulfiram (Non-proprietary)**

    **Disulfiram 200 mg**
    Disulfiram 200 mg tablets | 50 tablet [PoT] £91.73 DT price = £91.73

    **Disulfiram 250 mg**
    Antabuse 250 mg tablets | 100 tablet [PoT] no price available

  **GAMMA-AMINOBUTYRIC ACID ANALOGUES AND DERIVATIVES**

  **Acamprosate calcium**

  - **INDICATIONS AND DOSE**
    Maintenance of abstinence in alcohol-dependent patients

    - **BY MOUTH**
      - Adult 18–65 years (body-weight up to 60 kg): 666 mg once daily at breakfast and 333 mg twice daily at midday and at night
      - Adult 18–65 years (body-weight 60 kg and above): 666 mg 3 times a day

  - **CAUTIONS**
    Continued alcohol abuse (risk of treatment failure)
Nervous system

BREAST FEEDING

Frequency not known

SIDE-EFFECTS

Common or very common Abdominal pain • diarrhoea • flatulence • frigidity • impotence • maculopapular rash • nausea • pruritus • vomiting

Very rare Angioedema • hypersensitivity reactions • urticaria

Frequency not known Fluctuation in libido • vesiculobullous skin reactions

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk.

BREAST FEEDING Avoid.

HEPATIC IMPAIRMENT Use with caution—avoid in severe impairment.

RENAL IMPAIRMENT Use with caution—avoid in severe impairment.

PRE-TREATMENT SCREENING Before initiating treatment, prescribers should evaluate the patient’s clinical status, alcohol dependence, and level of alcohol consumption. Nalmefene should only be prescribed for patients who continue to have a high drinking risk level two weeks after the initial assessment.

MONITORING REQUIREMENTS During treatment, patients should be monitored regularly and the need for continued treatment assessed.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Nalmefene for reducing alcohol consumption in people with alcohol dependence (November 2014) NICE TA325

Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for patients with alcohol dependence:

- who have a high drinking risk level (defined as alcohol consumption of more than 60 g per day for men and more than 40 g per day for women, according to the World Health Organization’s drinking risk levels) without physical withdrawal symptoms, and
- who do not require immediate detoxification.

The marketing authorisation states that nalmefene should:

- only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption, and
- be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment.

www.nice.org.uk/TA325

OPINIONS

OPIOID RECEPTOR ANTAGONISTS

Nalmefene

INDICATIONS AND DOSE

Reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms, and who do not require immediate detoxification

BY MOUTH

Adult: 18 mg daily if required, taken on each day there is a risk of drinking alcohol, preferably taken 1–2 hours before the anticipated time of drinking, if a dose has not been taken before drinking alcohol, 1 dose should be taken as soon as possible; maximum 18 mg per day

CONTRA-INDICATIONS

Recent history of acute alcohol withdrawal syndrome • recent or current opioid use

CAUTIONS

Continued treatment for more than 1 year • history of seizure disorders (including alcohol withdrawal seizures) • psychiatric illness

INTERACTIONS

Avoid concomitant use of opioids—discontinue treatment 1 week before anticipated use of opioids; if emergency analgesia is required during treatment, an increased dose of opioid analgesic may be necessary (monitor for opioid intoxication).

SIDE-EFFECTS

Common or very common Confusion • decreased appetite • decreased libido • disturbance in attention • dizziness • dry mouth • headache • hyperhidrosis • hypoaesthesia • malaise • muscle spasms • nausea • palpitation • paraesthesia • restlessness • sleep disorders • somnolence • tachycardia • tremor • vomiting • weight loss

Frequency not known Dissociation • hallucinations

PREGNANCY Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

Use with caution—avoid in severe impairment.

RENAL IMPAIRMENT

Use with caution—avoid in severe impairment.

PRE-TREATMENT SCREENING

Before initiating treatment, prescribers should evaluate the patient’s clinical status, alcohol dependence, and level of alcohol consumption. Nalmefene should only be prescribed for patients who continue to have a high drinking risk level two weeks after the initial assessment.

MONITORING REQUIREMENTS

During treatment, patients should be monitored regularly and the need for continued treatment assessed.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Nalmefene for reducing alcohol consumption in people with alcohol dependence (November 2014) NICE TA325

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- who have a high drinking risk level (defined as alcohol consumption of more than 60 g per day for men and more than 40 g per day for women, according to the World Health Organization’s drinking risk levels) without physical withdrawal symptoms, and
- who do not require immediate detoxification.

The marketing authorisation states that nalmefene should:

- only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption, and
- be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment.

www.nice.org.uk/TA325

METHOLOGICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 21, 25 ELECTROLYTES: May contain Calcium

Acamprosate calcium (Non-proprietary)

Acamprosate calcium 333 mg Acamprosate 333mg gastro-resistant tablets 168 tablet £33.75 DT price = £32.59

Campral EC (Merck Serono Ltd)

Acamprosate calcium 333 mg Campral EC 333mg tablets 168 tablet £28.80 DT price = £32.59

Naltrexone hydrochloride

DRUG ACTION Naltrexone is an opioid-receptor antagonist.

INDICATIONS AND DOSE

Adjunct to prevent relapse in formerly opioid-dependent patients (who have remained opioid-free for at least 7–10 days) (initiated under specialist supervision)

BY MOUTH

Adult: Initially 25 mg daily, then increased to 50 mg daily, total weekly dose may be divided and given on 3 days of the week for improved compliance (e.g. 100 mg on Monday and Wednesday, and 150 mg on Friday); maximum 350 mg per week

Adjunct to prevent relapse in formerly alcohol-dependent patients (initiated under specialist supervision)

BY MOUTH

Adult: 25 mg once daily on the first day, then increased if tolerated to 50 mg daily

UNLICENSED USE

25 mg dose for adjunct to prevent relapse in formerly alcohol-dependent patients is an unlicensed dose.

CONTRA-INDICATIONS

Patients currently dependent on opioids
**8.2 Nicotine dependence**

**ANTIDEPRESSANTS › SEROTONIN AND NORADRENALINE RE-UPTAKE INHIBITORS**

**Bupropion hydrochloride**

(Amfebutamone hydrochloride)

- **INDICATIONS AND DOSE**
  To aid smoking cessation in combination with motivational support in nicotine-dependent patients
  - **BY MOUTH**
    - Adult: Initially 150 mg daily for 6 days, then 150 mg twice daily (max. per dose 150 mg), minimum 8 hours between doses; period of treatment 7–9 weeks, start treatment 1–2 weeks before target stop date, discontinue if abstinence not achieved at 7 weeks, consider maximum 150 mg daily in patients with risk factors for seizures; maximum 300 mg per day
    - Elderly: 150 mg daily for 7–9 weeks, start treatment 1–2 weeks before target stop date, discontinue if abstinence not achieved at 7 weeks; maximum 150 mg per day

- **CONTRA-INDICATIONS**
  - Acute alcohol withdrawal • acute benzodiazepine withdrawal • bipolar disorder • CNS tumour • eating disorders • history of seizures • severe hepatic cirrhosis
  - **CAUTIONS**
    - Alcohol abuse • diabetes • elderly • history of head trauma • predisposition to seizures (prescribe only if benefit clearly outweighs risk)
  - **INTERACTIONS**
    - Appendix 1 (bupropion).
    - Caution with concomitant use of drugs that lower seizure threshold.

- **SIDE-EFFECTS**
  - **Common or very common**
    - Agitation • anxiety • depression • dizziness • dry mouth • fever • gastro-intestinal disturbances • headache • impaired concentration • insomnia (reduced by avoiding dose at bedtime) • pruritus • rash • sweating • taste disturbance • tremor
  - **Uncommon**
    - Anorexia • asthenia • chest pain • confusion • flushing • hypertension • tachycardia • tinnitus • visual disturbances
  - **Rare**
    - Abnormal dreams • ataxia • blood-glucose changes • depersonalisation • dystonia • exacerbation of psoriasis • hallucinations • hepatitis • hostility • impaired memory • incoordination • irritability • jaundice • palpitation • paraesthesia • postural hypotension • seizures • Stevens–Johnson syndrome • twitching • urinary frequency • urinary retention • vasodilatation
  - **Very rare**
    - Aggression • delusions • paranoid ideation • restlessness
  - **Frequency not known**
    - Suicidal ideation

- **PREGNANCY**
  - Avoid—no information available.

- **BREAST FEEDING**
  - Present in milk—avoid.

- **HEPATIC IMPAIRMENT**
  - Reduce dose to 150 mg daily. Avoid in severe hepatic cirrhosis.

- **RENAL IMPAIRMENT**
  - Reduce dose to 150 mg daily.

- **MONITORING REQUIREMENTS**
  - Measure blood pressure before and during treatment.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - May impair performance of skilled tasks (e.g. driving).
Nervous system

NICOTINIC RECEPTOR AGONISTS

Nicotine

INDICATIONS AND DOSE

Nicotine replacement therapy in individuals who smoke fewer than 20 cigarettes each day

- **BY MOUTH USING CHEWING GUM**
  - Adult: 2 mg as required, chew 1 piece of gum when the urge to smoke occurs or to prevent cravings, if attempting smoking cessation, treatment should continue for 3 months before reducing the dose.

Nicotine replacement therapy in individuals who smoke more than 20 cigarettes each day or who require more than 15 pieces of 2-mg strength gum each day

- **BY MOUTH USING CHEWING GUM**
  - Adult: 4 mg as required, chew 1 piece of gum when the urge to smoke occurs or to prevent cravings, individuals should not exceed 15 pieces of 4-mg strength gum daily, if attempting smoking cessation, treatment should continue for 3 months before reducing the dose.

Nicotine replacement therapy in individuals who smoke more than 20 cigarettes each day

- **BY SUBLINGUAL ADMINISTRATION USING SUBLINGUAL TABLETS**
  - Adult: 1 tablet every 1 hour, increased to 2 tablets every 1 hour if required, if attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose; maximum 40 tablets per day.

Nicotine replacement therapy

- **BY INHALATION USING INHALATOR**
  - Adult: As required, the cartridges can be used when the urge to smoke occurs or to prevent cravings, individuals should not exceed 12 cartridges of the 10-mg strength daily, or 6 cartridges of the 15-mg strength daily.

- **BY MOUTH USING LOZENGES**
  - Adult: 1 lozenge every 1–2 hours as required, one lozenge should be used when the urge to smoke occurs, individuals who smoke less than 20 cigarettes each day should usually use the lower-strength lozenges; individuals who smoke more than 20 cigarettes each day and those who fail to stop smoking with the low-strength lozenges should use the higher-strength lozenges; if attempting smoking cessation, treatment should continue for 6–12 weeks before attempting a reduction in dose; maximum 15 lozenges per day.

- **BY MOUTH USING OROMUCOSAL SPRAY**
  - Adult: 1–2 sprays as required, individuals can spray in the mouth when the urge to smoke occurs or to prevent cravings, individuals should not exceed 2 sprays per episode (up to 4 sprays every hour); maximum 64 sprays per day.

- **BY INTRanasal ADMINISTRATION USING NASAL SPRAY**
  - Adult: 1 spray as required, individuals can spray into each nostril when the urge to smoke occurs, up to twice every hour for 16 hours daily, if attempting smoking cessation, treatment should continue for 8 weeks before reducing the dose; maximum 64 sprays per day.

- **BY TRANSDERMAL APPLICATION USING PATCHES**
  - Adult: Individuals who smoke more than 10 cigarettes daily should apply a high-strength patch daily for 6–8 weeks, followed by the medium-strength patch for 2 weeks, and then the low-strength patch for the final 2 weeks; individuals who smoke fewer than 10 cigarettes daily can usually start with the medium-strength patch for 6–8 weeks, followed by the low-strength patch for 2–4 weeks; a slower titration schedule can be used in individuals who are not ready to quit but want to reduce cigarette consumption before a quit attempt; if abstinence is not achieved, or if withdrawal symptoms are experienced, the strength of the patch used should be maintained or increased until the patient is stabilised; individuals using the high-strength patch who experience excessive side-effects, that do not resolve within a few days, should change to a medium-strength patch for the remainder of the initial period and then use the low-strength patch for 2–4 weeks.

CAUTIONS

GENERAL CAUTIONS

Diabetes mellitus—blood-glucose concentration should be monitored closely when initiating treatment.

- Haemodynamically unstable patients hospitalised with cerebrovascular accident
- Haemodynamically unstable patients hospitalised with myocardial infarction
- Haemodynamically unstable patients hospitalised with severe arrhythmias
- Phaeochromocytoma
- Uncontrolled hyperthyroidism

SPECIFIC CAUTIONS

- When used by inhalation
  - Bronchospastic disease
  - Chronic throat disease
  - Obstructive lung disease

- With intranasal use
  - Bronchial asthma (may exacerbate)

- With oral (topical) use
  - Gum may also stick to and damage dentures

- With oral use
  - Gastritis (can be aggravated by swallowed nicotine)
  - Oesophagitis (can be aggravated by swallowed nicotine)
  - Peptic ulcers (can be aggravated by swallowed nicotine)

- With transdermal use
  - Patches should not be placed on broken skin

CAUTIONS, FURTHER INFORMATION

Most warnings for nicotine replacement therapy also apply to continued cigarette smoking, but the risk of continued smoking outweighs any risks of using nicotine preparations.

Specific cautions for individual preparations are usually related to the local effect of nicotine.

INTERACTIONS

Appendix 1 (nicotine).

SIDE-EFFECTS

- **Common or very common**
  - Bloating
  - Blurred vision
  - Constipation
  - Coughing
  - Diarrhoea
  - Dry mouth
  - Dyspepsia
  - Dysphagia
  - Epistaxis
  - Flatulence
  - Gastritis
  - Gastrointestinal disturbances (may be caused by swallowed nicotine)
  - Hiccups
  - Increased salivation
  - Irritation of the throat
  - Mild local reactions at the beginning of treatment

- **Rare**
  - Arrhythmia
  - Uncommon
  - Gingival bleeding
  - Halitosis
  - Thirst

- **Very rare**
  - Reversible atrial fibrillation

- **Frequency not known**
  - Abdominal pain
  - Abnormal dreams (may occur with patches, removal of the patch before bed may help)
  - Arthralgia
  - Chest pain
  - Flatulence
  - Hot flushes

**Sympathetic nervous system**
myalgia • palpitations • rash • sweating • taste disturbance • ulcerative stomatitis

SIDE-EFFECTS, FURTHER INFORMATION

Side-effects listed have been reported with use of various nicotine replacement therapy preparations. See Nicotine replacement therapy, under Substance dependence p. 456 for further details on individual preparations.

- Nicotine withdrawal  Some systemic effects occur on initiation of therapy, particularly if the patient is using high-strength preparations; however, the patient may confuse side-effects of the nicotine-replacement preparation with nicotine withdrawal symptoms. Common symptoms of nicotine withdrawal include malaise, headache, dizziness, sleep disturbance, coughing, influenza-like symptoms, depression, irritability, increased appetite, weight gain, restlessness, anxiety, drowsiness, aphthous ulcers, decreased heart rate, and impaired concentration.

- PREGNANCY  The use of nicotine replacement therapy in pregnancy is preferable to the continuation of smoking, but should be used only if smoking cessation without nicotine replacement fails. Intermittent therapy is preferable to patches but should be used only if smoking cessation without nicotine replacement fails. Intermittent therapy is preferably to patches but should be avoided if pregnancy-related nausea and vomiting. If patches are used, they should be removed before bed.

- BREAST FEEDING  Nicotine is present in milk; however, the amount to which the infant is exposed is small and less hazardous than second-hand smoke. Intermittent therapy is preferred.

- HEPATIC IMPAIRMENT  Use with caution in moderate to severe hepatic impairment.

- RENAL IMPAIRMENT  Use with caution in severe renal impairment.

- DIRECTIONS FOR ADMINISTRATION  Acidic beverages, such as coffee or fruit juice, may decrease the absorption of nicotine through the buccal mucosa and should be avoided for 15 minutes before the use of oral nicotine replacement therapy. Administration by transdermal patch  Patches should be applied on waking to dry, non-hairy skin on the hip, trunk, or upper arm and held in position for 10–20 seconds to ensure adhesion; place next patch on a different area and avoid using the same site for several days. Administration by nasal spray  Initially 1 spray should be used in both nostrils but when withdrawing from therapy, the dose can be gradually reduced to 1 spray in 1 nostril. Administration by oral spray  The oral spray should be released into the mouth, holding the spray as close to the mouth as possible and avoiding the lips. The patient should not inhale while spraying and avoid swallowing for a few seconds after use. If using the oral spray for the first time, or if unit not used for 2 or more days, prime the unit before administration. Administration by sublingual tablet  Each tablet should be placed under the tongue and allowed to dissolve. Administration by lozenge  Slowly allow each lozenge to dissolve in the mouth; periodically move the lozenge from one side of the mouth to the other. Lozenges last for 10–30 minutes, depending on their size. Administration by inhalation  Insert the cartridge into the device and draw in air through the mouthpiece; each session can last for approximately 5 minutes. The amount of nicotine from 1 puff of the cartridge is less than that from a cigarette, therefore it is necessary to inhale more often than when smoking a cigarette. A single 10 mg cartridge lasts for approximately 20 minutes of intense use; a single 15 mg cartridge lasts for approximately 40 minutes of intense use.

Administration by medicated chewing gum  Chew the gum until the taste becomes strong, then rest it between the cheek and gum; when the taste starts to fade, repeat this process. One piece of gum lasts for approximately 30 minutes.

- PRESCRIBING AND DISPENSING INFORMATION  Flavours of chewing gum and lozenges may include mint, freshfruit, freshmint, icy white, or cherry.

- PATIENT AND CARER ADVICE  Patient or carers should be given advice on how to administer nicotine chewing gum, inhalators, lozenges, sublingual tablets, oral spray, nasal spray and patches.

- MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Sublingual tablet

| CAUTIONARY AND ADVISORY LABELS 26 |
| Nicotine (Non-proprietary) |
| Nicotine (as Nicotine cyclodextrin complex) 2 mg Nicotine 2mg sublingual tablets sugar-free | 100 tablet GSL | no price available DT price = £13.12 |
| Brands may include Nicorette Microtab |

Lozenge

| EXCIPIENTS: May contain Aspartame |
| ELECTROLYTES: May contain Sodium |
| Nicotine (Non-proprietary) |
| Nicotine (as Nicotine bitartrate) 1 mg Nicotine 1mg lozenges sugar-free | 96 lozenge GSL | no price available DT price = £9.12 |
| Nicotine (as Nicotine bitartrate) 2 mg Nicotine 2mg lozenges sugar-free | 96 lozenge GSL | no price available |
| Brands may include NiQuitin, Nicorette, Nicotinell |

Medicated chewing-gum

| Nicotine (Non-proprietary) |
| Nicotine 2 mg Nicotine 2mg medicated chewing gum sugar-free | 105 piece GSL | no price available |
| Nicotine 4 mg Nicotine 4mg medicated chewing gum sugar-free | 105 piece GSL | no price available |
| Brands may include NiQuitin, Nicorette, Nicorette Icy White, Nicotinell |

Inhalation vapour

| Nicotine (Non-proprietary) |
| Nicotine 15 mg Nicotine 15mg inhalator | 4 cartridge GSL | no price available DT price = £4.27 | 20 cartridge GSL | no price available DT price = £15.11 |
| Brands may include NiQuitin, Nicorette, Nicorette Icy White, Nicotinell |

Transdermal patch

| Nicotine (Non-proprietary) |
| Nicotine 7 mg per 24 hour Nicotine 7mg/24hours transdermal patches | 7 patch GSL | no price available |
| Nicotine 10 mg per 16 hour Nicotine 10mg/16hours patches | 7 patch GSL | no price available DT price = £10.37 |
| Nicotine 14 mg per 24 hour Nicotine 14mg/24hours transdermal patches | 7 patch GSL | no price available |
| Nicotine 15 mg per 16 hour Nicotine 15mg/16hours patches | 7 patch GSL | no price available DT price = £10.37 |
| Nicotine 21 mg per 24 hour Nicotine 21mg/24hours transdermal patches | 7 patch GSL | no price available DT price = £9.97 |
| Nicotine 25 mg per 16 hour Nicotine 25mg/16hours patches | 7 patch GSL | no price available DT price = £10.37 |
| Brands may include NiQuitin, NiQuitin Clear, Nicorette invisi, Nicotinell TTS |

Spray

| EXCIPIENTS: May contain Ethanol |
| Nicotine (Non-proprietary) |
| Nicotine 500 microgram per 1 actuation Nicotine 10mg/ml nasal spray | 10 ml GSL | no price available DT price = £13.80 |
| Brands may include Nicorette, Nicorette QuickMist |
Varenicline

**DRUG ACTION** Varenicline is a selective nicotine-receptor partial agonist.

**INDICATIONS AND DOSE**

To aid smoking cessation

- **BY MOUTH**
  - Adult: Initially 500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks; reduced if not tolerated to 500 micrograms twice daily, usually to be started 1–2 weeks before target stop date but can be started up to a maximum of 5 weeks before target stop date, 12-week course can be repeated in abstinent individuals to reduce risk of relapse.

**CAUTIONS** Conditions that may lower seizure threshold: history of cardiovascular disease, history of psychiatric illness (may exacerbate underlying illness including depression), predisposition to seizures.

**SIDE-EFFECTS**

- Common or very common Taste disturbance, abnormal dreams, appetite changes, dizziness, drowsiness, dry mouth, gastrointestinal disturbances, headache, sleep disorders.
- Uncommon Acne, anxiety, apathy, somnolence, arthralgia, asthma, atrial fibrillation, chest pain, depression, dysarthria, dysuria, eye pain, gingival pain, hallucinations, hypotension, hypertonia, hypoaesthesia, impaired temperature regulation, incoordination, lacrimation, menorrhagia, mood swings, muscle spasm, palpitation, panic attack, pruritus, rash, restlessness, seizure, sexual dysfunction, sweating, tachycardia, thirst, tinnitus, tremor, vaginal discharge, visual disturbances, weight gain.
- Rare Cerebrovascular accident.
- Frequency not known Aggression, diabetes mellitus, hyperglycaemia, irritable behaviour, myocardiard infarction, psychosis, sleep-walking, Stevens-Johnson syndrome, suicidal ideation.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**RENAL IMPAIRMENT** If eGFR less than 30 mL/minute/1.73 m², initial dose 500 micrograms once daily, increased after 3 days to 1 mg once daily.

**TREATMENT CESSATION** Risk of relapse, irritability, depression, and insomnia on discontinuation; consider dose tapering on completion of 12-week course.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Varenicline for smoking cessation (July 2007) NICE TA123
  Varenicline is recommended, within its licensed indications, as an option for smokers who have expressed a desire to quit smoking; it should normally be prescribed only as part of a programme of behavioural support. www.nice.org.uk/TA123

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVISE: SUICIDAL BEHAVIOUR AND VARENICLINE

Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation, depressed mood, or suicidal thoughts. Patients with a history of psychiatric illness should be monitored closely while taking varenicline.

**SIDE-EFFECTS**

- Rare
- Uncommon
- Common or very common

**IMPORTANT SAFETY INFORMATION**

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Champix (Pfizer Ltd)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Varenicline (as Varenicline tartrate) 500 microgram</strong> Champix 0.5mg tablets</td>
<td>11 tablet [PSt] no price available</td>
</tr>
<tr>
<td><strong>Varenicline (as Varenicline tartrate) 1 mg</strong> Champix 1mg tablets</td>
<td>14 tablet [PSt] no price available</td>
</tr>
<tr>
<td>Champix 0.5mg/1mg 2 week treatment initiation pack</td>
<td>25 tablet [PSt] £27.30 DT price = £27.30</td>
</tr>
<tr>
<td>Champix 0.5mg/1mg 4 week treatment initiation pack</td>
<td>53 tablet [PSt] £54.60</td>
</tr>
</tbody>
</table>

8.3 Opioid dependence

Other drugs used for Opioid dependence Naltrexone hydrochloride, p. 460

**ANALGESICS**

**Methadone hydrochloride**

**INDICATIONS AND DOSE**

Severe pain

- **BY MOUTH, OR BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 5–10 mg every 6–8 hours, adjusted according to response, on prolonged use not to be given more frequently than every 12 hours.

Adjunct in treatment of opioid dependence

- **BY MOUTH USING ORAL SOLUTION**
  - Adult: Initially 10–30 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily.

Adjunct in treatment of opioid dependence if tolerance low or not known

- **BY MOUTH USING ORAL SOLUTION**
  - Adult: Initially 20–30 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily.

Adjunct in treatment of opioid dependence if tolerance high (under expert supervision)

- **BY MOUTH USING ORAL SOLUTION**
  - Adult: Initially up to 40 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily.

Cough in terminal disease

- **INITIALLY BY MOUTH USING LINCTUS**
  - Adult: 1–2 mg every 4–6 hours, (by mouth) reduced to 1–2 mg twice daily, use twice daily frequency if prolonged use

**DOSE EQUIVALENCE AND CONVERSION**

- See p. 417 for dose adjustments in opioid substitution therapy, for patients taking methadone who want to switch to buprenorphine.
**UNLICENSED USE** Methadone hydrochloride doses for opioid dependence in the BNF may differ from those in the product literature.

**IMPORTANT SAFETY INFORMATION**
Methadone oral solution 1 mg/mL is at least 2½ times the strength of Methadone Linctus (2 mg/5mL). Many preparations of Methadone oral solution are licensed for opioid drug addiction only but some are also licensed for analgesia in severe pain.

**CONTRA-INDICATIONS** Phaeochromocytoma

**CAUTIONS** Family history of sudden death (ECG monitoring recommended) · history of cardiac conduction abnormalities

**CAUTIONS, FURTHER INFORMATION**
- QT-interval prolongation Patients with the following risk factors for QT-interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring more than 100 mg daily should also be monitored.

**SIDE-EFFECTS** Dry eyes · dysmenorrhoea · hyperprolactinaemia · hypothermia · QT-interval prolongation · raised intracranial pressure · restlessness · tarsode de pointes

**SIDE-EFFECTS, FURTHER INFORMATION**
Methadone is a long-acting opioid therefore effects may be cumulative.

Methadone, even in low doses is a special hazard for children; non-dependent adults are also at risk of toxicity; dependent adults are at risk if tolerance is incorrectly assessed during induction.

**Overdose**
Methadone has a very long duration of action; patients may need to be monitored for long periods following large overdoses.

**BREAST FEEDING** Withdrawal symptoms in infant; breast-feeding permissible during maintenance but dose should be as low as possible and infant monitored to avoid sedation (high doses of methadone carry an increased risk of sedation and respiratory depression in the neonate).

**RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**TREATMENT CESSATION** Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION** Syrup preserved with hydroxybenzoate (parabens) esters may be incompatible with methadone hydrochloride.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include tolu.

**METHADOSE** The final strength of the methadone mixture to be dispensed to the patient must be specified on the prescription.

Important—care is required in prescribing and dispensing the correct strength since any confusion could lead to an overdose; this preparation should be dispensed only after dilution as appropriate with Methadose Diluent (life of diluted solution 3 months) and is for drug dependent persons.

**NATIONAL FUNDING/ACCESS DECISIONS**
- **NICE technology appraisals (TAs)**
- Methadone and buprenorphine for the management of opioid dependence (January 2007) NICE TA114
- Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable.

**LESS SUITABLE FOR PRESCRIBING** Methadone linctus is less suitable for prescribing for cough in terminal disease (has a tendency to accumulate).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, solution for injection

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS**
- Methadone hydrochloride 5 mg Physeptone 5mg tablets | 50
- **Oral solution**
- **CAUTIONARY AND ADVISORY LABELS**
- Methadone hydrochloride (Non-proprietary)

- Methadone hydrochloride 1 mg per 1 ml Methadone 1mg/ml oral solution | 100 ml (Pom) £1.23–£1.30 DT price + £1.30 (CD) | 500 ml (Pom) £6.50 DT price + £6.50 (CD) | 2500 ml (Pom) £30.75–£32.50 (CD)
- Methadone 1mg/ml oral solution sugar free sugar-free | 50 ml (Pom) £1.04 DT price + £1.04 (CD) sugar-free | 100 ml (Pom) £2.08 DT price + £2.08 (CD) sugar-free | 500 ml (Pom) £6.50 DT price + £6.30 (CD) sugar-free | 2500 ml (Pom) £31.50–£32.50 (CD)
- Methadose (Rosemont Pharmaceuticals Ltd)

- **Methadone hydrochloride 10 mg per 1 ml Methadone 10mg/ml oral solution concentrate sugar-free | 150 ml (Pom) £12.01 (CD)
- Methadone hydrochloride 20 mg per 1 ml Methadone 20mg/ml oral solution concentrate sugar-free | 150 ml (Pom) £24.02 (CD)
- **Methadose** (Rosemont Pharmaceuticals Ltd)

- Methadone hydrochloride 1 mg per 1 ml Methadose 1mg/ml oral solution sugar free sugar-free | 500 ml (Pom) £6.82 DT price = £6.30 (CD)
- Physeptone (Martindale Pharmaceuticals Ltd)

- Methadone hydrochloride 1 mg per 1 ml Physeptone 1mg/ml mixture | 100 ml (Pom) £1.08 DT price + £1.30 (CD) | 500 ml (Pom) £5.46 DT price + £5.50 (CD) | 2500 ml (Pom) £27.29 (CD)
- Physeptone 1mg/ml mixture sugar free sugar-free | 100 ml (Pom) £1.08 DT price + £2.08 (CD) sugar-free | 500 ml (Pom) £5.46 DT price + £6.30 (CD) sugar-free | 2500 ml (Pom) £27.29 (CD)

**Solution for injection**
- **Methadone hydrochloride (Non-proprietary)**

- Methadone hydrochloride 10 mg per 1 ml Methadone 35mg/3.5ml solution for injection ampoules | 10 ampoule (Pom) £13.92 DT price = £12.87 (CD)
- Methadone hydrochloride 25 mg per 1 ml Methadone 50mg/2ml solution for injection ampoules | 10 ampoule (Pom) no price available (CD)
- Methadone hydrochloride 50 mg per 1 ml Methadone 50mg/1ml solution for injection ampoules | 10 ampoule (Pom) no price available (CD)
- Physeptone (Martindale Pharmaceuticals Ltd)

- Methadone hydrochloride 10 mg per 1 ml Physeptone 35mg/3.5ml solution for injection ampoules | 10 ampoule (Pom) £12.87 DT price = £12.87 (CD)
- Physeptone 50mg/5ml solution for injection ampoules | 10 ampoule (Pom) £13.88 DT price = £13.88 (CD)
- Physeptone 10mg/1ml solution for injection ampoules | 10 ampoule (Pom) £6.49 DT price + £6.49 (CD) | 100 ampoule (Pom) £62.10 (CD)
- Physeptone 20mg/2ml solution for injection ampoules | 10 ampoule (Pom) £11.17 DT price = £11.17 (CD)
- Methadone hydrochloride 25 mg per 1 ml Physeptone 50mg/2ml solution for injection ampoules | 10 ampoule (Pom) £15.06 (CD)
- Methadone hydrochloride 50 mg per 1 ml Physeptone 50mg/1ml solution for injection ampoules | 10 ampoule (Pom) £15.06 (CD)
OPPIOID RECEPTOR ANTAGONISTS

Buprenorphine with naloxone

The properties listed below are those particular to the combination only. For the properties of the components please consider, buprenorphine p. 417, naloxone hydrochloride p. 1214.

● INDICATIONS AND DOSE
Adjuvant in the treatment of opioid dependence (dose expressed as buprenorphine)

▷ BY SUBLINGUAL ADMINISTRATION
▷ Adult: Initially 2–4 mg once daily, an additional dose of 2–4 mg may be administered on day 1 depending on the individual patient’s requirement, increased in steps of 2–8 mg; adjusted according to response, total weekly dose may be divided and given on alternate days or 3 times weekly; maximum 24 mg per day

● NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (February 2007) that Suboxone® should be restricted for use in patients in whom methadone is not suitable.

● MEDICINAL FORMS

Scottish Medicines Consortium (SMC) Decisions

Table: Medicinal Forms

<table>
<thead>
<tr>
<th>Tablet</th>
<th>PATIENT AND CARER ADVICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BritLofex (Britannia Pharmaceuticals Ltd)</td>
<td>The patient should take part of the dose at bedtime to offset insomnia associated with opioid withdrawal.</td>
</tr>
<tr>
<td>Lofexidine hydrochloride 200 microgram</td>
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<tr>
<td>BritLofex 200microgram tablets</td>
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<tr>
<td>60 tablet (POM)</td>
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SYMPATHOMIMETICS > ALPHA₂-ADRENOCEPTOR AGONISTS

Lofexidine hydrochloride

● DRUG ACTION
Lofexidine is an alpha₂-adrenergic agonist.

● INDICATIONS AND DOSE
Management of symptoms of opioid withdrawal

▷ BY MOUTH
▷ Adult: Initially 800 micrograms daily in divided doses, increased in steps of 400–800 micrograms daily (max. per dose 800 micrograms) as required recommended duration of treatment 7–10 days if no opioid use (but longer may be required); maximum 2.4 mg per day

● CAUTIONS
Bradycardia · cerebrovascular disease · depression · history of QT prolongation · hypotension (monitor pulse rate and blood pressure) · metabolic disturbances · recent myocardial infarction · severe coronary insufficiency

● INTERACTIONS
Appendix 1 (lofexidine).
Caution with concomitant administration of drugs that prolong QT interval.

● SIDE-EFFECTS
Bradycardia · dizziness · drowsiness · dry mucous membranes · hypotension · QT-interval prolongation

● PREGNANCY
Use only if benefit outweighs risk—no information available.

● BREAST FEEDING
Use only if benefit outweighs risk—no information available.

● RENAL IMPAIRMENT
Caution in chronic impairment.

● MONITORING REQUIREMENTS
Monitoring of blood pressure and pulse rate is recommended on initiation, for at least 72 hours or until a stable dose is achieved, and on discontinuation.

● TREATMENT CESSATION
Treatment should be withdrawn gradually over 2–4 days (or longer) to reduce the risk of rebound hypertension and associated symptoms.

● PRESCRIBING AND DISPENSING INFORMATION
Lofexidine has been used in children over 12 years in the management of symptoms of opioid withdrawal.

● PATIENT AND CARER ADVICE
The patient should take part of the dose at bedtime to offset insomnia associated with opioid withdrawal.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
Chapter 5
Infection

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1 Amoebic infection

Other drugs used for Amoebic infection Metronidazole, p. 499 · Tinidazole, p. 501

ANTIPROTOZOALS

Diloxanide furoate

- INDICATIONS AND DOSE
  Chronic amoebiasis | Acute amoebiasis as adjunct to metronidazole or tinidazole
  ▶ BY MOUTH
    Child 12–17 years: 500 mg 3 times a day for 10 days
    Adult: 500 mg 3 times a day for 10 days

- UNLICENSED USE Not licensed for use in children under 25 kg body-weight.
- SIDE-EFFECTS Flatulence · pruritus · urticaria · vomiting
- PREGNANCY Manufacturer advises avoid—no information available.
- BREAST FEEDING Manufacturer advises avoid.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

Mepacrine hydrochloride

- INDICATIONS AND DOSE
  Giardiasis
  ▶ BY MOUTH
    Adult: 100 mg every 8 hours for 5–7 days

- UNLICENSED USE Not licensed for use in giardiasis.

2 Bacterial infection

Antibacterials, principles of therapy

Choice of a suitable drug

Before selecting an antibacterial the clinician must first consider two factors—the patient and the known or likely causative organism. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity, in association with the above factors, will suggest one or more antibacterials, the final choice depending on the microbiological, pharmacological, and toxicological properties.

An example of a rational approach to the selection of an antibacterial is treatment of a urinary-tract infection in a
Infection

Samples should be taken for culture and sensitivity before starting therapy. Viral infections should not be treated with antibacterials. Antibacterial policies permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases. A policy may indicate a range of drugs for general use, and local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate renal and hepatic function, increasing bacterial resistance, and information on side-effects. Duration of therapy, dosage, and route of administration depend on site, type and severity of infection and response.

Antibacterial policies

Local policies often limit the antibacterials that may be used to treat infections, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

Before starting therapy

The following precepts should be considered before starting:

- Viral infections should not be treated with antibacterials. However, antibacterials may be used to treat secondary bacterial infections (e.g. bacterial pneumonia secondary to influenza);
- Samples should be taken for culture and sensitivity testing; ‘blind’ antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- Knowledge of prevalent organisms and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available. Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is clear evidence of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- The dose of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection. The prescribing of the so-called ‘standard’ dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- The route of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate. Whenever possible, painful intramuscular injections should be avoided in children;
- Duration of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods. Conversely a single dose of an antibacterial may cure uncomplicated urinary-tract infections. The prescription for an antibacterial should specify the duration of treatment or the date when treatment is to be reviewed.

Superinfection

In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms e.g. fungal infections or antibiotic-associated colitis (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

Therapy

When the pathogen has been isolated treatment may be changed to a more appropriate antibacterial if necessary. If no bacterium is cultured the antibacterial can be continued or stopped on clinical grounds.

Notifiable diseases

Doctors must notify the Proper Officer of the local authority (usually the consultant in communicable disease control) when attending a patient suspected of suffering from any of the diseases listed below; a form is available from the Proper Officer.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antimicrobial Treatment</th>
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<tbody>
<tr>
<td>Anthrax</td>
<td>Mumps</td>
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<td>Botulism</td>
<td>Paratyphoid fever</td>
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<tr>
<td>Brucellosis</td>
<td>Plague</td>
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<td>Cholera</td>
<td>Poliomyelitis, acute</td>
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<td>Diarrhoea (infectious bloody)</td>
<td>Rabies</td>
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<tr>
<td>Diphtheria</td>
<td>Rubella</td>
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<td>Encephalitis, acute</td>
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<td>Food poisoning</td>
<td>Scarlet fever</td>
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<td>Haemolytic uraemic syndrome</td>
<td>Smallpox</td>
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<tr>
<td>Haemorrhagic fever (viral)</td>
<td>Streptococcal disease (Group A, invasive)</td>
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<tr>
<td>Hepatitis, viral</td>
<td>Tetanus</td>
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<tr>
<td>Legionnaires’ disease</td>
<td>Tuberculosis</td>
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<td>Leprosy</td>
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<td>Malaria</td>
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<td>Measles</td>
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<td>Meningitis</td>
<td>Yellow fever</td>
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<tr>
<td>Meningococcal septicaemia</td>
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</table>

Note: It is good practice for doctors to also inform the consultant in communicable disease control of instances of other infections (e.g. psittacosis) where there could be a public health risk.

Antibacterials, use for prophylaxis

Prevention of recurrence of rheumatic fever

- Phenoxyemethylenicillin p. 505 or sulfadiazine p. 520.

Prevention of secondary case of invasive group A streptococcal infection

- Phenoxyemethylenicillin.
  Patients who are penicillin allergic, either erythromycin p. 497 or azithromycin p. 495 [unlicensed indication].
  For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Public Health England Laboratory).

Prevention of secondary case of meningococcal meningitis

- Ciprofloxacin p. 514 or rifampicin p. 535 or i/m ceftriaxone p. 489 [unlicensed indication].
For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Public Health England laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis.

Prevention of secondary case of **Haemophilus influenzae** type b disease

- Rifampicin or (if rifampicin cannot be used) i/m or i/v ceftriaxone [unlicensed indication].

For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Public Health England laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis.

Within 4 weeks of illness onset in an index case with confirmed or suspected invasive **Haemophilus influenzae** type b disease, give antibacterial prophylaxis to all household contacts if there is a vulnerable individual in the household. Also, give antibacterial prophylaxis to the index case if they are in contact with vulnerable household contacts or if they are under 10 years of age. Vulnerable individuals include the immunocompromised, those with asplenia, or children under 10 years of age. If there are 2 or more cases of invasive **Haemophilus influenzae** type b disease within 120 days in a pre-school or primary school, antibacterial prophylaxis should also be given to all room contacts (including staff). Also see immunisation against **Haemophilus influenzae** type b disease.

Prevention of secondary case of diphtheria in non-immune patient

- Erythromycin (or another macrolide e.g. azithromycin or clarithromycin p. 496).

Treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment.

Prevention of pertussis

- Clarithromycin (or azithromycin or erythromycin).

Within 3 weeks of onset of cough in the index case, give antibacterial prophylaxis to all close contacts if amongst them there is at least one unimmunised or partially immunised child under 1 year of age, or if there is at least one individual who has not received a pertussis-containing vaccine more than 1 week and less than 5 years ago (so long as that individual lives or works with children under 4 months of age, is pregnant at over 32 weeks gestation, or is a healthcare worker who works with children under 1 year of age or with pregnant women).

Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease

- Phenoxybenzylpenicillin.

  If penicillin-allergic, erythromycin.

  Antibacterial prophylaxis is not fully reliable. Antibacterial prophylaxis may be discontinued in children over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection.

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive

- Isoniazid p. 541 or isoniazid + rifampicin or (if isoniazid-resistant tuberculosis in patients under 35 years) rifampicin.

For details of those who should receive chemoprophylaxis contact the lead clinician for local tuberculosis services (or a consultant in communicable disease control).

Prevention of infection from animal and human bites

- Co-amoxiclav p. 508 alone (or doxycycline p. 521 + metronidazole p. 499 if penicillin-allergic).

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin p. 1143 (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection).

Consider rabies prophylaxis for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.

Antibacterial prophylaxis recommended for wounds less than 48–72 hours old when the risk of infection is high (e.g. bites from humans or cats; bites to the hand, foot, face, or genital area; bites involving oedema, crush or puncture injury, or other moderate to severe injury; wounds that cannot be debrided adequately; patients with diabetes mellitus, cirrhosis, asplenia, prosthetic joints or valves, or those who are immunocompromised). Give antibacterial prophylaxis for up to 5 days.

Prevention of early-onset neonatal infection

- i/v benzylpenicillin sodium p. 504 (or i/v clindamycin p. 493 if history of allergy to penicillins).

Give intrapartum prophylaxis to women with group B streptococcal colonisation, bacteriuria, or infection in the current pregnancy, or to women who had a previous baby with an invasive group B streptococcal infection. Consider prophylaxis for women in preterm labour if there is prelabour rupture of membranes or if intrapartum rupture of membranes lasting more than 18 hours is suspected.

Prevention of infection in gastro-intestinal procedures

**Operations on stomach or oesophagus**

- Single dose of i/v gentamicin p. 479 or i/v cefuroxime p. 486 or i/v co-amoxiclav (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Add i/v teicoplanin p. 491 (or vancomycin p. 492) if high risk of meticillin-resistant *Staphylococcus aureus*.

**Open biliary surgery**

- Single dose of i/v cefuroxime + i/v metronidazole or i/v gentamicin + i/v metronidazole or i/v co-amoxiclav alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant *Staphylococcus aureus*. 

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Resections of colon and rectum for carcinoma, and resections in inflammatory bowel disease, and appendicectomy

- Single dose of i/v gentamicin + i/v metronidazole or i/v cefuroxime + i/v metronidazole or i/v co-amoxiclav alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Where i/v metronidazole p. 499 is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Add i/v teicoplanin p. 491 (or vancomycin p. 492) if high risk of meticillin-resistant Staphylococcus aureus.

Endoscopic retrograde cholangiopancreatography

- Single dose of i/v gentamicin p. 479 or oral i/v ciprofloxacin p. 514.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Prophylaxis recommended if pancreatic pseudocyst, immunocompromised, history of liver transplantation, or risk of incomplete biliary drainage. For biliary complications following liver transplantation, add i/v amoxicillin p. 506 or i/v teicoplanin (or vancomycin).

Percutaneous endoscopic gastrostomy or jejunostomy

- Single dose of i/v co-amoxiclav p. 508 or i/v cefuroxime p. 486.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v teicoplanin (or vancomycin) if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant Staphylococcus aureus.

Prevention of infection in orthopaedic surgery

Joint replacement including hip and knee

- Single dose of i/v cefuroxime alone or i/v flucloxacin p. 511 + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant Staphylococcus aureus, use single dose of i/v teicoplanin (or vancomycin) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Closed fractures

- Single dose of i/v cefuroxime or i/v flucloxacillin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant Staphylococcus aureus, use single dose of i/v teicoplanin (or vancomycin) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Open fractures

- Use i/v co-amoxiclav alone or i/v cefuroxime + i/v metronidazole (or i/v clindamycin p. 493 alone if history of allergy to penicillins or to cephalosporins).

Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant Staphylococcus aureus. Start prophylaxis within 3 hours of injury and continue until soft tissue closure (max. 72 hours).

At first debridement also use a single dose of i/v cefuroxime + i/v metronidazole + i/v gentamicin or i/v co-amoxiclav + i/v gentamicin (or i/v clindamycin + i/v gentamicin if history of allergy to penicillins or to cephalosporins).

At time of skeletal stabilisation and definitive soft tissue closure use a single dose of i/v gentamicin + i/v teicoplanin (or vancomycin) (intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure).

High lower-limb amputation

- Use i/v co-amoxiclav alone or i/v cefuroxime + i/v metronidazole.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Continue antibacterial prophylaxis for at least 2 doses after procedure (max. duration of prophylaxis 5 days). If history of allergy to penicillin or to cephalosporins, or if high risk of meticillin-resistant Staphylococcus aureus, use i/v teicoplanin (or vancomycin) + i/v gentamicin + i/v metronidazole.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Prevention of infection in urological procedures

Transrectal prostate biopsy

- Single dose of oral ciprofloxacin + oral metronidazole or i/v gentamicin + i/v metronidazole (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin + i/v metronidazole if high risk of meticillin-resistant Staphylococcus aureus (additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss).

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Transurethral resection of prostate

- Single dose of oral ciprofloxacin or i/v gentamicin or i/v cefuroxime (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin if high risk of meticillin-resistant Staphylococcus aureus (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Prevention of infection in obstetric and gynaecological surgery

Caesarean section

- Single dose of i/v cefuroxime (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Substitute i/v clindamycin if history of allergy to penicillins or cephalosporins. Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant Staphylococcus aureus.

Hysterectomy

- Single dose of i/v cefuroxime + i/v metronidazole or i/v gentamicin + i/v metronidazole or i/v co-amoxiclav alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).
Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin + i/v metronidazole or add i/v teicoplanin (or vancomycin) to other regimens if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

**Termination of pregnancy**

- Single dose of oral metronidazole (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

If genital chlamydial infection cannot be ruled out, give doxycycline p. 521 postoperatively.

**Prevention of infection in cardiology procedures**

**Cardiac pacemaker insertion**

- Single dose of i/v cefuroxime alone or i/v flucloxacillin + i/v gentamicin or i/v teicoplanin (or vancomycin) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v teicoplanin (or vancomycin) + i/v cefuroxime or i/v teicoplanin (or vancomycin) + i/v gentamicin if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Prevention of infection in vascular surgery**

**Reconstructive arterial surgery of abdomen, pelvis or legs**

- Single dose of i/v cefuroxime p. 486 alone or i/v flucloxacillin p. 511 + i/v gentamicin p. 479 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Add i/v metronidazole p. 499 for patients at risk from anaerobic infections including those with diabetes, gangrene, or undergoing amputation. Use single dose of i/v teicoplanin p. 491 (or vancomycin p. 492) + i/v gentamicin if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Prevention of endocarditis**

**NICE guidance: Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (March 2008)**

- Antibacterial prophylaxis and chlorhexidine mouthwash are not recommended for the prevention of endocarditis in patients undergoing dental procedures.

Antibacterial prophylaxis is not recommended for the prevention of endocarditis in patients undergoing procedures of the:

- upper and lower respiratory tract (including ear, nose, and throat procedures and bronchoscopy);
- genito-urinary tract (including urological, gynaecological, and obstetric procedures);
- upper and lower gastro-intestinal tract.

Whilst these procedures can cause bacteraemia, there is no clear association with the development of infective endocarditis. Prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

If patients at risk of endocarditis are undergoing a gastrointestinal or genito-urinary tract procedure at a site where infection is suspected, they should receive appropriate antibacterial therapy that includes cover against organisms that cause endocarditis.

Patients at risk of endocarditis should be:

- advised to maintain good oral hygiene;
- told how to recognise signs of infective endocarditis, and advised when to seek expert advice.

Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis.

**Dermatological procedures**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who undergo dermatological procedures do not require antibacterial prophylaxis against endocarditis.

The British Association of Dermatologists Therapy Guidelines and Audit Subcommittee advise that such dermatological procedures include skin biopsies and excision of moles or of malignant lesions.

**Joint prosthesis and dental treatment**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive.

The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

**Immunosuppression and indwelling intraperitoneal catheters**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis.

The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.
Blood infections, bacterial

Antibacterial therapy for septicaemia: community-acquired
- A broad-spectrum antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 503, ticarcillin with clavulanic acid p. 504) or a broad-spectrum cephalosporin (e.g. cefuroxime p. 486)
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin p. 492 (or teicoplanin p. 491).
- If anaerobic infection suspected, add metronidazole p. 499 to broad-spectrum cephalosporin.
- If other resistant micro-organisms suspected, use a more broad-spectrum beta-lactam antibacterial (e.g. meropenem p. 483).

Antibacterial therapy for septicaemia: hospital-acquired
- A broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. piperacillin with tazobactam, ticarcillin with clavulanic acid, ceftazidime p. 488, imipenem with cilastatin p. 482, or meropenem).
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin (or teicoplanin).
- If anaerobic infection suspected, add metronidazole to broad-spectrum cephalosporin.

Septicaemia related to vascular catheter
- Vancomycin (or teicoplanin).
- If Gram-negative sepsis suspected, especially in the immunocompromised, add a broad-spectrum antipseudomonal beta-lactam.
- Consider removing vascular catheter, particularly if infection caused by *Staphylococcus aureus*, pseudomonas, or *Candida* species.

Meningococcal septicaemia
If meningococcal disease suspected, a single dose of benzylpenicillin sodium p. 504 should be given before urgent transfer to hospital, so long as this does not delay the transfer; cefotaxime p. 487 may be an alternative in penicillin allergy; chloramphenicol p. 524 may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.
- Benzylpenicillin sodium or cefotaxime (or ceftriaxone p. 489).
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol.
- To eliminate nasopharyngeal carriage, ciprofloxacin p. 514, or rifampicin p. 535, or ceftriaxone may be used.

Cardiovascular system infections, bacterial

Antibacterial therapy for endocarditis: initial ‘blind’ therapy
- *Native valve endocarditis*, amoxicillin p. 506 (or ampicillin p. 507)
- Consider adding low-dose gentamicin p. 479
- If penicillin-allergic, or if meticillin-resistant *Staphylococcus aureus* suspected, or if severe sepsis, use vancomycin p. 492 + low-dose gentamicin
- If severe sepsis with risk factors for Gram-negative infection, use vancomycin + meropenem p. 483
- If *prosthetic valve endocarditis*, vancomycin + rifampicin p. 535 + low-dose gentamicin

Antibacterial therapy for native-valve endocarditis caused by staphylococci
- Flucloxacillin p. 511
- *Suggested duration of treatment* 4 weeks (at least 6 weeks if secondary lung abscess or osteomyelitis also present)
- If penicillin-allergic or if meticillin-resistant *Staphylococcus aureus*, vancomycin + rifampicin
- *Suggested duration of treatment* 4 weeks (at least 6 weeks if secondary lung abscess or osteomyelitis also present)

Antibacterial therapy for prosthetic valve endocarditis caused by staphylococci
- Flucloxacillin + rifampicin + low-dose gentamicin
- *Suggested duration of treatment* at least 6 weeks; review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- If penicillin-allergic or if meticillin-resistant *Staphylococcus aureus*, vancomycin + rifampicin + low-dose gentamicin
- *Suggested duration of treatment* at least 6 weeks; review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks

Antibacterial therapy for endocarditis caused by fully-sensitive streptococci
- Benzylpenicillin sodium p. 504
- *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis)
- If penicillin-allergic, vancomycin (or teicoplanin p. 491) + low-dose gentamicin
- *Suggested duration of treatment* 4–6 weeks (stop gentamicin after 2 weeks)

Antibacterial therapy for endocarditis caused by less-sensitive streptococci
- Benzylpenicillin sodium + low-dose gentamicin
- *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks; stop gentamicin at 2 weeks if micro-organisms moderately sensitive to penicillin
- If penicillin-allergic or highly penicillin-resistant, vancomycin (or teicoplanin) + low-dose gentamicin
- *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks; stop gentamicin at 2 weeks if micro-organisms moderately sensitive to penicillin

Antibacterial therapy for endocarditis caused by enterococci
- Amoxicillin (or ampicillin) + low dose gentamicin or benzylpenicillin sodium + low-dose gentamicin
- *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- If penicillin-allergic or penicillin-resistant, vancomycin (or teicoplanin) + low-dose gentamicin
- *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- If gentamicin resistant, amoxicillin (or ampicillin)
- Add streptomycin p. 480 (if susceptible) for 2 weeks
- *Suggested duration of treatment* at least 6 weeks
Antibacterial therapy for endocarditis caused by *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* species (‘HACEK’ micro-organisms)

- Amoxicillin (or ampicillin) + low-dose gentamicin
- **Suggested duration of treatment** 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks
- If amoxicillin -resistant, ceftriaxone p. 489 (or cefotaxime p. 487) + low-dose gentamicin
- **Suggested duration of treatment** 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

**Central nervous system infections, bacterial**

**Antibacterial therapy for meningitis: initial empirical therapy**

- Transfer patient to hospital urgently.
- If *meningococcal disease* (meningitis with non-blanching rash or meningococcal septicaemia) suspected, benzylpenicillin sodium p. 504 should be given before transfer to hospital, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, benzylpenicillin sodium should be given before the transfer. Cefotaxime p. 487 may be an alternative in penicillin allergy; chloramphenicol p. 524 may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.
- In hospital, consider adjunctive treatment with dexamethasone p. 618 (particularly if pneumococcal meningitis suspected in adults), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial; avoid dexamethasone in septic shock, meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery.
  - In hospital, if aetiology unknown:
    - **Adult and child 3 months–50 years**, cefotaxime (or ceftriaxone p. 489)
      - Consider adding vancomycin p. 492 if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.
      - **Suggested duration of treatment** at least 10 days
    - **Adult over 50 years** cefotaxime (or ceftriaxone) + amoxicillin p. 506 (or ampicillin p. 507)
      - Consider adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.
      - **Suggested duration of treatment** at least 10 days

**Antibacterial therapy for meningitis caused by *meningococci***

- Benzylpenicillin sodium or cefotaxime (or ceftriaxone)
- **Suggested duration of treatment** 7 days.
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol
- **Suggested duration of treatment** 7 days.

**Antibacterial therapy for meningitis caused by pneumococci**

- Cefotaxime (or ceftriaxone)
  - Consider adjunctive treatment with dexamethasone, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.
  - **Suggested duration of antibacterial treatment** 10 days.
  - For *H. influenzae* type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts
  - If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, or if micro-organism resistant to cefotaxime, chloramphenicol
    - Consider adjunctive treatment with dexamethasone, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.
    - **Suggested duration of antibacterial treatment** 10 days.
  - For *H. influenzae* type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts

**Antibacterial therapy for meningitis caused by *Listeria***

- Amoxicillin (or ampicillin) + gentamicin p. 479
  - **Suggested duration of treatment** 21 days.
  - Consider stopping gentamicin after 7 days.
  - If history of immediate hypersensitivity reaction to penicillin, co-trimoxazole p. 518
  - **Suggested duration of treatment** 21 days.

**Ear infections, bacterial**

**Antibacterial therapy for otitis externa**

For topical treatments, consider *Otitis externa,* under Ear p. 1050.
- Consider systemic antibacterial if spreading cellulitis or patient systemically unwell.
  - Flucloxacillin p. 511
  - If *penicillin-allergic,* clarithromycin p. 496 (or azithromycin p. 495 or erythromycin p. 497)
  - If *pseudomonas suspected,* ciprofloxacin p. 514 (or an aminoglycoside)

**Antibacterial therapy for otitis media**

Many infections are caused by viruses. Most uncomplicated cases resolve without antibacterial treatment. In children without systemic features, antibacterial treatment may be started after 72 hours if no improvement. Consider earlier treatment if deterioration, if systemically unwell, if at high risk of serious complications (e.g. in immunosuppression,
Eye infections, bacterial

Antibacterial therapy for purulent conjunctivitis
- Chloramphenicol eye drops p. 524.

Gastro-intestinal system infections, bacterial

**Antibacterial therapy for gastro-enteritis**
Frequently self-limiting and may not be bacterial.
- Antibacterial not usually indicated

**Antibacterial therapy for campylobacter enteritis**
Frequently self-limiting; treat if immunocompromised or if severe infection.
- Clarithromycin p. 496 (or azithromycin p. 495 or erythromycin p. 497)
- Alternative, ciprofloxacin p. 514
- Strains with decreased sensitivity to ciprofloxacin isolated frequently

**Antibacterial therapy for salmonella (non-typhoid)**
Treat invasive or severe infection. Do not treat less severe infection unless there is a risk of developing invasive infection (e.g. immunocompromised patients, those with haemoglobinopathy, or children under 6 months of age).
- Ciprofloxacin or cefotaxime p. 487

**Antibacterial therapy for shigellosis**
Antibacterial not indicated for mild cases.
- Ciprofloxacin or azithromycin
- Alternatives if micro-organism sensitive, amoxicillin p. 506 or trimethoprim p. 529

**Antibacterial therapy for typhoid fever**
Infections from Middle-East, South Asia, and South-East Asia may be multiple-antibacterial-resistant and sensitivity should be tested.
- Cefotaxime (or ceftriaxone p. 489)
- Azithromycin may be an alternative in mild or moderate disease caused by multiple-antibacterial-resistant organisms.
- Alternative if micro-organism sensitive, ciprofloxacin

**Antibacterial therapy for Clostridium difficile infection**
- For first episode of mild to moderate infection, oral metronidazole p. 499
- Suggested duration of treatment 10–14 days
- For second or subsequent episode of infection, for severe infection, for infection not responding to metronidazole, or in patients intolerant of metronidazole, oral vancomycin p. 492
- For severe infection in patients with multiple co-morbidities who are receiving treatment with other antibacterials, or for second or subsequent episode of infection, fidaxomicin p. 525 can replace vancomycin
- Suggested duration of treatment 10–14 days
- For infection not responding to vancomycin or fidaxomicin, for life-threatening infection, or in patients with ileus, oral vancomycin + i/v metronidazole
- For infection not responding to vancomycin in patients without life-threatening infection or ileus, fidaxomicin can be used instead of vancomycin + metronidazole
- Suggested duration of treatment 10–14 days

**Antibacterial therapy for biliary-tract infection**
- Ciprofloxacin or gentamicin p. 479 or a cephalosporin

**Antibacterial therapy for peritonitis**
- A cephalosporin + metronidazole or gentamicin + metronidazole or gentamicin + clindamycin p. 493 or piperacillin with tazobactam p. 503 alone

**Antibacterial therapy for peritonitis: peritoneal dialysis-associated**
- Vancomycin (or teicoplanin p. 491) + ceftazidime p. 488 added to dialysis fluid or vancomycin added to dialysis fluid + ciprofloxacin by mouth
- Suggested duration of treatment 14 days or longer

Genital system infections, bacterial

**Antibacterial therapy for bacterial vaginosis**
- Oral metronidazole p. 499
- Suggested duration of treatment 5–7 days (or high-dose metronidazole as a single dose)
- Alternatively, topical metronidazole for 5 days or topical clindamycin p. 493 for 7 days

**Antibacterial therapy for uncomplicated genital chlamydial infection, non-gonococcal urethritis, and non-specific genital infection**
Contact tracing recommended.
- Azithromycin p. 495 or doxycycline p. 521
- Suggested duration of treatment azithromycin as a single dose or doxycycline for 7 days
- Alternatively, erythromycin p. 497.
- Suggested duration of treatment 14 days

**Antibacterial therapy for gonorrhoea: uncomplicated**
Contact tracing recommended. Consider chlamydia co-infection. Choice of alternative antibacterial regimen depends on locality where infection acquired.
- Azithromycin + i/m ceftriaxone p. 489
- Suggested duration of treatment is a single-dose of each antibacterial
- Alternatively, when parenteral administration is not possible, cefixime p. 487 + azithromycin
- Suggested duration of treatment is a single-dose of each antibacterial
- Alternatively, if micro-organism is sensitive to a quinolone, ciprofloxacin p. 514 + azithromycin
**Antibacterial therapy for pelvic inflammatory disease**

Contact tracing recommended.

- Doxycycline + metronidazole + single-dose of i/m ceftriaxone or ofloxacin p. 517 + metronidazole
- **Suggested duration of treatment** 14 days (except i/m ceftriaxone).
- In severely ill patients initial treatment with doxycycline + i/v ceftriaxone + i/v metronidazole, then switch to oral treatment with doxycycline + metronidazole to complete 14 days’ treatment

**Antibacterial therapy for early syphilis (infection of less than 2 years)**

Contact tracing recommended.

- Benzathine benzylpenicillin [unlicensed]
- **Suggested duration of treatment** single-dose (repeat dose after 7 days for women in the third trimester of pregnancy)
- Alternatively, doxycycline or erythromycin
- **Suggested duration of treatment** 14 days

**Antibacterial therapy for late latent syphilis (asymptomatic infection of more than 2 years)**

Contact tracing recommended.

- Benzathine benzylpenicillin [unlicensed]
- **Suggested duration of treatment** once weekly for 2 weeks
- Alternatively, doxycycline
- **Suggested duration of treatment** 28 days

**Asymptomatic contacts of patients with infectious syphilis**

- Doxycycline
- **Suggested duration of treatment** 14 days

**Musculoskeletal system infections, bacterial**

**Antibacterial therapy for osteomyelitis**

Seek specialist advice if chronic infection or prostheses present.

- Flucloxacillin p. 511
- Consider adding fusidic acid p. 527 or rifampicin p. 535 for initial 2 weeks.
- **Suggested duration of treatment** 6 weeks for acute infection
- If penicillin-resistant, clindamycin p. 493
- Consider adding fusidic acid or rifampicin for initial 2 weeks.
- **Suggested duration of treatment** 6 weeks for acute infection
- If meticillin-resistant Staphylococcus aureus suspected, vancomycin p. 492 (or teicoplanin p. 491)
- Consider adding fusidic acid or rifampicin for initial 2 weeks.
- **Suggested duration of treatment** 6 weeks for acute infection

**Antibacterial therapy for septic arthritis**

Seek specialist advice if prostheses present.

- Flucloxacillin
- **Suggested duration of treatment** 4–6 weeks (longer if infection complicated).

- If penicillin-allergic, clindamycin
- **Suggested duration of treatment** 4–6 weeks (longer if infection complicated).
- If meticillin-resistant Staphylococcus aureus, vancomycin (or teicoplanin)
- **Suggested duration of treatment** 4–6 weeks (longer if infection complicated).
- If gonococcal arthritis or Gram-negative infection suspected, cefotaxime p. 487 (or ceftriaxone p. 489)
- **Suggested duration of treatment** 4–6 weeks (longer if infection complicated; treat gonococcal infection for 2 weeks).

**Nose infections, bacterial**

**Antibacterial therapy for sinusitis**

Antibacterial therapy should usually be used only for persistent symptoms and purulent discharge lasting at least 7 days or if severe symptoms. Also, consider antibacterial therapy for those at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis).

- Amoxicillin p. 506 (or ampicillin p. 507) or doxycycline p. 521 or clarithromycin p. 496 (or azithromycin p. 495 or erythromycin p. 497)
- **Suggested duration of treatment** 7 days.
- Consider oral co-amoxiclav p. 508 if no improvement after 48 hours.
- In severe infection, initial parenteral therapy with co-amoxiclav or cefuroxime p. 486 may be required.

**Oral bacterial infections**

**Antibacterial drugs**

Antibacterial drugs should only be prescribed for the treatment of oral infections on the basis of defined need. They may be used in conjunction with (but not as an alternative to) other appropriate measures, such as providing drainage or extracting a tooth.

The ‘blind’ prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. In severe oral infections, a sample should always be taken for bacteriology.

Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acutely created oral-antral communication (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be required if treatment has to be delayed, in immunocompromised patients, or in those with conditions such as diabetes or Paget’s disease. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial spaces such as Ludwig’s angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial spaces (where it can cause airway obstruction), or into the bloodstream (where it can lead to cavernous sinus thrombosis and other serious complications). Extension of an infection can also lead to maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced.

If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be...

- If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be...

- In severely ill patients initial treatment with amoxicillin + i/v ceftriaxone + i/v metronidazole, then switch to oral treatment with amoxicillin + metronidazole to complete 14 days’ treatment
Infection treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes. It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent’s infection) and pericoronitis; amoxicillin is a suitable alternative. For these purposes metronidazole for 3 days is sufficient, but the duration of treatment may need to be longer in pericoronitis. Tinidazole p. 501 is licensed for the treatment of acute ulcerative gingivitis.

**Penicillins**
Phenoxyethylpenicillin p. 505 is effective for dentoalveolar abscess.

**Broad-spectrum penicillins**
Amoxicillin p. 506 is as effective as phenoxyethylpenicillin but is better absorbed; however, it may encourage emergence of resistant organisms.

Like phenoxyethylpenicillin, amoxicillin is ineffective against bacteria that produce beta-lactamases. Amoxicillin may be useful for short course oral regimens.

Co-amoxiclav p. 508 is active against beta-lactamase-producing bacteria that are resistant to amoxicillin. Co-amoxiclav may be used for severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial treatment.

**Cephalosporins**
The cephalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) has reduced their usefulness for the treatment of destructive (refractory) forms of periodontal disease. Doxycycline p. 521 has a longer duration of action than tetracycline p. 523 or oxytetracycline p. 523 and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.

Doxycycline may have a role in the treatment of recurrent aphthous ulceration, or as an adjunct to gingival scaling and root planing for periodontitis.

**Macrolides**
The macrolides are an alternative for oral infections in penicillin-allergic patients or where a beta-lactamase producing organism is involved. However, many organisms are now resistant to macrolides or rapidly develop resistance; their use should therefore be limited to short courses.

**Clindamycin**
Clindamycin p. 493 should not be used routinely for the treatment of oral infections because it may be no more effective than penicillins against anaerobes and there may be cross-resistance with erythromycin p. 497-resistant bacteria. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

**Metronidazole and tinidazole**
Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is changed, preferably on the basis of bacteriological investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance.

Combination of a penicillin (or a macrolide) with metronidazole p. 499 may sometimes be helpful for the treatment of severe oral infections or oral infections that have not responded to initial antibacterial treatment.

**Respiratory system infections, bacterial**

**Antibacterial therapy for *Haemophilus influenzae* epiglottitis**
- Cefotaxime p. 487 (or ceftriaxone p. 489)
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol p. 524

**Antibacterial therapy for chronic bronchitis: acute exacerbations**
Treat if increase in sputum purulence accompanied by an increase in sputum volume or increase in dyspnoea.
- Amoxicillin p. 506 (or ampicillin p. 507) or a tetracycline p. 523
- Some pneumococci and *Haemophilus influenzae* strains tetracycline-resistant; approx. 20% *H. influenzae* strains amoxicillin-resistant
- **Suggested duration of treatment** 5 days; longer treatment may be necessary in severely ill patients
- **Alternative**, clarithromycin p. 496 (or azithromycin p. 495 or erythromycin p. 497)
- **Suggested duration of treatment** 5 days; longer treatment may be necessary in severely ill patients

**Antibacterial therapy for pneumonia: low-severity community-acquired**
- Amoxicillin (or ampicillin)
- Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
- If typical pathogens suspected, add clarithromycin (or azithromycin or erythromycin).
- If staphylococci suspected (e.g. in influenza or measles), add flucoxacillin p. 511.
- **Suggested duration of treatment** 7 days (14–21 days for infections caused by staphylococci)
- **Alternatives**, doxycycline p. 521 or clarithromycin (or azithromycin or erythromycin)
- **Suggested duration of treatment** 7 days (14–21 days for infections caused by staphylococci)

**Antibacterial therapy for pneumonia: moderate-severity community-acquired**
- Amoxicillin (or ampicillin) + clarithromycin (or azithromycin or erythromycin) or doxycycline alone
- Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin p. 492 (or teicoplanin p. 491).
- **Suggested duration of treatment** 7 days (14–21 days for infections caused by staphylococci)

**Antibacterial therapy for pneumonia: high-severity community-acquired**
- Benzylpenicillin sodium p. 504 + clarithromycin (or azithromycin or erythromycin) or benzylpenicillin sodium + doxycycline
Skin infections, bacterial

Antibacterial therapy for impetigo: small areas of skin infected
Seek local microbiology advice before using topical treatment in hospital.
- Topical fusidic acid p. 527
- Suggested duration of treatment 7 days is usually adequate (max. 10 days).
- Alternatively, if meticillin-resistant Staphylococcus aureus, topical mupirocin p. 1086
- Suggested duration of treatment 7 days is usually adequate (max. 10 days).

Impetigo: widespread infection
- Oral flucloxacillin p. 511
  - If streptococci suspected in severe infection, add penicillin p. 505.
  - Suggested duration of treatment 7 days.
- If penicillin–allergic, oral clarithromycin p. 496 or erythromycin p. 497
  - Suggested duration of treatment 7 days.

Antibacterial therapy for erysipelas
- Phenoxybenzamine p. 504
  - If severe infection, replace phenoxybenzamine or benzylpenicillin with high-dose flucloxacillin
  - Suggested duration of treatment at least 7 days.
- If penicillin–allergic, clindamycin p. 493 or clarithromycin (or erythromycin)
  - Suggested duration of treatment at least 7 days.

Antibacterial therapy for cellulitis
- Flucloxacillin (high-dose)
  - If streptococcal infection confirmed, replace flucloxacillin with phenoxybenzamine or benzylpenicillin sodium
  - If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibacterials.
- If penicillin–allergic, clindamycin or clarithromycin (or erythromycin) or vancomycin p. 492 (or teicoplanin p. 491)
  - If Gram-negative bacteria suspected, use broad-spectrum antibacterials.

Antibacterial therapy for animal and human bites
Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin p. 1143 (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection). Consider rabies prophylaxis for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.
- Co-amoxiclav p. 508
- If penicillin–allergic, doxycycline p. 521 + metronidazole p. 499

Antibacterial therapy for mastitis during breastfeeding
Treat if severe, if systemically unwell, if nipple fissure present, if symptoms do not improve after 12–24 hours of effective milk removal, or if culture indicates infection.
- Flucloxacillin, if penicillin–allergic, erythromycin
  - Continue breast-feeding or expressing milk during treatment.
  - Suggested duration of treatment 10–14 days.

Antibacterial therapy for pneumonia possibly caused by atypical pathogens
- Clarithromycin (or azithromycin or erythromycin)
  - If high-severity Legionella infection, add rifampicin p. 535 for the first few days.
  - Suggested duration of treatment 14 days (usually 7–10 days for Legionella)
- Alternative if Legionella infection suspected, a quinolone
  - If high–severity Legionella infection, add clarithromycin (or azithromycin or erythromycin) or rifampicin for the first few days.
  - Suggested duration of treatment usually 7–10 days
- Alternative for chlamydial or mycoplasma infections, doxycycline
  - Suggested duration of treatment 14 days.

Antibacterial therapy for pneumonia: hospital-acquired
- Early-onset infection less than 5 days after admission to hospital, co-amoxiclav or cefuroxime
  - If life-threatening infection, or if history of antibiotic treatment in the last 3 months, or if resistant microorganisms suspected, treat as for late-onset hospital-acquired pneumonia.
  - Suggested duration of treatment 7 days
- Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 503) or a broad-spectrum cephalosporin (e.g. ceftazidime p. 488) or another antipseudomonal beta-lactam or a quinolone (e.g. ciprofloxacin p. 514)
  - If meticillin-resistant Staphylococcus aureus suspected, add vancomycin.
  - For severe illness caused by Pseudomonas aeruginosa, consider adding an aminoglycoside.
  - Suggested duration of treatment 7 days (longer if Pseudomonas aeruginosa confirmed)

- If meticillin-resistant Staphylococcus aureus suspected, add vancomycin (or teicoplanin).
- Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci suspected)
- If life-threatening infection, or if Gram-negative infection suspected, or if co-morbidities present, or if living in long-term residential or nursing home, co-amoxiclav p. 508 + clarithromycin (or azithromycin or erythromycin)
- If meticillin-resistant Staphylococcus aureus suspected, add vancomycin (or teicoplanin).
- Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)
- Alternatives if life-threatening infection, or if Gram-negative infection suspected, or if co-morbidities present, or if living in long-term residential or nursing home, cefuroxime p. 486 + clarithromycin (or azithromycin or erythromycin) or ceftaxime (or ceftriaxone) + clarithromycin (or azithromycin or erythromycin)
- If meticillin-resistant Staphylococcus aureus suspected, add vancomycin (or teicoplanin).
- Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)

Antibacterial therapy for cellulitis
- Oral clindamycin or clarithromycin (or erythromycin)
  - If penicillin–allergic, clindamycin p. 493 or clarithromycin (or erythromycin)
  - Suggested duration of treatment at least 7 days.

- If high–severity Legionella infection, add clarithromycin (or azithromycin or erythromycin) or rifampicin for the first few days.
- Suggested duration of treatment usually 7–10 days
- Alternative for chlamydial or mycoplasma infections, doxycycline
  - Suggested duration of treatment 14 days.

Antibacterial therapy for pneumonia possibly caused by atypical pathogens
- Clarithromycin (or azithromycin or erythromycin)
  - If high-severity Legionella infection, add rifampicin p. 535 for the first few days.
  - Suggested duration of treatment 14 days (usually 7–10 days for Legionella)

Antibacterial therapy for pneumonia: hospital-acquired
- Early-onset infection less than 5 days after admission to hospital, co-amoxiclav or cefuroxime
  - If life-threatening infection, or if history of antibiotic treatment in the last 3 months, or if resistant microorganisms suspected, treat as for late-onset hospital-acquired pneumonia.
  - Suggested duration of treatment 7 days
- Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 503) or a broad-spectrum cephalosporin (e.g. ceftazidime p. 488) or another antipseudomonal beta-lactam or a quinolone (e.g. ciprofloxacin p. 514)
  - If meticillin-resistant Staphylococcus aureus suspected, add vancomycin.
  - For severe illness caused by Pseudomonas aeruginosa, consider adding an aminoglycoside.
  - Suggested duration of treatment 7 days (longer if Pseudomonas aeruginosa confirmed)
Aminoglycosides

Overview

These include amikacin p. 479, gentamicin p. 479, neomycin sulfate p. 480, streptomycin p. 480, and tobramycin p. 481. Aminoglycosides are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against Pseudomonas aeruginosa; streptomycin is active against Mycobacterium tuberculosis and is now almost entirely reserved for tuberculosis.

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections.

Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the ‘blind’ therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole p. 499 (or both). Gentamicin is used together with another antibiotic for the treatment of endocarditis. Tobramycin may be used as an alternative in gentamicin-resistant enterococcal endocarditis.

Loading and maintenance doses of gentamicin may be calculated on the basis of the patient’s weight and renal function (e.g. using a nomogram); adjustments are then made according to serum-gentamicin concentrations. High doses are occasionally indicated for serious infections, especially in the neonate, in the patient with cystic fibrosis, or in the immunocompromised patient. Whenever possible treatment should not exceed 7 days.

Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

Tobramycin has similar activity to gentamicin. It is slightly more active against Ps. aeruginosa but shows less activity against certain other Gram-negative bacteria. Tobramycin can be administered by nebuliser or by inhalation of powder on a cyclical basis (28 days of tobramycin followed by a 28-day tobramycin-free interval) for the treatment of chronic pulmonary Ps. aeruginosa infection in cystic fibrosis; however, resistance may develop and some patients do not respond to treatment.

Neomycin sulfate is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin sulfate may be absorbed from the gut in patients with hepatic failure and, as these patients may also be uraemic, cumulation may occur with resultant ototoxicity.

Once daily dosage

Once daily administration of aminoglycosides is more convenient, provides adequate serum concentrations, and in many cases has largely superseded multiple daily dose regimens (given in 2–3 divided doses during the 24 hours). Local guidelines on dosage and serum concentrations should be consulted. A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with endocarditis due to Gram-positive bacteria, HACEK endocarditis, burns of more than 20% of the total body surface area, or creatinine clearance less than 20 mL/minute. There is insufficient evidence to recommend a once daily, high-dose regimen of an aminoglycoside in pregnancy.

Serum concentrations

Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. Serum-aminoglycoside concentrations should be monitored in patients receiving parenteral aminoglycosides and must be determined in the elderly, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

Aminoglycosides (by injection)

- **CONTRA-INDICATIONS** Myasthenia gravis (aminoglycosides may impair neuromuscular transmission)
- **CAUTIONS** Care must be taken with dosage (the main side-effects of the aminoglycosides are dose-related); conditions characterised by muscular weakness (aminoglycosides may impair neuromuscular transmission) - if possible, dehydration should be corrected before starting an aminoglycoside - whenever possible, parenteral treatment should not exceed 7 days
- **INTERACTIONS** → Appendix 1 (aminoglycosides).
  - If possible, aminoglycosides should not be given with potentially ototoxic drugs (e.g. cisplatin). Administration of an aminoglycoside and of an ototoxic diuretic (e.g. furosemide) should be separated by as long a period as practicable.
- **SIDE-EFFECTS**, **FURTHER INFORMATION**
  - **Nephrotoxicity**
    - Rare Antibiotic-associated colitis - electrolyte disturbances - hypocalcaemia - hypokalaemia - hypomagnesaemia on prolonged therapy - nausea - peripheral neuropathy - stomatitis - vomiting
  - **Very rare** Blood disorders - CNS effects - convulsions - encephalopathy - headache
  - **Frequency not known** Auditory damage - impaired neuromuscular transmission - irreversible ototoxicity - nephrotoxicity - transient myasthenic syndrome in patients with normal neuromuscular function with large doses given during surgery - vestibular damage
  - **SIDE-EFFECTS** Further information:
    - Nephrotoxicity
      - In adults Occurs most commonly in the elderly; therefore, monitoring is particularly important in these patients, who may require reduced doses.
      - In children Occurs most commonly in children with renal failure.
  - **PREGNANCY** There is a risk of auditory or vestibular nerve damage in the infant when aminoglycosides are used in the second and third trimesters of pregnancy. The risk is greatest with streptomycin. The risk is probably very small with gentamicin and tobramycin, but their use should be avoided unless essential.
    - If given during pregnancy, serum-aminoglycoside concentration monitoring is essential.
  - **RENAL IMPAIRMENT** If there is impairment of renal function, the interval between doses must be increased; if the renal impairment is severe, the dose itself should be reduced as well. Excretion of aminoglycosides is principally via the kidney and accumulation occurs in renal impairment.
    - Ototoxicity and nephrotoxicity occur commonly in patients with renal failure. Serum-aminoglycoside concentrations must be monitored in patients with renal impairment; earlier and more frequent measurement of aminoglycoside concentration may be required.
      - In adults A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with a creatinine clearance less than 20 mL/minute.
      - In children A once-daily, high-dose regimen of an aminoglycoside should be avoided in children over
1 month of age with a creatinine clearance less than 20 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Serum concentrations: Serum concentration monitoring avoids both excessive and subtherapeutic concentrations and hence preventing toxicity and ensuring efficacy. Serum-aminoglycoside concentrations should be measured in all patients receiving parenteral aminoglycosides and must be determined in obesity, if high doses are being given and in cystic fibrosis.
- In adults: Serum aminoglycoside concentrations must be determined in the elderly. In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen and after a dose change. For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration ('peak' concentration) and also just before the next dose ('trough' concentration). If the pre-dose ('trough') concentration is high, the interval between doses must be increased. If the post-dose ('peak') concentration is high, the dose must be decreased. For once daily dose regimens, consult local guidelines on serum concentration monitoring.
- In children: In children with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen. Blood samples should be taken just before the next dose is administered ('trough' concentration). If the pre-dose ('trough') concentration is high, the interval between doses must be increased. For multiple daily dose regimens, blood samples should also be taken approximately 1 hour after intramuscular or intravenous administration ('peak' concentration). If the post-dose ('peak') concentration is high, the dose must be decreased.
- Renal function should be assessed before starting an aminoglycoside and during treatment.
- Auditory and vestibular function should also be monitored during treatment.

### Amikacin

**INDICATIONS AND DOSE**

**Serious Gram-negative infections resistant to gentamicin (multiple daily dose regimen)**

- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
- **Adult:** 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses for up to 10 days, higher dose to be used in severe infections; maximum 1.5 g per day; maximum 15 g per course

**Serious Gram-negative infections resistant to gentamicin (once daily dose regimen)**

- **By intravenous infusion**
- **Adult:** Initially 15 mg/kg (max. per dose 1.5 g once daily), dose to be adjusted according to serum-amikacin concentration; maximum 15 g per course

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and monitor serum-amikacin concentration closely.

**SIDE-EFFECTS**

- Uncommon: Rash

**MONITORING REQUIREMENTS**

- **Multiple daily dose regimen:** one-hour ('peak') serum concentration should not exceed 30 mg/litre; pre-dose ('trough') concentration should be less than 10 mg/litre.
- **Once daily dose regimen:** pre-dose ('trough') concentration should be less than 5 mg/litre.

### Gentamicin

**INDICATIONS AND DOSE**

**Gram-positive bacterial endocarditis or HACEK endocarditis (in combination with other antibacterials)**

- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
- **Adult:** 1 mg/kg every 12 hours, intravenous injection to be administered over at least 3 minutes, to be given in a multiple daily dose regimen

**Septicaemia | Meningitis and other CNS infections | Biliary tract infection | Acute pyelonephritis | Endocarditis | Pneumonia in hospital patients | Adjunct in listerial meningitis | Prostatitis**

- **By intravenous infusion, or by slow intravenous injection, or by intramuscular injection**
- **Adult:** 3–5 mg/kg daily in 3 divided doses, to be given in a multiple daily dose regimen, divided doses to be given every 8 hours, intravenous injection to be administered over at least 3 minutes

- **By intravenous infusion**
- **Adult:** Initially 5–7 mg/kg, subsequent doses adjusted according to serum-gentamicin concentration, to be given in a once daily dose regimen

**CNS infections (administered on expert advice)**

- **By intrathecal injection**
- **Adult:** 1 mg daily, increased if necessary to 5 mg daily, seek specialist advice

**Surgical prophylaxis**

- **By slow intravenous injection**
- **Adult:** 1.5 mg/kg, intravenous injection to be administered over at least 3 minutes, administer dose up to 30 minutes before the procedure, dose may be repeated every 8 hours for high-risk procedures; up to 3 further doses may be given

**Surgical prophylaxis (including joint replacement surgery)**

- **By intravenous infusion**
- **Adult:** 5 mg/kg for 1 dose, administer dose up to 30 minutes before the procedure

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, use ideal weight for height to calculate parenteral dose and monitor serum-gentamicin concentration closely.

**SIDE-EFFECTS**

- Uncommon: Rash

**MONITORING REQUIREMENTS**

- For multiple daily dose regimen, one-hour ('peak') serum concentration should be 5–10 mg/litre; pre-dose ('trough') concentration should be less than 2 mg/litre.
- For multiple daily dose regimen in endocarditis, one-hour ('peak') serum concentration should be 3–5 mg/litre;
pre-dose (‘trough’) concentration should be less than 1 mg/litre. Serum-gentamicin concentration should be measured after 3 or 4 doses, then at least every 3 days and after a dose change (more frequently in renal impairment).

- For once-daily dose regimen, consult local guidelines on monitoring serum-gentamicin concentration.

**DIRECTIONS FOR ADMINISTRATION**
- With intrathecal use For intrathecal injection, use preservative-free intrathecal preparations only.
- With intravenous use For intravenous infusion (Cidomycin®); Gentamicin paediatric injection, Beacon; Gentamicin injection Hospira), give intermittently or via drip tubing in Glucose 5% or Sodium Chloride 0.9%. Suggested volume for intermittent infusion 50–100 ml given over 20–30 minutes (given over 60 minutes for once daily dose regimen).

**PRESCRIBING AND DISPENSING INFORMATION**
- With intravenous use Local guidelines may vary in the dosing advice provided for once daily administration.
- With intrathecal use Only preservative-free intrathecal preparation should be used.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Gentamicin (Non-proprietary)**
  - Gentamicin (as Gentamicin sulfate) 5 mg per 1 ml Gentamicin Intrathecal 5mg/1ml solution for injection ampoules 15 ampoule (POM) £36.28 (Hospital only)
  - Gentamicin (as Gentamicin sulfate) 10 mg per 1 ml Gentamicin 20mg/2ml solution for injection ampoules 5 ampoule (POM) £11.25
    - Gentamicin Paediatric 20mg/2ml solution for injection vials 5 vial (POM) £11.25 DT price = £11.25
    - Gentamicin (as Gentamicin sulfate) 40 mg per 1 ml Gentamicin 80mg/2ml solution for injection vials 5 vial (POM) £20.00
    - Gentamicin 80mg/2ml solution for injection ampoules 5 ampoule (POM) £6.88 10 ampoule (POM) £10.00
- **Cidomycin (Sanofi)**
  - Gentamicin (as Gentamicin sulfate) 40 mg per 1 ml Cidomycin Adult Injectable 80mg/2ml solution for injection ampoules 5 vial (POM) £6.88
  - Cidomycin Adult Injectable 80mg/2ml solution for injection ampoules 5 ampoule (POM) £6.88

**Infusion**

- **Gentamicin (Non-proprietary)**
  - Gentamicin (as Gentamicin sulfate) 1 mg per 1 ml Gentamicin 80mg/80ml infusion bags 20 bag (POM) £39.00
  - Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml Gentamicin 240mg/80ml infusion bags 20 bag (POM) £119.00
  - Gentamicin 360mg/120ml infusion bags 20 bag (POM) £169.00

**SIDE-EFFECTS**
- Uncommon Rash
- Frequency not known Impaired intestinal absorption with steatorrhoea and diarrhoea - increased salivation

**SIDE-EFFECTS, FURTHER INFORMATION**

Although neomycin is associated with the same side effects as other aminoglycosides it is generally considered too toxic for systemic use and is poorly absorbed after oral administration.

- **PREGNANCY** There is a risk of auditory or vestibular nerve damage in the infant when aminoglycosides are used in the second and third trimesters of pregnancy.
- **HEPATIC IMPAIRMENT** Absorbed from gastro-intestinal tract in liver disease—increased risk of ototoxicity.
- **RENAL IMPAIRMENT** Avoid—risk of ototoxicity and nephrotoxicity.

- **MONITORING REQUIREMENTS**
  - Renal function should be assessed before starting an aminoglycoside and during treatment.
  - Auditory and vestibular function should also be monitored during treatment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

- **Neomycin sulfate (Non-proprietary)**
  - Neomycin sulfate 500 mg Neomycin 500mg tablets 100 tablet (POM) £34.69 DT price = £34.69

**Oral solution**

- **Neomycin sulfate (Non-proprietary)**
  - Neomycin sulfate 25 mg per 1 ml Neo-Fradin 125mg/5ml oral solution 480 ml (POM) no price available

**Streptococcal endocarditis**
- Adult: (consult local protocol)

**SBE**
- Common or very common Rash
- Frequency not known Hypersensitivity reactions - paraesthesia of mouth

**RENAI IMPAIRMENT**
- Should preferably be avoided. If essential, use with great care and consider dose reduction.

**MONITORING REQUIREMENTS**
- One-hour (‘peak’) concentration should be 15–40 mg/litre; pre-dose (‘trough’) concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or in those over 50 years).

**Neomycin sulfate**

**INDICATIONS AND DOSE**

**Bowel sterilisation before surgery**

- **BY MOUTH**
  - Adult: 1 g every 1 hour for 4 hours, then 1 g every 4 hours for 2–3 days

**Hepatic coma**

- **BY MOUTH**
  - Adult: Up to 4 g daily in divided doses usually for 5–7 days

**CONTRA-INDICATIONS**
Intestinal obstruction - myasthenia gravis (aminoglycosides may impair neuromuscular transmission)

**CAUTIONS**
Avoid prolonged use

**CAUTIONS, FURTHER INFORMATION**

Although neomycin is associated with the same cautions as other aminoglycosides it is generally considered too toxic for systemic use.

**INTERACTIONS**
Appendix 1 (aminoglycosides).
**Tobramycin**

**INDICATIONS AND DOSE**

Septicaemia | Meningitis and other CNS infections | Biliary-tract infection | Acute pyelonephritis or prostatitis | Pneumonia in hospital patients

- By intramuscular injection, or by slow intravenous injection, or by intravenous infusion
  - Adult: 3 mg/kg daily in 3 divided doses; increased if necessary up to 5 mg/kg daily in 3–4 divided doses, increased dose used in severe infection; dose to be reduced back to 3 mg/kg daily as soon as clinically indicated

**Urinary-tract infection**

- By intramuscular injection
  - Adult: 2–3 mg/kg for 1 dose

**Chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis**

- By inhalation of nebulised solution
  - Adult: 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution
  - By inhalation of powder
  - Adult: 112 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, use ideal weight for height to calculate parenteral dose and monitor serum-tobramycin concentration closely.

**VANTOBRA® NEBULISER SOLUTION**

**Chronic pulmonary Pseudomonas aeruginosa infection in patients with cystic fibrosis**

- By inhalation of nebulised solution
  - Adult: 170 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution

**CAUTIONS**

- When used by inhalation: Conditions characterised by muscular weakness—may impair neuromuscular transmission—history of prolonged previous or concomitant intravenous aminoglycosides—increased risk of ototoxicity • renal impairment—limited information available • severe haemoptysis—risk of further haemorrhage

**SIDE-EFFECTS**

- Common or very common
  - When used by inhalation: Malaise • rhinitis • tinnitus
  - Uncommon
  - With systemic use: Rash
  - Rare
  - When used by inhalation: Aphonía • hearing loss
  - Very rare
  - When used by inhalation: Pruritus • urticaria
  - Frequency not known
  - When used by inhalation: Bronchospasm • cough (more frequent by inhalation of powder) • dysphonia • epistaxis • haemoptysis • laryngitis • mouth ulcers • pharyngitis • salivary hypersecretion • taste disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

- Ear effects
- When used by inhalation: Manufacturer advises monitor serum-tobramycin concentration in patients with known or suspected signs of auditory dysfunction; if ototoxicity develops—discontinue treatment until serum concentration falls below 2 mg/litre.

**VANTOBRA® NEBULISER SOLUTION**

- Uncommon: Dyspnoea
- Rare: Anorexia • asthenia • asthma • chest discomfort • dizziness • headache • nausea • pyrexia • vomiting
- Very rare: Abdominal pain • back pain • diarrhoea • ear pain • fungal infection • hyperventilation • hypoxia • lymphadenopathy • sinusitis • somnolence

**RENAL IMPAIRMENT**

- When used by inhalation: Manufacturer advises monitor serum-tobramycin concentration; if nephrotoxicity develops—discontinue treatment until serum concentration falls below 2 mg/litre.

**MONITORING REQUIREMENTS**

- With intramuscular use or intravenous use: One-hour (‘peak’) serum concentration should not exceed 10 mg/litre; pre-dose (‘trough’) concentration should be less than 2 mg/litre.
- When used by inhalation: Measure lung function before and after initial dose of tobramycin and monitor for bronchospasm; if bronchospasm occurs in a patient not using a bronchodilator, repeat test using bronchodilator. Manufacturer advises monitor renal function before treatment and then annually.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use: For intravenous infusion (Nebcin®); intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%. For adult intermittent infusion suggested volume 50–100 mL given over 20–60 minutes.
- When used by inhalation: Other inhaled drugs should be administered before tobramycin.

**PATIENT AND CARER ADVICE**

- When used by inhalation: Patient counselling is advised for Tobramycin dry powder for inhalation (administration).

**VANTOBRA® NEBULISER SOLUTION**

**Missed doses**

Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Tobramycin by dry powder inhalation for pseudomonal lung infection in cystic fibrosis (March 2013) NICE TA276

Tobramycin dry powder for inhalation is recommended for chronic pulmonary infection caused by Pseudomonas aeruginosa in patients with cystic fibrosis only if there is an inadequate response to colistimethate sodium, or if colistimethate sodium cannot be used because of contraindications or intolerance. The manufacturer must provide tobramycin dry powder for inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS. Patients currently receiving tobramycin dry powder for inhalation can continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA276

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Solution for Injection**

- Tobramycin (Non-proprietary)
- Tobramycin (as Tobramycin sulphate) 40 mg per 1 ml
- Tobramycin 40 mg/1 ml solution for injection vials | 10 vial £37.00
- Tobramycin 80 mg/2 ml solution for injection vials | 5 vial £20.80
- Tobramycin 240 mg/6 ml solution for injection vials | 1 vial £19.20

**Bacterial infection**

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Overview

The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; imipenem (imipenem with cilastatin below) and meropenem p. 483 have good activity against Pseudomonas aeruginosa. The carbapenems are not active against metillin-resistant Staphylococcus aureus and Enterococcus faecium.

Imipenem (imipenem with cilastatin) and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections including septicemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary tract infections.

Ertapenem below is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin-resistant pneumococci. It is also licensed for treating foot infections of the skin and soft tissue in patients with diabetes. Unlike the other carbapenems, ertapenem is not active against Pseudomonas or against Acinetobacter spp.

Imipenem is partially inactivated in the kidney by enzymatic activity and is therefore administered in combination with cilastatin (imipenem with cilastatin), a specific enzyme inhibitor, which blocks its renal metabolism. Meropenem and ertapenem are stable to the renal enzyme which inactivates imipenem and therefore can be given without cilastatin.

Side-effects of imipenem with cilastatin are similar to those of other beta-lactam antibiotics. Meropenem has less seizure-inducing potential and can be used to treat central nervous system infection.

Ertapenem

- **INDICATIONS AND DOSE**
  - Abdominal infections
  - Acute gynaecological infections
  - Community-acquired pneumonia
  - BY INTRAVENOUS INFUSION
  - Adult: 1 g once daily

Diabetic foot infections of the skin and soft-tissue

- BY INTRAVENTOUS INFUSION
  - Adult: 1 g once daily

Surgical prophylaxis, colorectal surgery

- BY INTRAVENOUS INFUSION
  - Adult: 1 g for 1 dose, to be completed within 1 hour before surgery

**CAUTIONS** CNS disorders—risk of seizures · elderly

**INTERACTIONS** → Appendix 1 (ertapenem).

**SIDE-EFFECTS**

- Common or very common Diarrhoea · headache · injection-site reactions · nausea · pruritus · raised platelet count · rash (also reported with eosinophilia and systemic symptoms) · vomiting

- Uncommon Abdominal pain · anorexia · antibiotic-associated colitis · asthenia · bradycardia · chest pain · confusion · constipation · dizziness · dry mouth · dyspepsia · dyspnoea · hypotension · melaena · oedema · pectechiae · pharyngeal discomfort · raised glucose · seizures · sleep disturbances · taste disturbances

- Rare Agitation · anxiety · arrhythmia · blood disorders · cholecystitis · cough · depression · dysphagia · electrolyte disturbances · haemorrhage · hypoglycaemia · increase in blood pressure · jaundice · liver disorder · muscle cramp · nasal congestion · neutropenia · pelvic peritonitis · renal impairment · scleral disorder · syncope · thrombocytopenia · tremor · wheezing

- Frequency not known Dyskinesia · hallucinations

- ALLERGY AND CROSS-SENSITIVITY Avoid if history of immediate hypersensitivity reaction to beta-lactam antibacterials.

- PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk.

- BREAST FEEDING Present in milk—manufacturer advises avoid.

- RENAL IMPAIRMENT Risk of seizures; max. 500 mg daily if eGFR less than 30 mL/minute/1.73 m².

- DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Invanz®), give intermittently in Sodium chloride 0.9%. Reconstitute 1 g with 10 mL. Water for injections or Sodium chloride 0.9%; dilute requisite dose in infusion fluid to a final concentration not exceeding 20 mg/mL; give over 30 minutes; incompatible with glucose solutions.

- MEDICINAL FORMS

  - There can be variation in the licensing of different medicines containing the same drug.

- Powder for solution for infusion

  - ELECTROLYTES: May contain Sodium
  - Invanz (Merck Sharp & Dohme Ltd)
    - Ertapenem (as Ertapenem sodium) 1 gram Invanz 1g powder for solution for infusion vials | 1 vial £31.65

Imipenem with cilastatin

- **INDICATIONS AND DOSE**
  - Aerobic and anaerobic Gram-positive and Gram-negative infections (not indicated for CNS infections) · Hospital-acquired septicemia
  - BY INTRAVENOUS INFUSION
  - Adult: 500 mg every 6 hours, alternatively 1 g every 8 hours

  - Infection caused by Pseudomonas or other less sensitive organisms · Empirical treatment of infection in febrile patients with neutropenia · Life-threatening infection
  - BY INTRAVENOUS INFUSION
  - Adult: 1 g every 6 hours
DOSE EQUIVALENCE AND CONVERSION

- Dose expressed in terms of imipenem.

- **CAUTIONS**  CNS disorders • epilepsy
- **INTERACTIONS**  Appendix 1 (imipenem with cilastatin).
- **SIDE-EFFECTS**
  - Common or very common  Diarrhoea • eosinophilia • nausea (may reduce rate of infusion) • rash • vomiting
  - Uncommon  Confusion • dizziness • drowsiness • hallucinations • hypotension • leucopenia • myoclonic activity • seizures • thrombocytopenia • thrombocytosis
  - Rare  Acute renal failure • anaphylactic reactions • antibiotic–associated colitis • encephalopathy • hearing loss • hepatitis • paraesthesia • polyuria • Stevens–Johnson syndrome • taste disturbances • tooth, tongue or urine discoloration • toxic epidermal necrosis • tremor
  - Very rare  Abdominal pain • aggravation of myasthenia gravis • asthenia • cyanosis • dyspnoea • flushing • glossitis • haemolytic anaemia • headache • heartburn • hyperhidrosis • hypersalivation • hyperventilation • palpitation • polyarthralgia • tachycardia • tinnitus
- **FREQUENCY not known**  Neurotoxicity (at high dose, renal failure, CNS disease)
- **ALLERGY AND CROSS-SENSITIVITY**  Avoid if history of immediate hypersensitivity reaction to beta-lactam antibiotics.
  - Use with caution in patients with sensitivity to beta-lactam antibacterials.
- **PREGNANCY**  Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies).
- **BREAST FEEDING**  Present in milk but unlikely to be absorbed.
- **RENAL IMPAIRMENT**  Risk of CNS side-effects; reduce dose if eGFR less than 70 mL/minute/1.73 m² — consult product literature.
- **EFFECT ON LABORATORY TESTS**  Positive Coombs’ test.
- **DIRECTIONS FOR ADMINISTRATION**  For intravenous infusion dilute to a concentration of 5 mg/asaline (imipenem)/mL in Sodium chloride 0.9%; give up to 500 mg (as imipenem) over 20–30 minutes, give dose greater than 500 mg (as imipenem) over 40–60 minutes.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**
    - **ELECTROLYTES:**  May contain Sodium
      - **Imipenem with cilastatin (Non-proprietary)**
        - Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg powder for solution for infusion vials | 1 vial (£80.00 (Hospital only) | 5 vial (£500.00 (Hospital only) | 10 vial (£875.45
      - **Primevac I.V. (Merck Sharp & Dohme Ltd)**
        - Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg Primerax IV 500mg powder for solution for infusion vials | 1 vial (£42.00

  - **Meropenem**

  - **INDICATIONS AND DOSE**
    - **Aerobic and anaerobic Gram-positive and Gram-negative infections • Hospital-acquired septicaemia**
      - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
        - Adult: 0.5–1 g every 8 hours
    - **Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis**
      - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
        - Adult: 2 g every 8 hours

  - **Antibacterials • Cephalosporins**

    - **Cephalosporins**

      - **Overview**
        - The cephalosporins are broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally...
renal. Cefalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; cefotaxime p. 487 and ceftriaxone p. 489 are suitable cefalosporins for infections of the CNS (e.g. meningitis).

The principal side-effect of the cefalosporins is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cefalosporins. If a cefalosporin is essential in patients with a history of immediate hypersensitivity to penicillin, because a suitable alternative antibacterial is not available, then cefixime p. 487, cefotaxime, cefazidime p. 488, ceftriaxone, or cefuroxime p. 486 can be used with caution; cefaclor p. 486, cefadroxil below, cefalexin p. 485, cefadrine p. 485, and cefetamet fosamil p. 490 should be avoided.

The orally active ‘first generation’ cefalosporins, cefalexin, cefadroxil and the ‘second generation’ cefalosporin, cefaclor, have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections. Cefaclor has good activity against H. influenzae. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against H. influenzae. Cefuroxime axetil, an ester of the ‘second generation’ cefalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed and needs to be given with food to maximise absorption.

Cefixime is an orally active ‘third generation’ cefalosporin. It has a longer duration of action than the other cefalosporins that are active by mouth. It is only licensed for acute infections.

Cefuroxime is a ‘second generation’ cefalosporin that is less susceptible than the earlier cefalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria which are resistant to the other drugs and has greater activity against Haemophilus influenzae.

Cefotaxime, cefazidime and ceftriaxone are ‘third generation’ cefalosporins with greater activity than the ‘second generation’ cefalosporins against certain Gram-negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably Staphylococcus aureus. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Cefazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria.

Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibiotic is stopped.

Cefetamet fosamil is a ‘fifth generation’ cefalosporin with bactericidal activity similar to cefotaxime; however, cefetamet fosamil has an extended spectrum of activity against Gram-positive bacteria that includes meticillin-resistant Staphylococcus aureus and multi-drug resistant Streptococcus pneumoniae. Cefetamet fosamil is licensed for the treatment of community-acquired pneumonia and complicated skin and soft-tissue infections, but there is no experience of its use in pneumonia caused by meticillin-resistant S. aureus.

### Antibacterials

#### Cefuroxime

- **Indications and Dose**
  - Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria
    - **By Mouth**
      - Child 6–17 years (body-weight up to 40 kg): 0.5 g twice daily
      - Child 6–17 years (body-weight 40 kg and above): 0.5–1 g twice daily
      - Adult: 0.5–1 g twice daily
  - **Skin infections / Soft-tissue infections / Uncomplicated urinary-tract infections**
    - **By Mouth**
      - Child 6–17 years (body-weight 40 kg and above): 1 g once daily
      - Adult: 1 g daily

- **Pregnancy** Not known to be harmful.
- **Breast Feeding** Present in milk in low concentration, but appropriate to use.
- **Renal Impairment**
  - In adults 1 g initially, then 500 mg every 12 hours if eGFR 26–50 mL/minute/1.73 m². 1 g initially, then 500 mg every 24 hours if eGFR 11–26 mL/minute/1.73 m². 1 g initially, then 500 mg every 36 hours if eGFR less than 11 mL/minute/1.73 m².
  - In children Reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m².

#### Side-effects

- **Rare** Antibiotic-associated colitis
- **Frequency not known** Abdominal discomfort, agranulocytosis, allergic reactions, anaphylaxis, aplastic anaemia, blood disorders, confusion, diarrhoea, disturbances in liver enzymes, dizziness, eosinophilia, haemolytic anaemia, hallucinations, headache, hyperactivity, hypertension, leucopenia, nausea, nervousness, pruritus, rashes, reversible interstitial nephritis, serum sickness–like reactions with rashes, fever and arthralgia, sleep disturbances, Stevens–Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, transient cholestatic jaundice, transient hepatitis, urticaria, vomiting

#### Drug Action

Cefalosporins are antibacterials that attach to penicillin binding proteins to interrupt cell wall biosynthesis, leading to bacterial cell lysis and death.

#### Interactions

Appendix 1 (cephalosporins).
Cefalexin
(Cephalexin)

**INDICATIONS AND DOSE**

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

- **BY MOUTH**
  - Child 1-11 months: 12.5 mg/kg twice daily, alternatively 125 mg twice daily
  - Child 1-4 years: 12.5 mg/kg twice daily, alternatively 125 mg 3 times a day
  - Child 5-11 years: 12.5 mg/kg twice daily, alternatively 250 mg 3 times a day
  - Child 12-17 years: 500 mg 2–3 times a day
  - Adult: 250 mg every 6 hours, alternatively 500 mg every 8–12 hours; increased to 1–1.5 g every 6–8 hours, increased dose to be used for severe infections

Serious susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

- **BY MOUTH**
  - Child 1 month-11 years: 25 mg/kg 2–4 times a day (max. per dose 1 g 4 times a day)
  - Child 12-17 years: 1–1.5 g 3–4 times a day

Prophylaxis of recurrent urinary-tract infection

- **BY MOUTH**
  - Child: 12.5 mg/kg once daily (max. per dose 125 mg), dose to be taken at night
  - Adult: 125 mg once daily, dose to be taken at night

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT**

- In adults Max. 3 g daily if eGFR 40–50 mL/minute/1.73 m². Max. 1.5 g daily if eGFR 10–40 mL/minute/1.73 m². Max. 750 mg daily if eGFR less than 10 mL/minute/1.73 m².
- In children Reduce dose in moderate impairment.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Cefalexin for bacterial infections www.medicinesforchildren.org.uk/cefalexin-bacterial-infections-0

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary Cefalexin Capsules may be prescribed. Cefalexin Tablets may be prescribed. Cefalexin Oral Suspension may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - **Cefadroxil** (Non-proprietary)
    - Cefadroxil (as Cefadroxil monohydrate) 500 mg Cefadroxil 500 mg capsules | 20 capsule | £11.90
  - **Cefalexin** (Non-proprietary)
    - Cefalexin 250 mg Cefalexin 250 mg capsules | 100 capsule | £11.50
    - Cefalexin 500 mg Cefalexin 500 mg capsules | 100 capsule | £22.38

**Cefalexin 500 mg**

Keflex 500 mg tablets | 21 tablet | £1.60 DT price = £1.80

**Capsule**

Cefalexin 500 mg | 28 capsule | £1.92

**Cefradine (Cephradine)**

**INDICATIONS AND DOSE**

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria | Surgical prophylaxis

- **BY MOUTH**
  - Child 7-11 years: 25–50 mg/kg daily in 2–4 divided doses
  - Child 12-17 years: 250–500 mg 4 times a day, alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections
  - Adult: 250–500 mg 4 times a day, alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT**

- In adults Use half normal dose if eGFR 5–20 mL/minute/1.73 m². Use one-quarter normal dose if eGFR less than 5 mL/minute/1.73 m².
- In children Reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary Cefradine Capsules may be prescribed.
**Cefaclor**

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria</th>
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</thead>
<tbody>
<tr>
<td><strong>BY MOUTH USING IMMEDIATE-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>Child 1–11 months: 20 mg/kg daily in 3 divided doses, alternatively 62.5 mg 3 times a day</td>
</tr>
<tr>
<td>Child 1–4 years: 20 mg/kg daily in 3 divided doses, alternatively 125 mg 3 times a day</td>
</tr>
<tr>
<td>Child 5–11 years: 20 mg/kg daily in 3 divided doses, usual max. 1 g daily, alternatively 250 mg 3 times a day</td>
</tr>
<tr>
<td>Child 12–17 years: 250 mg 3 times a day; maximum 4 g per day</td>
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<tr>
<td>Adult: 250 mg 3 times a day; maximum 4 g per day</td>
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<thead>
<tr>
<th>Severe susceptible infections due to sensitive Gram-positive and Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH USING IMMEDIATE-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>Child 1–11 months: 40 mg/kg daily in 3 divided doses, usual max. 1 g daily, alternatively 125 mg 3 times a day</td>
</tr>
<tr>
<td>Child 1–4 years: 40 mg/kg daily in 3 divided doses, usual max. 1 g daily, alternatively 250 mg 3 times a day</td>
</tr>
<tr>
<td>Child 5–11 years: 40 mg/kg daily in 3 divided doses, usual max. 1 g daily</td>
</tr>
<tr>
<td>Child 12–17 years: 500 mg 3 times a day; maximum 4 g per day</td>
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<tr>
<td>Adult: 500 mg 3 times a day; maximum 4 g per day</td>
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<thead>
<tr>
<th>Pneumonia</th>
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<tbody>
<tr>
<td><strong>BY MOUTH USING MODIFIED-RELEASE TABLETS</strong></td>
</tr>
<tr>
<td>Child 12–17 years: 750 mg every 12 hours, dose to be taken with food</td>
</tr>
<tr>
<td>Adult: 750 mg every 12 hours, dose to be taken with food</td>
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<thead>
<tr>
<th>Lower urinary-tract infections</th>
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<tbody>
<tr>
<td><strong>BY MOUTH USING MODIFIED-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>Child 12–17 years: 375 mg every 12 hours, dose to be taken with food</td>
</tr>
<tr>
<td>Adult: 375 mg every 12 hours, dose to be taken with food</td>
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<thead>
<tr>
<th>Asymptomatic carriage of <em>Haemophilus influenzae</em> or mild exacerbations in cystic fibrosis</th>
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</thead>
<tbody>
<tr>
<td><strong>BY MOUTH USING IMMEDIATE-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>Child 1–11 months: 125 mg every 8 hours</td>
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<tr>
<td>Child 1–6 years: 250 mg 3 times a day</td>
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<tr>
<td>Child 7–17 years: 500 mg 3 times a day</td>
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**SIDE-EFFECTS**

Skin reactions: Cefaclor is associated with protracted skin reactions, especially in children.

PREGNANCY: Not known to be harmful.

BREAST FEEDING: Present in milk in low concentration, but appropriate to use.

RENA L IMPAIRMENT: No dose adjustment required. Manufacturer advises caution.

**Cefuroxime**

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Susceptible infections due to Gram-positive and Gram-negative bacteria</th>
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<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
</tr>
<tr>
<td>Child 3 months–1 year: 10 mg/kg twice daily (max. per dose 125 mg)</td>
</tr>
<tr>
<td>Child 2–11 years: 15 mg/kg twice daily (max. per dose 250 mg)</td>
</tr>
<tr>
<td>Child 12–17 years: 250 mg twice daily, dose may be doubled in severe lower respiratory-tract infections if pneumonia is suspected</td>
</tr>
<tr>
<td>Adult: 250 mg twice daily, dose may be doubled in severe lower respiratory-tract infections if pneumonia is suspected</td>
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<table>
<thead>
<tr>
<th>BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION</th>
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<tbody>
<tr>
<td>Child: 20 mg/kg every 8 hours (max. per dose 750 mg); increased to 50–60 mg/kg every 6–8 hours (max. per dose 1.5 g), increased dose used for severe infection and cystic fibrosis</td>
</tr>
<tr>
<td>Adult: 750 mg every 6–8 hours; increased if necessary up to 1.5 g every 6–8 hours, increased dose used for severe infections</td>
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<tr>
<th>Lyme disease</th>
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<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>Adult: 500 mg twice daily for 14–21 days (for 28 days in Lyme arthritis)</td>
</tr>
</tbody>
</table>
**Lower urinary-tract infection**
- **BY MOUTH**
  - Child 12-17 years: 125 mg twice daily
  - Adult: 125 mg twice daily

**Pyelonephritis**
- **BY MOUTH**
  - Adult: 250 mg twice daily

**Surgical prophylaxis**
- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 1.5 g, to be administered up to 30 minutes before the procedure, then (by intravenous injection or by intramuscular injection) 750 mg every 8 hours if required for up to 3 doses (in high risk procedures)

**Open fractures, prophylaxis**
- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: 1.5 g every 8 hours until soft tissue closure (maximum duration 72 hours)

**Antibacterials > Cephalosporins, Third-Generation**

**Cefuroxime (as Cefuroxime sodium)**
- **1.5 gram** Zinacef 1.5g powder for injection vials | 1 vial (£0.52) | £5.00
- **750 mg** Zinacef 750mg powder for injection vials | 5 vial (£0.52) | £25.20

**Cefuroxime**

- **INDICATIONS AND DOSE**
  - **Acute infections due to sensitive Gram-positive and Gram-negative bacteria**
    - **BY MOUTH**
      - Child 6–11 months: 75 mg daily
      - Child 1–4 years: 100 mg daily
      - Child 5–9 years: 200 mg daily
      - Child 10–17 years: 200–400 mg daily, alternatively 100–200 mg twice daily
    - **Adult:** 200–400 mg daily in 1–2 divided doses

**Uncomplicated gonorrhoea**
- **BY MOUTH**
  - Adult: 400 mg for 1 dose

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS 9**
  - Suprax (Sanofi)
  - Cefuroxime 200 mg Suprax 200mg tablets | 7 tablet (£0.52) | £13.22 DT price = £13.23

**Cefotaxime**

- **INDICATIONS AND DOSE**
  - **Uncomplicated gonorrhoea**
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: 500 mg for 1 dose

  - **Infections due to sensitive Gram-positive and Gram-negative bacteria** | Surgical prophylaxis | Haemophilus influenzae
    - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** 1 g every 12 hours

- **Severe susceptible infections due to sensitive Gram-positive and Gram-negative bacteria** | Meningitis
  - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - **Adult:** 8 g daily in 4 divided doses, increased if necessary to 12 g daily in 3–4 divided doses, intramuscular doses over 1 g should be divided between more than one site

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**Medication Administration**

- **According to patients’ medical condition**
  - For intravenous use in children
    - Single doses over 750 mg should be administered by the intravenous route only.
      - With intravenous use in children: Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%; give over 30 minutes.
      - With intravenous use in adults: For intravenous infusion (Zinacef®), give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Dissolve initially in water for injections (at least 2 mL for each 250 mg; 15 mL for 1.5 g); suggested volume 50–100 mL given over 30 minutes.

- **Open fractures, prophylaxis**
  - Adult: 1.5 g every 8 hours until soft tissue closure (maximum duration 72 hours)

- **Pyelonephritis**
  - Adult: 250 mg twice daily

- **Surgical prophylaxis**
  - Adult: 1.5 g, to be administered up to 30 minutes before the procedure, then (by intravenous injection or by intramuscular injection) 750 mg every 8 hours if required for up to 3 doses (in high risk procedures)

- **With intravenous use in children**
  - Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%; give over 30 minutes.

- **With intravenous use in adults**
  - For intravenous infusion (Zinacef®), give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Dissolve initially in water for injections (at least 2 mL for each 250 mg; 15 mL for 1.5 g); suggested volume 50–100 mL given over 30 minutes.
Emergency treatment of suspected bacterial meningitis or meningococcal disease, before urgent transfer to hospital, in patients who cannot be given benzylpenicillin (e.g. because of an allergy)

- **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Child 1 month–11 years: 50 mg/kg for 1 dose
  - Child 12–17 years: 1 g for 1 dose
  - Adult: 1 g for 1 dose

- **SIDE-EFFECTS**
  - Rare  Arrhythmias (following rapid injection)

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

- **RENAL IMPAIRMENT**
  - In adults If eGFR less than 5 mL/minute/1.73 m², initial dose of 1 g then use half normal dose.
  - In children Usual initial dose, then use half normal dose if estimated glomerular filtration rate less than 5 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion dilute in glucose 5% or sodium chloride 0.9%; administer over 20–60 minutes; incompatible with alkaline solutions.
  - With intravenous use in adults For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%. Suggested volume 40–100 mL given over 20–60 minutes; incompatible with alkaline solutions.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Cefotaxime (Non-proprietary)**
  - Cefotaxime (as Cefotaxime sodium) 2 gram Cefotaxime 2g powder for solution for injection vials | 1 vial (£1.50) 10 vial (£25.20)
  - Cefotaxime (as Cefotaxime sodium) 500 mg Cefotaxime 500mg powder for solution for injection vials | 1 vial (£1.50) 10 vial (£25.50–£30.00)
  - Cefotaxime (as Cefotaxime sodium) 1 gram Cefotaxime 1g powder for solution for injection vials | 1 vial (£3.00) 10 vial (£35.00)

**Ceftazidime**

- **INDICATIONS AND DOSE**

  **Prophylaxis for transurethral resection of prostate**
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 1 g, single dose to be administered up to 30 minutes before procedure and may be repeated if necessary when catheter removed

  **Pseudomonal lung infection in cystic fibrosis**
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 100–150 mg/kg daily in 3 divided doses; maximum 9 g per day

  **Complicated urinary-tract infection**
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–79 years: 1–2 g every 8–12 hours
  - Adult 80 years and over: 1–2 g every 8–12 hours; maximum 3 g per day

  **Septicaemia | Hospital-acquired pneumonia**
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–79 years: 2 g every 8 hours
  - Adult 80 years and over: 2 g every 8 hours; maximum 3 g per day

  **Febrile neutropenia**
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–79 years: 2 g every 8 hours
  - Adult 80 years and over: 2 g every 8 hours; maximum 3 g per day

  **Meningitis**
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–79 years: 2 g every 8 hours
  - Adult 80 years and over: 2 g every 8 hours; maximum 3 g per day

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18–79 years: 1–2 g every 8 hours
  - Adult 80 years and over: 1–2 g every 8 hours; maximum 3 g per day

- **SIDE-EFFECTS** Paraesthesia · taste disturbances

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.

- **RENAL IMPAIRMENT** Reduce dose if eGFR less than 50 mL/minute/1.73 m²—consult product literature.

- **DIRECTIONS FOR ADMINISTRATION** Intramuscular administration used when intravenous administration not possible; single doses over 1 g by intravenous route only.
  - With intravenous use For intravenous infusion give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Dissolve 2 g initially in 10 mL (3 g in 15 mL) infusion fluid. For Fortum® dilute further to a concentration of 40 mg/mL. For Kefadin® dilute further to a concentration of 20 mg/mL. Give over up to 30 minutes.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Powder for solution for injection**

- **Cefotaxime (Non-proprietary)**
  - Cefotaxime (as Cefotaxime pentahydrate) 500 mg Cefotaxime 500mg powder for solution for injection vials | 1 vial (£1.50) 10 vial (£25.50–£30.00)
  - Cefotaxime (as Cefotaxime pentahydrate) 2 gram Cefotaxime 2g powder for solution for injection vials | 1 vial (£2.50) 10 vial (£40.00)
  - Cefotaxime (as Cefotaxime pentahydrate) 1 gram Cefotaxime 1g powder for solution for injection vials | 1 vial (£3.50) 10 vial (£35.00)
  - Cefotaxime (as Cefotaxime pentahydrate) 10 gram Cefotaxime 10g powder for solution for injection vials | 1 vial (£45.00) 10 vial (£395.00)
  - Cefotaxime (as Cefotaxime pentahydrate) 50 gram Cefotaxime 50g powder for solution for injection vials | 1 vial (£200.00) 10 vial (£2000.00)

- **Fortum** (GlaxoSmithKline UK Ltd)
  - Cefotaxime (as Cefotaxime pentahydrate) 1 gram Fortum 1g powder for solution for injection vials | 1 vial (£8.79) 10 vial (£87.90)
  - Cefotaxime (as Cefotaxime pentahydrate) 2 gram Fortum 2g powder for solution for injection vials | 1 vial (£17.59) 10 vial (£175.90)
  - Cefotaxime (as Cefotaxime pentahydrate) 3 gram Fortum 3g powder for solution for injection vials | 1 vial (£25.76) 10 vial (£257.60)
  - Cefotaxime (as Cefotaxime pentahydrate) 50 gram Fortum 50g powder for solution for injection vials | 1 vial (£4.40) 10 vial (£44.00)
Ceftriaxone

**INDICATIONS AND DOSE**

Community-acquired pneumonia | Hospital-acquired pneumonia | Intra-abdominal infections | Complicated urinary-tract infections | Acute exacerbations of chronic obstructive pulmonary disease

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases

Complicated skin and soft tissue infections | Infections of bones and joints

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 2 g once daily

**Suspected bacterial infection in neutropenic patients**

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases

**Bacterial meningitis | Bacterial endocarditis**

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases
  - By intravenous infusion
  - Child 1 month–11 years (body-weight up to 50 kg): 80–100 mg/kg once daily, 100 mg/kg once daily dose should be used for bacterial endocarditis; maximum 4 g per day
  - Child 9–11 years (body-weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases
  - Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases
  - By intravenous injection
  - Child 9–11 years (body-weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases
  - Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases
  - By deep intramuscular injection
  - Child 1 month–11 years (body-weight up to 50 kg): 80–100 mg/kg once daily, 100 mg/kg once daily dose should be used for bacterial endocarditis; maximum 4 g per day
  - Child 9–11 years (body-weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases
  - Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases

**Surgical prophylaxis**

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 2 g for 1 dose, dose to be administered 30–90 minutes before procedure

**Uncomplicated gonorrhoea | Pelvic inflammatory disease**

- By deep intramuscular injection
  - Adult: 500 mg for 1 dose

**Syphilis**

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 0.5–1 g once daily for 10–14 days, dose increased to 2 g once daily for neurosyphilis

**Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])**

- By intravenous infusion, or by intravenous injection, or by deep intramuscular injection
  - Adult: 2 g once daily for 14–21 days, the recommended treatment durations vary and national or local guidelines should be taken into consideration

**Prevention of secondary case of meningococcal meningitis**

- By intramuscular injection
  - Adult: 250 mg for 1 dose

**Prevention of secondary case of Haemophilus influenzae type b disease**

- By intramuscular injection
  - Adult: 1 g daily for 2 days

**Acute otitis media**

- By deep intramuscular injection
  - Adult: 1–2 g for 1 dose, dose can be given for 3 days if severely ill or previous therapy failed

**UNLICENSED USE**

Not licensed for prophylaxis of Haemophilus influenzae type b disease. Not licensed for prophylaxis of meningococcal meningitis.

Dose not licensed for treatment of pelvic inflammatory disease in adults.

**CAUTIONS**

**GENERAL CAUTIONS**

History of hypercalciuria | history of kidney stones

**SPECIFIC CAUTIONS**

- With intravenous use | concomitant treatment with intravenous calcium (including total parenteral nutrition containing calcium) (in adults)

**SIDE-EFFECTS**

**Common or very common**

Calcium ceftriaxone precipitates in gall bladder—consider discontinuation if symptomatic.

Calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobile—consider discontinuation if symptomatic.

**Uncommon**

Gental fungal infection

**Rare**

Bronchospasm | glycosuria | haematuria | prolongation of prothrombin time

**Frequency not known**

Convulsion | glossitis | oliguria | pancreatitis | stomatitis | toxic epidermal necrolysis | vertigo

**PREGNANCY**

Manufacturer advises use only if benefit outweighs risk—limited data available but not known to be harmful in animal studies. Specialist sources indicate suitable for use in pregnancy.

**BREAST FEEDING**

Specialist sources advise ceftriaxone is compatible with breastfeeding—present in milk in low concentration but limited effects to breast-fed infant.

**RENAL IMPAIRMENT**

Manufacturer advises reduce dose and monitor efficacy in patients with severe renal impairment in combination with hepatic impairment—no information available.

In adults

Manufacturer advises reduce dose if eGFR less than 10 mL/minute/1.73 m^2 (max. 2 g daily).

In children

Manufacturer advises reduce dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m^2 max. 50 mg/kg daily or max. 2 g daily.

**MONITORING REQUIREMENTS**

Manufacturer advises to monitor full blood count regularly during prolonged treatment.

**DIRECTIONS FOR ADMINISTRATION**

- With intramuscular use or intravenous use Twice daily dosing may be considered for doses greater than 2 g daily.

- With intravenous use in children For intravenous infusion (preferred route), dilute reconstituted solution with Glucose 5% (or 10% in neonates) or Sodium Chloride 0.9%;
give over at least 30 minutes (60 minutes in neonates—may displace bilirubin from serum albumin). Not to be given simultaneously with parenteral nutrition or infusion fluids containing calcium, even by different infusion lines; in children, may be infused sequentially with infusion fluids containing calcium if flush with sodium chloride 0.9% between infusions or give infusions by different infusion lines at different sites. Displacement value may be significant, consult local guidelines.

For intravenous injection, give over 5 minutes; intravenous doses of 50 mg/kg or more in children under 12 years should be given by infusion.

- With intramuscular use in children For intramuscular injection, may be mixed with 1% Lidocaine Hydrochloride Injection to reduce pain at intramuscular injection site. Intramuscular injection should only be considered when the intravenous route is not possible or less appropriate. If administered by intramuscular injection, the lower end of the dose range should be used for the shortest time possible; volume depends on the age and size of the child, but doses over 1 g must be divided between more than one site. The maximum intramuscular dose is 2 g, doses greater than 2 g must be given by intravenous injection (see above). Displacement value may be significant, consult local guidelines.

- With intravenous use in adults For intravenous infusion (preferred route) (Rocephin®, Ceftriaxone Injection, Genus), give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Reconstitute 2-g vial with 40 mL infusion fluid. Give by intermittent infusion over at least 30 minutes. Not to be given simultaneously with total parenteral nutrition or infusion fluids containing calcium, even by different infusion lines. May be infused sequentially with infusion fluids containing calcium if flush with sodium chloride 0.9% between infusions or give infusions by different infusion lines at different sites.

For intravenous injection, give over 5 minutes.

- With intramuscular use in adults For intramuscular injection, doses over 1 g must be divided between more than one site. The maximum intramuscular dose is 2 g, doses greater than 2 g must be given by intravenous administration. Displacement value may be significant, consult local guidelines.

### Powder for solution for injection

#### ELECTROLYTES: May contain Sodium

- Ceftriaxone (as Ceftriaxone sodium) 250 mg Ceftriaxone 250mg powder for injection vials | 1 vial £1.80–£2.30 DT price = £2.40
- Ceftriaxone (as Ceftriaxone sodium) 1 gram Ceftriaxone 1g powder for solution for injection vials | 1 vial no price available DT price = £9.58 | 5 vial £45.75 | 10 vial £11.00
- Ceftriaxone (as Ceftriaxone sodium) 2 gram Ceftriaxone 2g powder for solution for injection vials | 1 vial £18.40 DT price = £19.18 | 10 vial £21.00
- Rocephin (Roche Products Ltd) Ceftriaxone (as Ceftriaxone sodium) 250 mg Rocephin 250mg powder for solution for injection vials | 1 vial £2.40 DT price = £2.40
- Ceftriaxone (as Ceftriaxone sodium) 1 gram Rocephin 1g powder for solution for injection vials | 1 vial £9.58 DT price = £9.58
- Ceftriaxone (as Ceftriaxone sodium) 2 gram Rocephin 2g powder for solution for injection vials | 1 vial £19.18 DT price = £19.18

### Ceftaroline fosamil

#### INDICATIONS AND DOSE

- Community-acquired pneumonia
  - BY INTRAVENOUS INFUSION
    - Adult: 600 mg every 12 hours for 5–7 days
- Complicated skin infections | Complicated soft-tissue infections
  - BY INTRAVENOUS INFUSION
    - Adult: 600 mg every 12 hours for 5–14 days

#### CAUTIONS

- Seizure disorders
- PREGNANCY Manufacturer advises avoid unless essential—no information available.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- RENAL IMPAIRMENT 400 mg every 12 hours if eGFR 30–50 mL/minute/1.73 m². Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m².
- DIRECTIONS FOR ADMINISTRATION For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute 600 mg with 20 mL water for injections, then dilute with 250 mL infusion fluid (in fluid restriction, may be diluted with 50–100 mL infusion fluid); give over 60 minutes.

### Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium, has advised (Dec 2012) that ceftaroline fosamil (Zinforo®) is accepted for restricted use within NHS Scotland when meticillin-resistant S. aureus is suspected in complicated skin and soft-tissue infection and vancomycin cannot be used.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

- Ceftriaxone (Non-proprietary) Ceftriaxone (as Ceftriaxone sodium) 250 mg Ceftriaxone 250mg powder for solution for injection vials | 1 vial £1.80–£2.30 DT price = £2.40
- Ceftriaxone (as Ceftriaxone sodium) 1 gram Ceftriaxone 1g powder for solution for injection vials | 1 vial no price available DT price = £9.58 | 5 vial £45.75 | 10 vial £11.00
- Ceftriaxone (as Ceftriaxone sodium) 2 gram Ceftriaxone 2g powder for solution for injection vials | 1 vial £18.40 DT price = £19.18 | 10 vial £21.00
- Ceftriaxone 2g powder for solution for infusion vials | 1 vial £17.70 DT price = £19.18
- Rocephin (Roche Products Ltd) Ceftriaxone (as Ceftriaxone sodium) 250 mg Rocephin 250mg powder for solution for injection vials | 1 vial £2.40 DT price = £2.40
- Ceftriaxone (as Ceftriaxone sodium) 1 gram Rocephin 1g powder for solution for injection vials | 1 vial £9.58 DT price = £9.58
- Ceftriaxone (as Ceftriaxone sodium) 2 gram Rocephin 2g powder for solution for injection vials | 1 vial £19.18 DT price = £19.18

### Ceftobiprole

#### INDICATIONS AND DOSE

Hospital-acquired pneumonia (excluding ventilator-associated pneumonia) | Community-acquired pneumonia

- BY INTRAVENOUS INFUSION
  - Adult: 500 mg every 8 hours

#### CAUTIONS

Pre-existing seizure disorder—increased risk of seizures · supra-normal creatinine clearance

#### CAUTIONS, FURTHER INFORMATION

Supra-normal creatinine clearance Manufacturer advises to measure baseline renal function and increase duration of infusion if creatinine clearance greater than 150 mL/minute.

#### SIDE-EFFECTS

- Common or very common Dysgeusia · dyspepsia
- Uncommon Agitation · asthma · dyspnoea · muscle spasm · pharyngolaryngeal pain · renal failure
- Frequency not known Convulsions
- PREGNANCY Manufacturer advises avoid unless essential—no information available.
Teicoplanin

**DRUG ACTION** The glycopeptide antibiotic teicoplanin has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides and increasing reports of glycopeptide-resistant enterococci. Teicoplanin is similar to vancomycin, but has a significantly longer duration of action, allowing once daily administration after the loading dose.

**INDICATIONS AND DOSE**

### Clostridium difficile infection

- **BY MOUTH**
  - Adult: 100–200 mg twice daily for 10–14 days

### Serious infections caused by Gram-positive bacteria (e.g. complicated skin and soft-tissue infections, pneumonia)

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRAMUSCULAR INJECTION**
  - Adult (body-weight up to 70 kg): Initially 400 mg every 12 hours for 3 doses, followed by 400 mg once daily
  - Adult (body-weight 70 kg and above): Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

### Streptococcal or enterococcal endocarditis (in combination with another antibiotic)

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 10 mg/kg every 12 hours for 3–5 doses, then 10 mg/kg once daily, subsequent doses can be given by intramuscular injection

### Bone and joint infections

- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: Initially 12 mg/kg every 12 hours for 3–5 doses, then 12 mg/kg once daily, subsequent doses can be given by intramuscular injection, increased risk of fever and rash with doses of 12 mg/kg

**Surgical prophylaxis**

- **BY INTRAVENOUS INJECTION**
  - Adult: 400 mg, to be administered up to 30 minutes before the procedure

**Surgical prophylaxis in open fractures**

- **BY INTRAVENOUS INFUSION**
  - Adult: 800 mg, to be administered up to 30 minutes before skeletal stabilisation and definitive soft-tissue closure

**Peritonitis associated with peritoneal dialysis (added to dialysis fluid)**

- **BY INTRAPERITONEAL INFUSION**
  - Adult: (consult local protocol)

**PHARMACOKINETICS**

Teicoplanin should not be given by mouth for systemic infections because it is not absorbed significantly.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Powder for solution for infusion

**ELECTROLYTES:** May contain Sodium

- **Zetera** (Basilea Pharmaceutica International Ltd) ▼
  - Cefotibiprole (as Cefotibiprole medocaril sodium) 500 mg Zetera 500mg powder for concentrate for solution for infusion vials | 10 vial £396.30 (Hospital only)

**ANTIBACTERIALS > GLYCOPEPTIDE ANTIBACTERIALS**

**UNLICENSED USE** Not licensed for surgical prophylaxis. Teicoplanin doses in BNF may differ from those in product literature.

**INTERACTIONS** → Appendix 1 (teicoplanin). If other nephrotoxic or neurotoxic drugs given, monitor renal and auditory function on prolonged administration.

**SIDE-EFFECTS**

- **Common or very common** Pruritus • rash
- **Uncommon** Bronchospasm • diarrhoea • dizziness • eosinophilia • fever • headache • leucopenia • mild hearing loss • nausea • thrombocytopenia • thrombophlebitis • tinnitus • vestibular disorders • vomiting
- **Frequency not known** Exfoliative dermatitis • nephrotoxicity • renal failure • Stevens-Johnson syndrome • toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Nephrotoxicity** Teicoplanin is associated with a lower incidence of nephrotoxicity than vancomycin.

**ALLERGY AND CROSS-SENSITIVITY** Caution if history of vancomycin sensitivity.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** No information available.

**RENAL IMPAIRMENT** Use normal dose regimen on days 1–4, then use normal maintenance dose every 48 hours if eGFR 30–80 mL/minute/1.73 m² and use normal maintenance dose every 72 hours if eGFR less than 30 mL/minute/1.73 m². Plasma-teicoplanin concentration should be monitored during parenteral maintenance treatment. Also monitor renal and auditory function during prolonged treatment in renal impairment.

**MONITORING REQUIREMENTS**

- With intramuscular use or intravenous use Plasma-teicoplanin concentration is not measured routinely because a relationship between plasma concentration and toxicity has not been established. However, the plasma-teicoplanin concentration can be used to optimise parenteral treatment in severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), endocarditis and in intravenous drug abusers.
  - Pre-dose ('trough') concentrations should be greater than 15 mg/litre (greater than 20 mg/litre in endocarditis or deep-seated infection such as bone and joint infection), but less than 60 mg/litre.
  - Plasma-teicoplanin concentration should be measured in elderly patients.
  - Blood counts and liver and kidney function tests required.
Telavancin

**Drug Action** Telavancin is a glycopeptide antibiotic; it has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci.

**Indications and Dose**

*Hospital-acquired pneumonia, known or suspected to be caused by meticillin-resistant Staphylococcus aureus when other antibacterials cannot be used*

- **By Intravenous Infusion**
  - Adult: 10 mg/kg once daily for 7–21 days

**Cautions** Conditions that predispose to renal impairment predisposition to QT interval prolongation (including electrolyte disturbances, congenital long QT syndrome, uncompensated heart failure, severe left ventricular hypertrophy)

**Interactions** → Appendix 1 (telavancin). Use with caution if concomitant use with nephrotoxic drugs, drugs that prolong the QT interval or potentially ototoxic drugs.

**Side-effects**

- **Common or very common** Acute renal failure, chills, constipation, diarrhoea, dizziness, fungal infection, headache, insomnia, malaise, nausea, pruritus, rash, taste disturbances, vomiting
- **Uncommon** Abdominal pain, agitation, altered sense of smell, angina, antibiotic-associated colitis, anxiety, arthralgia, atrial fibrillation, back pain, blood disorders, blurred vision, bradyarrhythmia, confusion, congestive cardiac failure, decreased appetite, depression, dry mouth, dyspepsia, dysphagia, dysuria, electrolyte disturbances, erythema, eye irritation, flatulence, flushing, haematuria, hepatitis, hiccups, hyperhidrosis, hypertension, hypotension, increased INR, microalbuminuria, myalgia, nasal congestion, oedema, oliguria, oral hypoesthesia, palpitation, paraesthesia, pharyngolaryngeal pain, phlebitis, polyuria, pyrexia, QT interval prolongation, sinus tachycardia, somnolence, supraventricular extrasystoles, tinnitus, tremor, respiratory tract infection, urticaria, ventricular extrasystoles
- **Rare** Deafness
- **Frequency not known** Flushing of the upper body (‘red man’ syndrome), non-cardiac chest pain

**Allergy and Cross-sensitivity** Use with caution in patients with vancomycin or teicoplanin sensitivity.

**Conception and Contraception** Effective contraception required during treatment.

**Pregnancy** Avoid (teratogenic in animal studies).

**Breast Feeding** Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**Hepatic Impairment** Manufacturer advises caution in severe impairment—no information available.

**Renal Impairment** In chronic renal failure, use 7.5 mg/kg once daily if eGFR 30–50 mL/minute/1.73 m². Avoid in acute renal failure—risk of mortality increased. In chronic renal failure, avoid if eGFR less than 30 mL/minute/1.73 m².

**Monitoring Requirements** Monitor renal function daily for at least the first 3–5 days, then every 2–3 days thereafter.

**Directions for Administration** For *intravenous infusion* (Vibativ®). Avoid rapid infusion (can cause ‘red man’ syndrome). Give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute each 750 mg with 45 mL glucose 5%, sodium chloride 0.9%, or water for injections to produce a 15 mg/mL solution; for doses of 150–800 mg, dilute requisite dose in 100 to 250 mL infusion fluid; for doses outside this range, dilute to a final concentration of 0.6–8 mg/mL; give over at least 60 minutes.

**Medicinal Forms**

- **Powder and solvent for solution for infusion**
  - Targocid (Sanofi)
  - Teicoplanin 200 mg Targocid 200 mg powder and solvent for solution for injection vials 1 vial £3.93
  - Teicoplanin 400 mg Targocid 400 mg powder and solvent for solution for injection vials 1 vial £7.32

**Vancomycin**

**Drug Action** The glycopeptide antibiotic vancomycin has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci. Penetration into cerebrospinal fluid is poor.

**Indications and Dose**

*Clostridium difficile infection*

- **By Mouth**
  - Adult: 125 mg 4 times a day for 10–14 days; dose may be increased if infection fails to respond or is life-threatening, increased if necessary up to 500 mg 4 times a day

**Infections due to Gram-positive bacteria including endocarditis, osteomyelitis, septicemia and soft-tissue infections**

- **By Intravenous Infusion**
  - Adult: 1–1.5 g every 12 hours
  - Elderly: 500 mg every 12 hours, alternatively 1 g once daily

**Surgical prophylaxis (when high risk of MRSA)**

- **By Intravenous Infusion**
  - Adult: 1 g for 1 dose

**Peritonitis associated with peritoneal dialysis**

- **By Intraperitoneal Administration**
  - Adult: (consult local protocol)

**Pharmacokinetics**

Vancomycin should not be given by mouth for systemic infections because it is not absorbed significantly.
UNLICENSED USE Vancomycin doses in BNF publications may differ from those in product literature. Use of vancomycin (added to dialysis fluid) for the treatment of peritonitis associated with peritoneal dialysis is an unlicensed route.

CAUTIONS

GENERAL CAUTIONS
Avoid if history of deafness - elderly

SPECIFIC CAUTIONS
- With oral use systemic absorption may follow oral administration especially in inflammatory bowel disorders or following multiple doses
- INTERACTIONS → Appendix 1 (vancomycin).

SIDE-EFFECTS
- Common or very common
  - With intravenous use Blood disorders, including neutropenia (usually after 1 week or cumulative dose of 25 g) - interstitial nephritis - nephrotoxicity - ototoxicity (discontinue if tinnitus occurs) - renal failure
- Rare
  - With intravenous use Agranulocytosis - thrombocytopenia
  - Frequency not known
  - With intravenous use Anaphylaxis - cardiac arrest on rapid infusion - chills - dyspnoea - eosinophilia - exfoliative dermatitis - fever - flushing of the upper body ('red man' syndrome) - nausea - pain and muscle spasm of back and chest - phlebitis (irritant to tissue) - pruritus - rashes - severe hypotension on rapid infusion - shock on rapid infusion - Stevens-Johnson syndrome - toxic epidermal necrolysis - urticaria - vasculitis - wheezing

SIDE-EFFECTS, FURTHER INFORMATION
- Nephrotoxicity Vancomycin is associated with a higher incidence of nephrotoxicity than teicoplanin.

ALLERGY AND CROSS-SENSITIVITY Caution if teicoplanin sensitivity.

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.
Plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity.

BREAST FEEDING Present in milk—significant absorption following oral administration unlikely.

RENAL IMPAIRMENT Reduce dose. In renal impairment monitor plasma-vancomycin concentration and renal function regularly. Also monitor auditory function.

MONITORING REQUIREMENTS
- All patients require plasma-vancomycin measurement (after 3 or 4 doses if renal function normal, earlier if renal impairment).
- With intravenous use Pre-dose ('trough') concentration should be 10–15 mg/litre (15–20 mg/litre for endocarditis or less sensitive strains of meticillin-resistant Staphylococcus aureus or for complicated infections caused by S. aureus). An initial loading dose, by intravenous infusion, may be considered—consult local guidelines.
- All patients require blood counts, urinalysis, and renal function tests.
- Monitor auditory function in elderly.

DIRECTIONS FOR ADMINISTRATION
- With intravenous use Avoid rapid infusion (risk of anaphylactoid reactions) and rotate infusion sites.
- With intravenous use For intravenous infusion (Vancocin ®), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute each 500 mg with 10 ml water for injections and dilute with infusion fluid to a concentration of up to 5 mg/ml (10 mg/ml in fluid restriction but increased risk of infusion-related effects); give over at least 60 minutes (rate not to exceed 10 mg/minute for doses over 500 mg); use continuous infusion only if intermittent not feasible.
- With oral use Injection can be used to prepare solution for oral administration; flavouring syrups may be added to the solution at the time of administration.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, pastille, solution for injection, infusion

Capsule

CAUTIONARY AND ADVISORY LABELS
- Vancomycin (Non-proprietary)
  - Vancomycin (as Vancomycin hydrochloride) 125 mg
  - Vancomycin 125mg capsules
  - 28 capsule (POM) £132.47 DT price = £132.47
  - Vancomycin (as Vancomycin hydrochloride) 250 mg
  - Vancomycin 250mg capsules
  - 28 capsule (POM) £140.08 DT price = £140.08

Powder for solution for infusion

- Vancomycin (Non-proprietary)
  - Vancomycin (as Vancomycin hydrochloride) 500 mg
  - Vancomycin 500mg powder for solution for infusion vials
  - 1 vial (POM) £7.25
  - (Hospital only) 1 vial (POM) £7.25
  - Vancomycin 500mg powder for concentrate for solution for infusion vials
  - 1 vial (POM) £8.50
  - 10 vial (POM) £62.50

Antibacterial Agents

Lincosamides

Clindamycin

DRUG ACTION Clindamycin is active against Gram-positive cocci, including streptococci and penicillin-resistant staphylococci, and also against many anaerobes, especially Bacteroides fragilis. It is well concentrated in bone and excreted in bile and urine.

INDICATIONS AND DOSE
Staphylococcal bone and joint infections such as osteomyelitis | Peritonitis | Intra-abdominal sepsis | Meticillin-resistant Staphylococcus aureus (MRSA) in bronchiectasis, bone and joint infections, and skin and soft-tissue infections | Erysipeloid or cellulitis in penicillin-allergic patients (alternative to macrolides)
- BY MOUTH
  - Child: 3–6 mg/kg 4 times a day (max. per dose 450 mg)
  - Adult: 150–300 mg every 6 hours; increased if necessary up to 450 mg every 6 hours if required, increased dose used in severe infection
- BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION
  - Adult: 0.6–2.7 g daily in 2–4 divided doses; increased if necessary up to 4.8 g daily, increased dose used in life-threatening infection, single doses above 600 mg to be administered by intravenous infusion only, single doses by intravenous infusion not to exceed 1.2 g

Treatment of mild to moderate pneumocystis pneumonia (in combination with primaquine)
- BY MOUTH
  - Adult: 600 mg every 8 hours

continued →
Treatment of falciparum malaria (to be given with or following quinine)

▶ BY MOUTH
- Child: 7–13 mg/kg every 8 hours (max. per dose 450 mg) for 7 days
- Adult: 450 mg every 8 hours for 7 days

UNLICENSED USE Not licensed for treatment of falciparum malaria. Not licensed for treatment of mild to moderate pneumocystis infection.

CONTRA-INDICATIONS Diarrhoeal states

CAUTIONS Avoid in acute porphyrias p. 930 • middle-aged and elderly women, especially after an operation (antibiotic-associated colitis more common)

INTERACTIONS → Appendix 1 (clindamycin).

SIDE-EFFECTS
- With intramuscular use Abscess • induration • pain
- With intravenous use Thrombophlebitis
- With systemic use Abdominal discomfort • anaphylactoid reactions • antibiotic-associated colitis • diarrhoea (discontinue treatment) • eosinophilia • exfoliative dermatitis • jaundice • leucopenia • nausea • oesophageal ulcers • oesophagitis • polyarthritits • pruritus • rash • Stevens-Johnson syndrome • taste disturbances • thrombocytopenia • toxic epidermal necrolysis • urticaria • vesiculobullous dermatitis • vomiting

SIDE-EFFECTS, FURTHER INFORMATION
- Antibiotic-associated colitis Clindamycin has been associated with antibiotic-associated colitis, which may be fatal. Although antibiotic-associated colitis can occur with most antibacterials, it occurs more frequently with clindamycin. Patients should therefore discontinue treatment immediately if diarrhoea develops.

PREGNANCY Not known to be harmful.

BREAST FEEDING Amount probably too small to be harmful but bloody diarrhoea reported in 1 infant.

MONITORING REQUIREMENTS
- Monitor liver and renal function if treatment exceeds 10 days.
- In children Monitor liver and renal function in neonates and infants.

DIRECTIONS FOR ADMINISTRATION Avoid rapid intravenous administration. For intravenous infusion (Dalacin™ Phosphate), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute to not more than 18 mg/mL and give over 10–60 minutes at a rate not exceeding 30 mg/minute (1.2 g over at least 60 minutes; higher doses by continuous infusion).

PATIENT AND CARER ADVICE Capsules should be swallowed with a glass of water. Patients and their carers should be advised to discontinue treatment and contact doctor if diarrhoea develops.

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Clindamycin capsules may be prescribed.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

**CAUTIONARY AND ADVISORY LABELS** 9, 27

Clindamycin (Non-proprietary)

Clindamycin (as Clindamycin hydrochloride) 150 mg Clindamycin 150mg capsules | 24 capsule (PSt) £13.72 DT price = £8.97 | 100 capsule (PSt) £55.21

Clindamycin (as Clindamycin hydrochloride) 300 mg Clindamycin 300mg capsules | 30 capsule (PSt) £46.00 DT price = £39.93

Dalacin C (Pfizer Ltd)

Clindamycin (as Clindamycin hydrochloride) 75 mg Dalacin C 75mg capsules | 24 capsule (PSt) £7.45 DT price = £7.45

**Solution for injection**

**EXCIPIENTS:** May contain Benzyl alcohol

Clindamycin (Non-proprietary)

Clindamycin (as Clindamycin phosphate) 150 mg per 1 ml Clindamycin 600mg/4ml solution for injection ampoules | 5 ampoule (PSt) £61.75

Clindamycin 300mg/2ml solution for injection ampoules | 5 ampoule (PSt) £28.50–£31.01

Dalacin C (Pfizer Ltd)

Clindamycin (as Clindamycin phosphate) 150 mg per 1 ml Dalacin C Phosphate 300mg/2ml solution for injection ampoules | 5 ampoule (PSt) £31.01

Dalacin C Phosphate 600mg/4ml solution for injection ampoules | 5 ampoule (PSt) £61.75

ANTIBACTERIALS › MACROLIDES

**Macrolides**

**Overview**

The macrolides have an antibacterial spectrum that is similar but not identical to that of penicillin; they are thus an alternative in penicillin-allergic patients. They are active against many–penicillin-resistant staphylococci, but some are now also resistant to the macrolides.

Indications for the macrolides include campylobacter enteritis, respiratory infections (including pneumonia, whooping cough, Legionella, chlamydia, and mycoplasma infection), and skin infections.

Erythromycin p. 497 is also used in the treatment of early syphilis, uncomplicated genital chlamydial infection, and non-gonococcal urethritis. Erythromycin has poor activity against *Haemophilus influenzae*. Erythromycin causes nausea, vomiting, and diarrhoea in some patients; in mild to moderate infections this can be avoided by giving a lower dose, but if a more serious infection, such as Legionella pneumonia, is suspected higher doses are needed.

Azithromycin p. 495 is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria, but enhanced activity against some Gram-negative organisms including *H. influenzae*. Plasma concentrations are very low, but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of uncomplicated genital chlamydial infection, non-gonococcal urethritis, uncomplicated gonorrhoea, typhoid [unlicensed indication], and trachoma [unlicensed indication].

Clarithromycin p. 496 is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. It is given twice daily. Clarithromycin is also used in regimens for *Helicobacter pylori* eradication.

Erythromycin, azithromycin, and clarithromycin have a role in the treatment of Lyme disease p. 533.

Spiramycin is also a macrolide which is used for the treatment of toxoplasmosis.

**Macrolides**

**CAUTIONS** Electrolyte disturbances (predisposition to QT interval prolongation) • may aggravate myasthenia gravis • predisposition to QT interval prolongation

**SIDE-EFFECTS**

Common or very common Abdominal discomfort • diarrhoea • nausea • vomiting

Uncommon Cholestatic jaundice • hepatotoxicity • rash

Rare Antibiotic-associated colitis • arrhythmias • pancreatitis • QT interval prolongation • Stevens-Johnson syndrome • toxic epidermal necrolysis
Azithromycin

**INDICATIONS AND DOSE**

- **Prevention of secondary case of invasive group A streptococcal infection in patients who are allergic to penicillin**
  - **BY MOUTH**
    - Child 6 months-11 years: 12 mg/kg once daily (max. per dose 500 mg) for 5 days
    - Child 12-17 years: 500 mg once daily for 5 days
    - Adult: 500 mg once daily for 5 days

- **Respiratory-tract infections, otitis media, skin and soft-tissue infections**
  - **BY MOUTH**
    - Child 6 months-17 years: 10 mg/kg once daily (max. per dose 500 mg) for 3 days
    - Child 6 months-17 years (body-weight 15-25 kg): 200 mg once daily for 3 days
    - Child 6 months-17 years (body-weight 26-35 kg): 300 mg once daily for 3 days
    - Child 6 months-17 years (body-weight 36-45 kg): 400 mg once daily for 3 days
    - Child 6 months-17 years (body-weight 46 kg and above): 500 mg once daily for 3 days
    - Child 6 months-17 years (body-weight 46 kg and above): 500 mg once daily for 3 days
    - Adult: 500 mg once daily for 3 days, alternatively initially 500 mg once daily for 1 day, then 250 mg once daily for 4 days

- **Uncomplicated genital chlamydial infections**
  - **Non-gonococcal urethritis**
    - **BY MOUTH**
      - Child 12-17 years: 1 g for 1 dose
      - Adult: 1 g for 1 dose

- **Uncomplicated gonorrhoea**
  - **BY MOUTH**
    - Adult: 1 g for 1 dose

- **Lyme disease (under expert supervision)**
  - **BY MOUTH**
    - Adult: 500 mg once daily for 7–10 days

- **Mild to moderate typhoid due to multiple-antibacterial resistant organisms**
  - **BY MOUTH**
    - Adult: 500 mg once daily for 7 days

- **Community-acquired pneumonia, low to moderate severity**
  - **BY MOUTH**
    - Adult: 500 mg once daily for 3 days, alternatively initially 500 mg once daily for 1 day, then 250 mg once daily for 4 days

- **Community-acquired pneumonia, high severity**
  - **INITIALLY BY INTRAVENOUS INFUSION**
    - Adult: Initially 500 mg once daily for at least 2 days, then (by mouth) 500 mg once daily for a total duration of 7–10 days

- **Antibacterial prophylaxis for insertion of intra-uterine device**
  - **BY MOUTH**
    - Adult: 1 g for 1 dose

**UNLICENSED USE**

- In children: Not licensed for typhoid fever or prophylaxis of group A streptococcal infection.
- In adults: Oral azithromycin not licensed for trachoma which results from chronic infection with *Chlamydia trachomatis*. Not licensed for uncomplicated gonorrhoea, mild or moderate typhoid due to multiple-antibacterial-resistant organisms, Lyme disease, or prophylaxis of group A streptococcal infection. Not licensed for community-acquired pneumonia (high severity) when oral treatment continues for more than 3 days.

**INTERACTIONS**

- Appendix 1 (macrolides).
- Caution with concomitant use of drugs that prolong the QT interval.

**SIDE-EFFECTS**

- **Common or very common** Anorexia · arthralgia · disturbances in taste · disturbances in vision · dizziness · dyspepsia · flatulence · headache · malaise · paraesthesia · reversible hearing loss (sometimes with tinnitus) after long-term therapy
- **Uncommon** Anxiety · chest pain · constipation · gastritis · hypoesthesia · leucopenia · oedema · photosensitivity · sleep disturbances
- **Rare** Agitation
- **Frequency not known** Acute renal failure · convulsions · haemolytic anaemia · interstitial nephritis · smell disturbances · syncope · thrombocytopenia · tongue discoloration

**PREGNANCY**

- Manufacturers advise use only if adequate alternatives not available.

**BREAST FEEDING**

- Present in milk; use only if no suitable alternatives.

**HEPATIC IMPAIRMENT**

- Manufacturers advise avoid in severe liver disease—no information available.

**RENAL IMPAIRMENT**

- In adults: Use with caution if eGFR less than 10 mL/minute.1.73 m².
- In children: Use with caution if estimated glomerular filtration rate less than 10 mL/minute.1.73 m².

**DIRECTIONS FOR ADMINISTRATION**

- For intravenous infusion (Zebdac®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute 500 mg with 4.8 mL water for injections to produce a 100 mg/mL solution, then dilute 5 mL of solution with infusion fluid to a final concentration of 1 or 2 mg/mL; give the 1 mg/mL solution over 3 hours or give the 2 mg/mL solution over 1 hour.

**PRESCRIBING AND DISPENSING INFORMATION**

- Flavours of oral liquid formulations may include cherry or banana.

**PATIENT AND CARER ADVICE**

- Medicines for Children leaflet: Azithromycin for bacterial infections www.medicinesforchildren.org.uk/azithromycin-bacterial-infections-0

**PROFESSION SPECIFIC INFORMATION**

- Dental practitioners’ formulary
  - Azithromycin Capsules may be prescribed. Azithromycin Tablets may be prescribed. Azithromycin Oral Suspension 200 mg/5 mL may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY**

- Azithromycin tablets can be sold to the public for the treatment of confirmed, asymptomatic *Chlamydia trachomatis* genital infection in those over 16 years of age, and for the epidemiological treatment of their sexual partners, subject to maximum single dose of 1 g, maximum daily dose 1 g, and a pack size of 1 g.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>S. 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 250 mg</td>
<td>Azithromycin 250 mg tablets</td>
</tr>
</tbody>
</table>
Azithromycin 500 mg Azithromycin 500mg tablets | 3 tablet £9.80 DT price = £1.32

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS 5, 9, 23**
  - Azithromycin (as Azithromycin dihydrate) 250 mg Azithromycin 250mg capsules | 4 capsule £10.10 | 6 capsule £15.15 DT price = £15.13
  - Zithromax (Pfizer Ltd)
  - Azithromycin (as Azithromycin dihydrate) 250 mg Zithromax 250mg capsules | 4 capsule £7.16 | 6 capsule £10.74 DT price = £15.13

**Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS 5, 9**
  - Azithromycin (as Azithromycin dihydrate) 500 mg Zithromax 500mg powder for suspension | 1 vial £9.50 (Hospital only)

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**Clarithromycin**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory-tract infections</strong></td>
</tr>
<tr>
<td><strong>BY MOUTH USING IMMEDIATE-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily</td>
</tr>
<tr>
<td>Child 1 month–11 years (body-weight 8–11 kg): 12.5 mg/kg twice daily</td>
</tr>
<tr>
<td>Child 1 month–11 years (body-weight 12–19 kg): 187.5 mg twice daily</td>
</tr>
<tr>
<td>Child 12–17 years: 500 mg twice daily</td>
</tr>
<tr>
<td><strong>BY MOUTH USING MODIFIED-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>Child 12–17 years: 500 mg once daily usually for 7–14 days, increased to 1 g once daily, if required in severe infections (e.g. pneumonia)</td>
</tr>
<tr>
<td>Adult: 500 mg once daily usually for 7–14 days, increased to 1 g once daily, if required in severe infections (e.g. pneumonia)</td>
</tr>
<tr>
<td><strong>BY INTRAVENOUS INFUSION</strong></td>
</tr>
<tr>
<td>Adult: 500 mg every 12 hours maximum duration 5 days, switch to oral route when appropriate, to be administered into a large proximal vein</td>
</tr>
</tbody>
</table>

**Lyne disease**

- **BY MOUTH**
  - Child 12–17 years: 500 mg twice daily for 14–21 days |
  - Adult: 500 mg twice daily for 14–21 days |

**Prevention of pertussis**

- **BY MOUTH**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 7 days |
  - Child 1 month–11 years (body-weight 8–11 kg): 12.5 mg twice daily for 7 days |
  - Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily for 7 days |
  - Child 12–17 years: 500 mg twice daily for 7 days |
  - Adult: 500 mg twice daily for 7 days |

**Helicobacter pylori eradication in combination with a proton pump inhibitor and amoxicillin**

- **BY MOUTH**
  - Adult: 500 mg twice daily |

**Helicobacter pylori eradication in combination with a proton pump inhibitor and metronidazole**

- **BY MOUTH**
  - Adult: 250 mg twice daily

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**SIDE-EFFECTS**

- **Common or very common** Dyspepsia, headache, hyperhidrosis, insomnia, taste disturbances
- **Uncommon** Anorexia, anxiety, blood disorders, chest pain, constipation, dizziness, dry mouth, flatulence, gastritis, glossitis, hepatic dysfunction including jaundice, leucopenia, malaise, myalgia, myopathy, nephritis, paraesthesia, psychotic disorders, renal failure, smell disturbances, tongue discoloration, tooth discoloration
- **PREGNANCY** Manufacturer advises avoid, particularly in the first trimester, unless potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid unless potential benefit outweighs risk—present in milk.
- **HEPATIC IMPAIRMENT** Avoid in severe impairment if renal impairment also present.
- **RENAI IMPAIRMENT** Avoid if severe hepatic impairment also present.
  - In adults Use half normal dose if eGFR less than 30 mL/minute/1.73 m², max. duration 14 days. Avoid Klaricid XL® or clarithromycin m/r preparations if eGFR less than 30 mL/minute/1.73 m².
  - In children Use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m², max. duration 14 days. Avoid Klaricid XL® or clarithromycin m/r preparations if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Klaricid® I.V.), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dissolve initially in water for injections (500 mg in 10 mL) then dilute to a concentration of 2 mg/mL; give over 60 minutes.
- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Clarithromycin for bacterial infections www.medicinesforchildren.org.uk/clarithromycin-bacterial-infections
  - PROFESSION SPECIFIC INFORMATION
    - Dental practitioners’ formulary
    - Clarithromycin Tablets may be prescribed. Clarithromycin Oral Suspension may be prescribed.
**Erythromycin**

**INDICATIONS AND DOSE**

Susceptible infections in patients with penicillin hypersensitivity (e.g. respiratory-tract infections (including Legionella infection), skin and oral infections, and campylobacter enteritis)

- **BY MOUTH**
  - Child 1 month-1 year: 125 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 250 mg 4 times a day, dose increase may be used in severe infections
  - Child 2-7 years: 250 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500 mg 4 times a day, dose increase may be used in severe infections
  - Child 8-17 years: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500–1000 mg 4 times a day, dose increase may be used in severe infections
  - Adult: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500–1000 mg 4 times a day, dose increase may be used in severe infections
- **BY INTRAVENOUS INFUSION**
  - Child: 12.5 mg/kg every 6 hours (max. per dose 1 g)

**Dosing**

**Adult:**
- 6.25 mg/kg every 6 hours, for mild infections when oral treatment not possible, increased to 12.5 mg/kg every 6 hours, dose increase may be used in severe infections

**Lyme disease (under expert supervision)**

- **BY MOUTH**
  - Adult: 500 mg 4 times a day for 14–21 days

**Early syphilis**

- **BY MOUTH**
  - Adult: 500 mg 4 times a day for 14 days

**Uncomplicated genital chlamydia | Non-gonococcal urethritis**

- **BY MOUTH**
  - Adult: 500 mg twice daily for 14 days

**Chronic prostatitis**

- **BY MOUTH**
  - Adult: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 4 g daily in divided doses, dose increase may be used in severe infections
- **BY INTRAVENOUS INFUSION**
  - Adult: 6.25 mg/kg every 6 hours, for mild infections when oral treatment is not possible, increased to 12.5 mg/kg every 6 hours, dose increase may be used in severe infections

**Prevention and treatment of pertussis**

- **BY MOUTH**
  - Child 1 month-1 year: 125 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 250 mg 4 times a day, dose increase may be used in severe infections
  - Child 2-7 years: 250 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500 mg 4 times a day, dose increase may be used in severe infections
  - Child 8-17 years: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500–1000 mg 4 times a day, dose increase may be used in severe infections
  - Adult: (consult local protocol)

**Prevention of secondary case of diphtheria in non-immune patient**

- **BY MOUTH**
  - Child 1 month-1 year: 125 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment
  - Child 2-7 years: 250 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment
  - Child 8-17 years: 500 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment
  - Adult: 500 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment

**Prevention of secondary case of invasive group A streptococcal infection in penicillin allergic patients**

- **BY MOUTH**
  - Child 1 month-1 year: 125 mg every 6 hours for 10 days
  - Child 2-7 years: 250 mg every 6 hours for 10 days
  - Child 8-17 years: 250–500 mg every 6 hours for 10 days
  - Adult: 250–500 mg every 6 hours for 10 days

**Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease (if penicillin-allergic)**

- **BY MOUTH**
  - Child 1 month-1 year: 125 mg twice daily, antibiotic prophylaxis is not fully reliable
  - Child 2-7 years: 250 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those over 5 years of age with sickle-cell...
disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection

- Child 8–17 years: 500 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection
- Adult: 500 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection

**Prevention of recurrence of rheumatic fever**

- **BY MOUTH**
  - Child 1 month–1 year: 125 mg twice daily
  - Child 2–17 years: 250 mg twice daily

**Rosacea**

- **BY MOUTH**
  - Adult: 500 mg twice daily courses usually last 6–12 weeks and are repeated intermittently

**Acne**

- **BY MOUTH**
  - Adult: 500 mg twice daily

- **CAUTIONS** Avoid in acute porphyrias p. 930
- **INTERACTIONS** → Appendix 1 (macrolides). Caution with concomitant use of drugs that prolong the QT interval.
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Only small amounts in milk—not known to be harmful.
- **HEPATIC IMPAIRMENT** May cause idiosyncratic hepatotoxicity.
- **RENAL IMPAIRMENT**
  - In adults Max. 1.5 g daily in severe renal impairment (ototoxicity).
  - In children Reduce dose in severe renal impairment (ototoxicity).
- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children Dilute reconstituted solution further in glucose 5% (neutralised with Sodium bicarbonate) or sodium chloride 0.9% to a concentration of 1–5 mg/mL; give over 20–60 minutes. Concentration of up to 10 mg/mL may be used in fluid-restriction if administered via a central venous catheter.
  - With intravenous use in adults For intravenous infusion (as lactobionate), give intermittently in Glucose 5% (neutralised with sodium bicarbonate) or Sodium chloride 0.9%; dissolve initially in water for injections (1 g in 20 mL) then dilute to a concentration of 1–5 mg/mL; give over 20–60 minutes.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include banana.
- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Erythromycin for bacterial infections www.medicinesforchildren.org.uk/erythromycin-for-bacterial-infections
- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Erythromycin tablets e/c may be prescribed. Erythromycin ethyl succinate oral suspension may be prescribed. Erythromycin stearate tablets may be prescribed. Erythromycin ethyl succinate tablets may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 9

- **Erythromycin (Non-proprietary)**
  - Erythromycin (as Erythromycin ethyl succinate) 500 mg Erythromycin ethyl succinate 500 mg tablets | 28 tablet (Pom) £15.95–£19.50 DT price = £10.78
  - Erythromycin (AMCo)
    - Erythromycin (as Erythromycin stearate) 250 mg Erythromycin 250 tablets | 100 tablet (Pom) £18.20 DT price = £18.20
    - Erythromycin (as Erythromycin stearate) 500 mg Erythromycin 500 tablets | 100 tablet (Pom) £36.40 DT price = £36.40
  - Erythrolar (Ennogen Pharma Ltd)
    - Erythromycin (as Erythromycin stearate) 250 mg Erythrolar 250mg tablets | 100 tablet (Pom) £22.80 DT price = £18.20
    - Erythromycin (as Erythromycin stearate) 500 mg Erythrolar 500mg tablets | 100 tablet (Pom) £45.60 DT price = £36.40
  - Erythroped A (AMCo)
    - Erythromycin (as Erythromycin ethyl succinate) 500 mg Erythroped A 500mg tablets | 28 tablet (Pom) £10.78 DT price = £10.78

**Gastro-resistant tablet**

**CAUTIONARY AND ADVISORY LABELS** 5, 9, 25

- **Erythromycin (Non-proprietary)**
  - Erythromycin 250 mg, Erythromycin 250mg gastro-resistant tablets | 28 tablet (Pom) £2.25 DT price = £1.33 | 500 tablet (Pom) £27.20

**Gastro-resistant capsule**

**CAUTIONARY AND ADVISORY LABELS** 5, 9, 25

- **Erythromycin (Non-proprietary)**
  - Erythromycin 250 mg Erythromycin 250mg gastro-resistant capsules | 28 capsule (Pom) no price available DT price = £5.61 | 30 capsule (Pom) no price available
  - Erymax (Teva UK Ltd)
    - Erythromycin 250 mg Erymax 250mg gastro-resistant capsules | 28 capsule (Pom) £5.61 DT price = £5.61 | 22 capsule (Pom) £22.44
  - Tiloryth (Tilomed Laboratories Ltd)
    - Erythromycin 250 mg Tiloryth 250mg gastro-resistant capsules | 30 capsule (Pom) £5.65 | 100 capsule (Pom) £18.66

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS** 9

- **Erythromycin (Non-proprietary)**
  - Erythromycin (as Erythromycin ethyl succinate) 25 mg per 1 ml Erythromycin ethyl succinate 125mg/5ml oral suspension | 100 ml (Pom) £4.05 DT price = £4.05
    - Erythromycin ethyl succinate 125 mg/5 ml oral suspension sugar free sugar-free | 100 ml (Pom) £4.99 DT price = £3.58
  - Erythromycin (as Erythromycin ethyl succinate) 50 mg per 1 ml Erythromycin ethyl succinate 250mg/5ml oral suspension | 100 ml (Pom) £6.38 DT price = £6.38
    - Erythromycin ethyl succinate 250 mg/5 ml oral suspension sugar free sugar-free | 100 ml (Pom) £7.99 DT price = £5.27
  - Erythromycin (as Erythromycin ethyl succinate) 100 mg per 1 ml Erythromycin ethyl succinate 500mg/5ml oral suspension | 100 ml (Pom) £11.24 DT price = £11.24
    - Erythromycin ethyl succinate 500 mg/5 ml oral suspension sugar free sugar-free | 100 ml (Pom) no price available
  - Erythroped (AMCo)
    - Erythromycin (as Erythromycin ethyl succinate) 25 mg per 1 ml Erythroped PI SF 125mg/5ml oral suspension sugar-free | 140 ml (Pom) £3.06
    - Erythromycin (as Erythromycin ethyl succinate) 50 mg per 1 ml Erythroped SF 250mg/5ml oral suspension sugar-free | 140 ml (Pom) £5.95
  - Erythromycin (as Erythromycin ethyl succinate) 100 mg per 1 ml Erythroped Forte SF 500mg/5ml oral suspension sugar-free | 140 ml (Pom) £10.56 DT price = £10.56

**Powder for solution for infusion**

- **Erythromycin (Non-proprietary)**
  - Erythromycin (as Erythromycin lactobionate)
    - 1 gram Erythromycin 1g powder for solution for infusion vials | 1 vial (Pom) £22.92
ANTIBACTERIALS > MONOBACTAMS

Aztreonam

- **DRUG ACTION** Aztreonam is a monobactam beta-lactam antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*; it should not be used alone for 'blind' treatment since it is not active against Gram-positive organisms. Aztreonam is also effective against *Neisseria gonorrhoeae* (but not against concurrent chlamydial infection).

- **INDICATIONS AND DOSE**
  - Gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*
    - By deep intramuscular injection, or by intravenous infusion, or by intravenous injection
    - Adult: 1 g every 8 hours, alternatively 2 g every 12 hours, single doses over 1 g intravenous route only
  - Severe gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria meningitidis*, and lung infections in cystic fibrosis
    - By intravenous infusion, or by intravenous injection
    - Adult: 2 g every 6–8 hours
  - Gonorrhoea | Cystitis
    - By intramuscular injection
    - Adult: 1 g for 1 single dose
  - Urinary-tract infections
    - By deep intramuscular injection, or by intravenous infusion, or by intravenous injection
    - Adult: 0.5–1 g every 8–12 hours
  - Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis
    - By inhalation of nebulised solution
    - Adult: 75 mg 3 times a day for 28 days, doses to be administered at least 4 hours apart, subsequent courses repeated after 28-day interval without aztreonam nebuliser solution

- **CAUTIONS**
  - When used by inhalation Haemoptysis — risk of further haemorrhage

- **INTERACTIONS**
  - Antibiotics

- **SIDE-EFFECTS**
  - General side-effects
    - Bronchospasm, rash
  - Specific side-effects
    - Rare
    - With systemic use
      - Antibiotic-associated colitis
      - Asthenia
      - Blood disorders
      - Breast tenderness
      - Chest pain
      - Confusion
      - Diplopia
      - Dizziness
      - Dyspnoea
      - Gastro-intestinal bleeding
      - Hallitosis
      - Headache
      - Hepatitis
      - Hypotension
      - Insomnia
      - Jaundice
      - Myalgia
      - Neutropenia
      - Paraesthesia
      - Seizures
      - Thrombocytopenia
      - Tinnitus
  - Frequency not known
    - When used by inhalation
      - Arthralgia
      - Cough
      - Haemoptysis
      - Pharyngolaryngeal pain
      - Pyrexia
      - Rhinorrhoea
      - Wheezing
    - With systemic use
      - Abdominal pain
      - Diarrhoea
      - Erythema multiforme
      - Flushing
      - Mouth ulcers
      - Nausea
      - Taste disturbances
      - Toxic epidermal necrolysis
      - Vomiting

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in aztreonam hypersensitivity.
  - Use with caution in patients with hypersensitivity to other beta-lactam antibiotics (although aztreonam may be less likely than other beta-lactams to cause hypersensitivity in penicillin-sensitive patients).

- **PREGNANCY**
  - With systemic use
    - No information available; manufacturer of injection advises avoid
  - When used by inhalation
    - No information available; manufacturer of powder for nebuliser solution advises avoid unless essential.

- **HEPATIC FEEDING**
  - Amount in milk probably too small to be harmful.

- **RENAI IMPAIRMENT**
  - With systemic use
    - If eGFR 10–30 mL/minute/1.73 m², usual initial dose of injection, then half normal dose. If eGFR less than 10 mL/minute/1.73 m², usual initial dose of injection, then one-quarter normal dose.

- **MONITORING REQUIREMENTS**
  - When used by inhalation
    - Measure lung function before and after initial dose of aztreonam and monitor for bronchospasm.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous injection, give over 3–5 minutes.
  - With intravenous use
    - For intravenous infusion (Azactam®), give intermittently in Glucose 5% or Sodium chloride 0.9%.
    - Dissolve initially in water for injections (1 g per 3 mL) then dilute to a concentration of less than 20 mg/mL; to be given over 20–60 minutes.
  - When used by inhalation
    - Other inhaled drugs should be administered before aztreonam; a bronchodilator should be administered before each dose.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions**
    - The Scottish Medicines Consortium has advised (December 2014) that aztreonam powder for nebuliser solution (*Cayston®*) is accepted for restricted use within NHS Scotland when inhaled colistimethate sodium and inhaled tobramycin are not tolerated or are not providing satisfactory therapeutic benefit (measured as ≥2% decline in forced expiratory volume in 1 second).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for injection**
    - Azactam (Bristol-Myers Squibb Pharmaceuticals Ltd)
    - Aztreonam 1 gram
      - Azactam 1g powder for solution for injection vials | £3.90 (Hospital only)
    - Aztreonam 2 gram
      - Azactam 2g powder for solution for injection vials | 1 vial POM £18.82 (Hospital only)
  - **Powder and solvent for nebuliser solution**
    - Cayston (Gilead Sciences International Ltd)
    - Aztreonam (as Aztreonam lysine) 75 mg
      - Cayston 75mg powder and solvent for nebuliser solution vials with Altera Nebuliser Handset | 84 vials POM £2,181.53

ANTIBACTERIALS > NITROIMIDAZOLE DERIVATIVES

Metronidazole

- **DRUG ACTION** Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

- **INDICATIONS AND DOSE**
  - **Anaerobic infections**
    - By mouth
      - Child 1 month: 7.5 mg/kg every 12 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
      - Child 2 months–11 years: 7.5 mg/kg every 8 hours (max. per dose 400 mg) usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
Infection

- **Child 12-17 years**: 400 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
- **Adult**: 400 mg every 8 hours, alternatively 500 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
  - **BY RECTUM**
  - **Child 1-11 months**: 125 mg 3 times a day for 3 days, then 125 mg twice daily, for usual total treatment duration of 7 days
  - **Child 1-4 years**: 250 mg 3 times a day for 3 days, then 250 mg twice daily, for usual total treatment duration of 7 days
  - **Child 5-9 years**: 500 mg 3 times a day for 3 days, then 500 mg twice daily, for usual total treatment duration of 7 days
  - **Child 10-17 years**: 1 g 3 times a day for 3 days, then 1 g twice daily, for usual total treatment duration of 7 days
  - **Adult**: 1 g 3 times a day for 3 days, then 1 g twice daily, for usual total treatment duration of 7 days
  - **BY INTRAVENOUS INFUSION**
  - **Adult**: 500 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection), to be given over 20 minutes

*Helicobacter pylori* eradication; in combination with clarithromycin and esomprazole; or in combination with clarithromycin and lansoprazole; or in combination with amoxicillin and lansoprazole; or in combination with clarithromycin and omeprazole; or in combination with clarithromycin and pantoprazole; or in combination with clarithromycin and rabeprazole
  - **BY MOUTH**
  - **Adult**: 400 mg twice daily

*Helicobacter pylori* eradication; in combination with amoxicillin and omeprazole
  - **BY MOUTH**
  - **Adult**: 400 mg 3 times a day

*Helicobacter pylori* eradication failure (two-week regimen comprising a proton pump inhibitor plus tripotassium dicitrato-bismuthate plus tetracycline)
  - **BY MOUTH**
  - **Adult**: 400–500 mg 3 times a day for 2 weeks

**Fistulating Crohn’s disease**
  - **BY MOUTH**
  - **Adult**: 10–20 mg/kg daily in divided doses, usual dose 400–500 mg 3 times a day usually given for 1 month but no longer than 3 months because of concerns about peripheral neuropathy

**Leg ulcers and pressure sores**
  - **BY MOUTH**
  - **Adult**: 400 mg every 8 hours for 7 days

**Bacterial vaginosis (notably *Gardnerella vaginalis* infection)**
  - **BY MOUTH**
  - **Adult**: 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose

**Bacterial vaginosis**
  - **BY VAGINA USING VAGINAL GEL**
  - **Adult**: 1 applicatorful daily for 5 days, dose to be administered at night

**DOSE EQUIVALENT AND CONVERSION**
  - 1 applicatorful delivers a 5g dose of metronidazole 0.75%.

**Pelvic inflammatory disease**
  - **BY MOUTH**
  - **Adult**: 400 mg twice daily for 14 days

**Acute ulcerative gingivitis**
  - **BY MOUTH**
  - **Child 1-2 years**: 50 mg every 8 hours for 3 days
  - **Child 3-6 years**: 100 mg every 12 hours for 3 days
  - **Child 7-9 years**: 100 mg every 8 hours for 3 days
  - **Child 10-17 years**: 200–250 mg every 8 hours for 3–7 days
  - **Adult**: 400 mg every 8 hours for 3–7 days

**Acute oral infections**
  - **BY MOUTH**
  - **Child 1-2 years**: 50 mg every 8 hours for 3–7 days
  - **Child 3-6 years**: 100 mg every 12 hours for 3–7 days
  - **Child 7-9 years**: 100 mg every 8 hours for 3–7 days
  - **Child 10-17 years**: 200–250 mg every 8 hours for 3–7 days
  - **Adult**: 400 mg every 8 hours for 3–7 days

**Surgical prophylaxis**
  - **BY MOUTH**
  - **Adult**: 400–500 mg, to be administered 2 hours before surgery, then 400–500 mg every 8 hours if required for up to 3 doses (in high-risk procedures)

  - **BY RECTUM**
  - **Adult**: 1 g, to be administered 2 hours before surgery, then 1 g every 8 hours if required for up to 3 doses (in high-risk procedures)

  - **BY INTRAVENOUS INFUSION**
  - **Adult**: 500 mg, to be administered up to 30 minutes before the procedure (if rectal administration inappropriate), then 500 mg every 8 hours if required for up to 3 further doses (in high-risk procedures)

**Invasive intestinal amoebiasis | Extra-intestinal amoebiasis (including liver abscess)**
  - **BY MOUTH**
  - **Child 1-2 years**: 200 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - **Child 3-6 years**: 200 mg 4 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - **Child 7-9 years**: 400 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - **Child 10-17 years**: 800 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - **Adult**: 800 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)

**Urogenital trichomoniasis**
  - **BY MOUTH**
  - **Child 1-2 years**: 50 mg 3 times a day for 7 days
  - **Child 3-6 years**: 100 mg twice daily for 7 days
  - **Child 7-9 years**: 100 mg 3 times a day for 7 days
  - **Child 10-17 years**: 200 mg 3 times a day for 7 days, alternatively 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose
  - **Adult**: 200 mg 3 times a day for 7 days, alternatively 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose

**Giardiasis**
  - **BY MOUTH**
  - **Child 1-2 years**: 500 mg once daily for 3 days
  - **Child 3-6 years**: 600–800 mg once daily for 3 days
  - **Child 7-9 years**: 1 g once daily for 3 days
  - **Child 10-17 years**: 2 g once daily for 3 days, alternatively 400 mg 3 times a day for 5 days, alternatively 500 mg twice daily for 7–10 days
  - **Adult**: 2 g once daily for 3 days, alternatively 400 mg 3 times a day for 5 days, alternatively 500 mg twice daily for 7–10 days

**Established case of tetanus**
  - **BY INTRAVENOUS INFUSION**
  - **Adult**: (consult product literature)

- **UNLICENSED USE**
- With systemic use in adults Metronidazole doses in the BNF may differ from those in product literature.
**Cautions**
- With vaginal use  Not recommended during menstruation • some systemic absorption may occur with vaginal gel

**Interactions**
- With systemic use  → Appendix 1 (metronidazole).  Caution—disulfiram-like reaction with alcohol.

**Side-effects**
- **Very rare**
  - With systemic use  Arthralgia • ataxia • darkening of urine • dizziness • drowsiness • erythema multiforme • headache • hepatitis • jaundice • leucopenia (on prolonged or intensive therapy) • myalgia • pancreatitis • pancytopenia • peripheral neuropathy (on prolonged or intensive therapy) • pruritus • psychiatric disorders • rash • thrombocytopenia • transient epileptiform seizures (on prolonged or intensive therapy) • visual disturbances

- **Frequency not known**
  - With systemic use  Anorexia • aseptic meningitis • furred tongue • gastro-intestinal disturbances • nausia • optic neuropathy • oral mucositis • taste disturbances • vomiting

- With vaginal use  Abnormal vaginal discharge • local irritation • pelvic discomfort • vaginal candidiasis

**Pregnancy**
- With systemic use  Manufacturer advises avoidance of high-dose regimens; use only if potential benefit outweighs risk.

**Breast Feeding**
- With systemic use  Significant amount in milk; manufacturer advises avoid large single doses though otherwise compatible; may give milk a bitter taste.

**Hepatic Impairment**
- With systemic use  In severe liver disease reduce total daily dose to one-third, and give once daily. Use with caution in hepatic encephalopathy.

**Monitoring Requirements**
- With systemic use  Clinical and laboratory monitoring advised if treatment exceeds 10 days.

**Directions for Administration**
- For intravenous infusion, give over 20–30 minutes.

**Prescribing and Dispensing Information**
- Metronidazole is well absorbed orally and the intravenous route is normally reserved for severe infections. Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible.

**Patient and Carer Advice**
- Medicines for Children leaflet: Metronidazole for bacterial infections  www.medicinesforchildren.org.uk/metronidazole-bacterial-infections

**Profession Specific Information**
- Dental practitioners’ formulary

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Tablet**
  - **Cautions and Advisory Labels**  4, 9, 21, 25, 27
  - **Metronidazole (Non-proprietary)**
    - Metronidazole 200 mg Metronidazole 200mg tablets  | 21 tablet PoMs £4.99 DT price = £2.12  | 250 tablet PoMs £19.69
    - Metronidazole 400 mg Metronidazole 400mg tablets  | 21 tablet PoMs £8.10 DT price = £1.47
    - Metronidazole 500 mg Metronidazole 500mg tablets  | 21 tablet PoMs £37.82 DT price = £37.82
    - **Flagyl** (Zentiva)
      - Metronidazole 200 mg Flagyl 200mg tablets  | 21 tablet PoMs £4.49 DT price = £2.12
      - Metronidazole 400 mg Flagyl 400mg tablets  | 14 tablet PoMs £6.34

**Oral Suspension**
- **Cautions and Advisory Labels**  4, 9
  - **Metronidazole (Non-proprietary)**
    - Metronidazole (as Metronidazole benzoate) 40 mg per 1 ml Metronidazole 200mg/5ml oral suspension  | 100 ml PoM £32.93 DT price = £32.93

**Infusion**
- **Electrolytes:** May contain Sodium
  - **Metronidazole (Non-proprietary)**
    - Metronidazole 5 mg per 1 ml Metronidazole 500mg/100ml infusion 100ml bags  | 20 bag PoMs £62.00
    - Metronidazole 500mg/100ml infusion 100ml MacfleX bags  | 1 bag PoMs no price available  | 60 bag PoMs no price available

**Suppository**
- **Cautions and Advisory Labels**  4, 9
  - **Flagyl** (Zentiva)
    - Metronidazole 1 gram Flagyl 1g suppositories  | 10 suppository PoMs £22.06
    - Metronidazole 500 mg Flagyl 500mg suppositories  | 10 suppository PoMs £15.18

**Vaginal Gel**
- **Excipients:** May contain Disodium edetate, hydroxybenzoates (parabens), propylene glycol
  - **Metronidazole (Non-proprietary)**
    - Metronidazole 7.5 mg per 1 gram Metronidazole 0.75% vaginal gel  | 40 gram PoMs no price available DT price = £4.31
    - **Zidoval** (Meda Pharmaceuticals Ltd)
      - Metronidazole 7.5 mg per 1 gram Zidoval 0.75% vaginal gel  | 40 gram PoMs £4.31 DT price = £4.31

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**Tinidazole**

**Drug Action**
- Tinidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa; it has a longer duration of action than metronidazole.

**Indications and Dose**
- **Anaerobic infections**
  - **By mouth**
    - Adult: Initially 2 g, followed by 1 g daily usually for 5–6 days, alternatively 500 mg twice daily usually for 5–6 days

**Bacterial Vaginosis**
- **Acute ulcerative gingivitis**
  - **By Mouth**
    - Adult: 2 g for 1 single dose

**Abdominal Surgery Prophylaxis**
- **By Mouth**
  - Adult: 2 g for 1 single dose, to be administered approximately 12 hours before surgery

**Intestinal amoebiasis**
- **By Mouth**
  - Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 3 days
  - Child 12–17 years: 2 g once daily for 2–3 days
  - Adult: 2 g once daily for 2–3 days

**Amebic involvement of liver**
- **By Mouth**
  - Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 5 days
  - Child 12–17 years: 1.5–2 g once daily for 3–6 days
  - Adult: 1.5–2 g once daily for 3–6 days

**Urogenital trichomoniasis**
- **Giardiasis**
  - **By Mouth**
    - Child 1 month–11 years: 50–75 mg/kg (max. per dose 2 g) for 1 single dose, dose may be repeated once if necessary
    - Child 12–17 years: 2 g for 1 single dose, dose may be repeated once if necessary
    - Adult: 2 g for 1 single dose

**Helicobacter pylori eradication**
- **By Mouth**
  - Adult: (consult local protocol)
Infection

Benzylpenicillin sodium p.

Penicillins

MONITORING REQUIREMENTS

BREAST FEEDING

▶ Very rare

SIDE-EFFECTS

▷ Common or very common Anorexia · furred tongue · gastrointestinal disturbances · nausea · oral mucositis · taste disturbances · vomiting

▷ Very rare Arthralgia · ataxia · darkening of urine · dizziness · drowsiness · erythema multiforme · headache · hepatitis · jaundice · leucopenia (on prolonged or intensive therapy) · myalgia · pancreatitis · pancytopenia · peripheral neuropathy (on prolonged or intensive therapy) · pruritus · psychotic disorders · rash · thrombocytopenia · transient epileptiform seizures (on prolonged or intensive therapy) · visual disturbances

▷ Frequency not known Aseptic meningitis · optic neuropathy

PREGNANCY

Manufacturer advises avoid in first trimester.

BREAST FEEDING

Present in milk—manufacturer advises avoid breast-feeding during and for 3 days after stopping treatment.

MONITORING REQUIREMENTS

Clinical and laboratory monitoring advised if treatment exceeds 10 days.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 4, 9, 21, 25

• Fasigyn (Pfizer Ltd)
  Tinidazole 500 mg Fasigyn 500mg tablets 16 tablet Pouch £11.04
  DT price = £11.04

ANTIBACTERIALS > PENICILLINS

Penicillins

Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin sodium p. 504 (Penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections and also for anthrax, diphtheria, gas-gangrene, leptospirosis, and treatment of Lyme disease. Pneumococci, meningococci, and gonococci which have decreased sensitivity to penicillin have been isolated; benzylpenicillin sodium is no longer the drug of first choice for pneumococcal meningitis. Although benzylpenicillin sodium is effective in the treatment of tetanus, metronidazole p. 499 is preferred. Benzylpenicillin is inactivated by gastric acid and absorption from the gastrointestinal tract is low; therefore it must be given by injection. Benzathine benzylpenicillin is used for the treatment of early syphilis and late latent syphilis; it is given by intramuscular injection.

Phenoxymethylpenicillin p. 505 (Penicillin V) has a similar antibacterial spectrum to benzylpenicillin sodium, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin sodium when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle-cell disease.

Penicillinase-resistant penicillins

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. Flucloxacillin p. 511, however, is not inactivated by these enzymes and is thus effective in infections caused by penicillin-resistant staphylococci, which is the sole indication for its use. Flucloxacillin is acid-stable and can, therefore, be given by mouth as well as by injection. Flucloxacillin is well absorbed from the gut.

Temocillin p. 512 is active against Gram-negative bacteria and is stable against a wide range of beta-lactamases. It should be reserved for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative bacteria, including those resistant to third-generation cephalosporins. Temocillin is not active against Pseudomonas aeruginosa or Acinetobacter spp.

Broad-spectrum penicillins

Ampicillin p. 507 is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases including those produced by Staphylococcus aureus and by common Gram-negative bacilli such as Escherichia coli. Almost all staphylococci, approx. 60% of E. coli strains and approx. 20% of Haemophilus influenzae strains are now resistant. The likelihood of resistance should therefore be considered before using ampicillin for the ‘blind’ treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

Ampicillin is well excreted in the bile and urine. It is principally indicated for the treatment of exacerbations of chronic bronchitis and middle ear infections, both of which may be due to Streptococcus pneumoniae and H. influenzae, and for urinary-tract infections.

Ampicillin can be given by mouth but less than half the dose is absorbed, and absorption is further decreased by the presence of food in the gut.

Maculopapular rashes commonly occur with ampicillin (and amoxicillin p. 506) but are not usually related to true penicillin allergy. They almost always occur in patients with glandular fever; broad-spectrum penicillins should not therefore be used for ‘blind’ treatment of a sore throat.

The risk of rash is also increased in patients with acute or chronic lymphocytic leukaemia or in cytomegalovirus infection.

Ampicillin is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach. Ampicillin may also be used for the treatment of Lyme disease (not licensed).

Co-amoxiclav p. 508 consists of amoxicillin with the betalactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin. These include resistant strains of Staph. aureus, E. coli, and H. influenzae, as well as many Bacteroides and Klebsiella spp. Co-amoxiclav should be reserved for infections likely, or known, to be caused by amoxicillin-resistant beta-lactamase-producing strains.

A combination of ampicillin with flucloxacillin (as co-fluampicil p. 508) is available to treat infections involving either streptococci or staphylococci (e.g. cellulitis).

Antipseudomonal penicillins

Piperacillin, a ureidopenicillin, is only available in combination with the beta-lactamase inhibitor tazobactam. Ticarcillin, a carboxypenicillin, is only available in combination with the beta-lactamase inhibitor clavulanic acid. Both preparations have a broad spectrum of activity against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Piperacillin with tazobactam p. 503 has activity against a wider range of Gram-negative
organisms than ticarcillin with clavulanic acid p. 504 and it is more active against *Pseudomonas aeruginosa*. These antibacterials are not active against MRSA. They are used in the treatment of septicaemia, hospital-acquired pneumonia, and complicated infections involving the urinary tract, skin and soft tissues, or intra-abdomen. For severe pseudomonas infections these antipseudomonal penicillins can be given with an aminoglycoside (e.g. gentamicin p. 479) since they have a synergistic effect.

**Mecillinams**

Pivmecillinam hydrochloride p. 510 has significant activity against many Gram-negative bacteria including *Escherichia coli*, klebsiella, enterobacter, and salmonellae. It is not active against *Pseudomonas aeruginosa* or enterococci. Pivmecillinam hydrochloride is hydrolysed to mecillinam, which is the active drug.

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**Penicillins**

- **DRUG ACTION** The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.
- **CAUTIONS** History of allergy
- **INTERACTIONS** → Appendix 1 (penicillins).
- **SIDE-EFFECTS**
  - Common or very common
    - Anaphylaxis • angioedema • diarrhoea • fever • hypersensitivity reactions • joint pains • rash • serum sickness–like reaction • urticaria
  - Rare
    - Cerebral irritation • CNS toxicity (including convulsions) • coagulation disorders • encephalopathy • haemolytic anaemia • interstitial nephritis • leucopenia • thrombocytopenia
  - Frequency not known
    - Antibiotic–associated colitis
- **SIDE-EFFECTS, FURTHER INFORMATION**
  - CNS toxicity A rare but serious toxic effect of the penicillins is encephalopathy due to cerebral irritation. This may result from excessively high doses or in patients with severe renal failure. The penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.
  - Diarrhoea Diarrhoea frequently occurs during oral penicillin therapy. It is most common with broad-spectrum penicillins, which can also cause antibiotic–associated colitis.
- **ALLERGY AND CROSS-SENSITIVITY** The most important side-effect of the penicillins is hypersensitivity which causes rashes and anaphylaxis and can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of anaphylactic reactions to penicillins. Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin; these individuals should not receive a penicillin. Individuals with a history of a minor rash (i.e. non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other beta-lactam antibiotics (including cephalosporins) can be used in these patients.

Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. Patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics. If a penicillin (or another beta-lactam antibiotic) is essential in an individual with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity.

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**Antibacterials > Penicillins, Antipseudomonal with beta-lactamase inhibitor**

**Piperacillin with tazobactam**

- **INDICATIONS AND DOSE**
  - Hospital-acquired pneumonia | Septicaemia | Complicated infections involving the urinary-tract | Complicated infections involving the skin | Complicated infections involving the soft-tissues
  - By intravenous infusion
    - Adult: 4.5 g every 8 hours; increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections
  - Infections in neutropenic patients
    - By intravenous infusion
    - Adult: 4.5 g every 6 hours

- **CAUTIONS** High doses may lead to hypernatraemia (owing to sodium content of preparations)
- **SIDE-EFFECTS**
  - Common or very common
    - Nausea • vomiting
  - Uncommon
    - Constipation • dyspepsia • headache • hypotension • injection-site reactions • insomnia • jaundice • stomatitis
  - Rare
    - Abdominal pain • eosinophilia • hepatitis
  - Very rare
    - Hypoglycaemia • hypokalaemia • pancytopenia • Steven–Johnson syndrome • toxic epidermal necrolysis
- **PREGNANCY** Manufacturers advise use only if potential benefit outweighs risk.
- **BREAST FEEDING** Trace amount in milk, but appropriate to use.
- **RENAL IMPAIRMENT**
  - Max. 4.5 g every 8 hours if eGFR 20–40 mL/minute/1.73 m². Max. 4.5 g every 12 hours if eGFR less than 20 mL/minute/1.73 m².
- **EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially (2.5 g in 10 mL, 4.5 g in 20 mL) with water for injections, or glucose 5% (*Tazocin*® brand only), or sodium chloride 0.9%, then dilute to 50–150 mL with infusion fluid; give over 30 minutes.
- **PRESCRIBING AND DISPENSING INFORMATION** Dose expressed as a combination of piperacillin and tazobactam (both as sodium salts) in a ratio of 8:1.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion
  - **Powder for solution for injection**
    - **ELECTROLYTES:** May contain Sodium
      - Piperacillin with tazobactam (Non-proprietary)
        - Piperacillin (as Piperacillin sodium) 2 gram, Tazobactam (as Tazobactam sodium) 250 mg
        - Piperacillin 2g / Tazobactam 250mg powder for solution for injection vials | 1 vial(P) £7.96 DT price + £7.91 (Hospital only) | 1 vial(P) £7.91 DT price + £7.91 | 10 vial(P) £10.31-£50.80
Piperacillin (as Piperacillin sodium) 4 gram, Tazobactam (as Tazobactam sodium) 500 mg Piperacillin 4g / Tazobactam 500mg powder for solution for injection vials | 1 vial | £15.77–£15.79
| (hospital only) | 1 vial | £12.90

- **Tazocin** (Pfizer Ltd)
  - Piperacillin (as Piperacillin sodium) 2 gram, Tazobactam (as Tazobactam sodium) 250 mg Tazocin 2.25g powder for solution for injection vials | 1 vial | £6.65 DT price + £7.91
  - Piperacillin (as Piperacillin sodium) 4 gram, Tazobactam (as Tazobactam sodium) 500 mg Tazocin 4.5g powder for solution for injection vials | 1 vial | £15.17 (Hospital only)

### Ticarcillin with clavulanic acid

#### INDICATIONS AND DOSE

**Infections due to *Pseudomonas* and *Proteus* spp.**

- **BY INTRAVENOUS INFUSION**
- **Child:** 3.2 g every 6–8 hours; increased if necessary to 3.2 g every 4 hours, increased frequency used for more severe infections

- **CAUTIONS**
  - High doses may lead to hypernatraemia (owing to sodium content of preparations)

- **CAUTIONS, FURTHER INFORMATION**
  - **Cholestatic jaundice**
    - Cholestatic jaundice is possibly associated with clavulanic acid. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav (amoxicillin, clavulanic acid) than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days.

- **SIDE-EFFECTS**
  - Eosinophilia, haemorrhagic cystitis (more frequent in children), hypokalaemia, injection-site reactions, nausea, Stevens-Johnson syndrome, toxic epidermal necrolysis, vomiting

- **PREGNANCY**
  - Not known to be harmful.

- **BREAST FEEDING**
  - Trace amounts in milk, but appropriate to use.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe impairment.

- **RENAL IMPAIRMENT**
  - Reduce dose to 3.2 g every eight hours if eGFR 30–60 mL/minute/1.73 m²; 1.6 g every eight hours if eGFR 10–30 mL/minute/1.73 m²; 1.6 g every twelve hours if eGFR less than 10 mL/minute/1.73 m². Accumulation of electrolytes contained in preparation can occur in patients with renal failure.

- **EFFECT ON LABORATORY TESTS**
  - False-positive urinary glucose (if tested for reducing substances).

- **DIRECTIONS FOR ADMINISTRATION**
  - For **intravenous infusion** (Timentin®), give intermittently in glucose 5%. Suggested volume (depending on dose) 100–150 mL; give over 30–40 minutes.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Dose is expressed as a combination of ticarcillin (as sodium salt) and clavulanic acid (as potassium salt) in a ratio of 15:1.

#### MEDICINAL FORMS

- **Powder for solution for infusion**
  - **ELECTROLYTES:** May contain potassium, sodium
    - Timentin (GlaxoSmithKline UK Ltd)
      - Clavulanic acid (as Potassium clavulanate) 200 mg, Ticarcillin (as Ticarcillin sodium) 3 gram Timentin 3.2g powder for solution for infusion vials | 4 vial | £21.32

### ANTIBACTERIALS > PENICILLINS, BETA-LACTAMASE SENSITIVE

#### Benzylpenicillin sodium

*(Penicillin G)*

#### INDICATIONS AND DOSE

- **Mild to moderate susceptible infections**
  - **Throat infections**
    - **Otis media**
    - **Cellulitis**
    - **Pneumonia**
      - **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
        - **Adult:** 0.6–1.2 g every 6 hours, dose may be increased if necessary in more serious infections (consult product literature), single doses over 1.2 g to be given by intravenous route only
      - **Endocarditis (in combination with other antibacterial if necessary)**
        - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
        - **Adult:** 1.2 g every 4 hours, increased if necessary to 2.4 g every 4 hours, dose may be increased in infections such as enterococcal endocarditis
      - **Anthrax (in combination with other antibacterials)**
        - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
        - **Adult:** 2.4 g every 4 hours
    - **Intraperitoneal prophylaxis against group B streptococcal infection**
      - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - **Adult:** Initially 3 g for 1 dose, then 1.5 g every 4 hours until delivery
    - **Meningitis | Meningococcal disease**
      - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - **Adult:** 2.4 g every 4 hours
      - **BY INTRAVENOUS INFUSION**
        - **Child:** 50 mg/kg every 4–6 hours (max. per dose 2.4 g every 4 hours)
    - **Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) prior to urgent transfer to hospital**
      - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
        - **Child 1–11 months:** 300 mg, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
        - **Child 1–9 years:** 600 mg, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
        - **Child 10–17 years:** 1.2 g, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
      - **BY INTRAVENOUS INFUSION**
        - **Adult:** 1.2 g, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
        - **Child 1–11 months:** 300 mg, administer as single dose prior to transfer to hospital
        - **Child 1–9 years:** 600 mg, administer as single dose prior to transfer to hospital
        - **Child 10–17 years:** 1.2 g, administer as single dose prior to transfer to hospital
      - **Suspected bacterial meningitis without non-blanching rash where patient cannot be transferred to hospital urgently**
        - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
        - **Child 1–11 months:** 300 mg, administer as single dose prior to transfer to hospital
        - **Child 1–9 years:** 600 mg, administer as single dose prior to transfer to hospital
        - **Child 10–17 years:** 1.2 g, administer as single dose prior to transfer to hospital
      - **Adult:** 1.2 g, administer as single dose prior to transfer to hospital
**Phenoxymethylpenicillin**

(Penicillin V)

### INDICATIONS AND DOSE

**Oral infections** | **Tonsillitis** | **Otitis media** | **Erysipelas** | **Cellulitis**
---|---|---|---|---
**BY MOUTH**
- **Child 1-11 months:** 62.5 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day.
- **Child 1-5 years:** 125 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day.
- **Child 6-11 years:** 250 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day.
- **Child 12-17 years:** 500 mg 4 times a day; increased if necessary up to 1 g 4 times a day.
- **Adult:** 500 mg every 6 hours, increased if necessary up to 1 g every 6 hours.

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**Prevention of recurrence of rheumatic fever**

- **BY MOUTH**
  - **Child 1 month–5 years:** 125 mg twice daily
  - **Child 6-17 years:** 250 mg twice daily
  - **Adult:** 250 mg twice daily

**Prevention of secondary case of invasive group A streptococcal infection**

- **BY MOUTH**
  - **Child 1-11 months:** 62.5 mg every 6 hours for 10 days
  - **Child 1-5 years:** 125 mg every 6 hours for 10 days
  - **Child 6-11 years:** 250 mg every 6 hours for 10 days
  - **Child 12-17 years:** 250–500 mg every 6 hours for 10 days
  - **Adult:** 250–500 mg every 6 hours for 10 days

**Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease**

- **BY MOUTH**
  - **Child 1-11 months:** 62.5 mg twice daily
  - **Child 1-4 years:** 125 mg twice daily
  - **Child 5-17 years:** 250 mg twice daily
  - **Adult:** 250 mg twice daily

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**Phenoxymethylpenicillin**

(Penicillin V)

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include:

- **Powder for solution for injection**
  - **Benzylpenicillin sodium (Non-proprietary)**
    - **Benzylpenicillin sodium 1.2 gram** Phenoxymethylpenicillin 1.2g powder for solution for injection vials | 25 vial | £78.64–£92.01 DT price = £85.33
    - **Benzylpenicillin sodium 600 mg** Phenoxymethylpenicillin 600mg powder for solution for injection vials | 2 vial | £4.67–£5.46 DT price = £5.46

**ELECTROLYTES:** May contain Sodium

- **Benzylpenicillin sodium (as Phenoxymethylpenicillin potassium)**
  - **250 mg** Phenoxymethylpenicillin potassium 250mg tablets | 28 tablet | £5.00 DT price = £1.04

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Phenoxymethylpenicillin (as Phenoxymethylpenicillin potassium)**
  - **25 mg per 1 ml** Phenoxymethylpenicillin 125mg/5ml oral solution | 100 ml | £34.00 DT price = £14.73
  - **50 mg per 1 ml** Phenoxymethylpenicillin 250mg/5ml oral solution sugar free sugar-free | 100 ml | £55.00 DT price = £16.02

**Oral solution**

- **Phenoxymethylpenicillin (as Phenoxymethylpenicillin potassium)**
  - **25 mg per 1 ml** Phenoxymethylpenicillin 125mg/5ml oral solution | 100 ml | £34.00 DT price = £14.73
  - **50 mg per 1 ml** Phenoxymethylpenicillin 250mg/5ml oral solution sugar free sugar-free | 100 ml | £55.00 DT price = £16.02
**Antibacterials > Penicillins, Broad-Spectrum**

**Amoxicillin**

**(Amoxicillin)**

- **Indications and Dose**

  **Susceptible infections (including urinary-tract infections, otitis media, sinusitis, uncomplicated community acquired pneumonia, salmonellosis, oral infections)**

  - **By Mouth**
    - Child 1-11 months: 125 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day
    - Child 1-4 years: 250 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day
    - Child 5-11 years: 500 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day (max. per dose 1 g)
    - Child 12-17 years: 500 mg 3 times a day; increased if necessary up to 1 g every 8 hours, increased dose in severe infections
    - Adult: 500 mg every 8 hours, increased if necessary to 1 g every 8 hours, increased dose used in severe infections
  
  - **By Intramuscular Injection**
    - Adult: 500 mg every 8 hours

  - **By Intravenous Infusion, or by Intravenous Infusion, or by Intravenous Infusion**
    - Adult: 500 mg every 8 hours, increased to 1 g every 8 hours, used increased dose in severe infections

- **Lyme disease (under expert supervision)**

  - **By Mouth**
    - Child 5-17 years: 500 mg 3 times a day for 14–21 days (for 28 days in Lyme arthritis)
    - Adult: 500 mg 3 times a day for 14–21 days (for 28 days in Lyme arthritis)

- **Anthrax (treatment and post-exposure prophylaxis)**

  - **By Mouth**
    - Child (body-weight up to 20 kg): 80 mg/kg daily in 3 divided doses
    - Child (body-weight 20 kg and above): 500 mg 3 times a day
    - Adult: 500 mg 3 times a day

- **Dental abscess (short course)**

  - **By Mouth**
    - Adult: 3 g, then 3 g after 8 hours

- **Urinary-tract infections (short course)**

  - **By Mouth**
    - Adult: 3 g, then 3 g after 10–12 hours

- **Listerial meningitis (in combination with another antibiotic)**

  - **By Intravenous Infusion**
    - Adult: 2 g every 4 hours

- **Endocarditis (in combination with another antibiotic if necessary)**

  - **By Intravenous Infusion**
    - Adult: 2 g every 4 hours

- **Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease—if cover also needed for Haemophilus influenzae**

  - **By Mouth**
    - Child 1 month–4 years: 125 mg twice daily
    - Child 5–11 years: 250 mg twice daily
    - Child 12-17 years: 500 mg twice daily

- **Helicobacter pylori eradication in combination with clarithromycin and esomeprazole; or in combination with clarithromycin and lansoprazole; or in combination with metronidazole and lansoprazole; or in combination with clarithromycin and omeprazole; or in combination with clarithromycin and pantoprazole; or in combination with clarithromycin and rabeprazole**

  - **By Mouth**
    - Adult: 1 g twice daily

**Helicobacter pylori eradication**

- **Unlicensed Use** Amoxicillin doses in BNF Publications may differ from those in product literature.

- **Cautions**

  **General Cautions**

  Acute lymphocytic leukaemia (increased risk of erythematous rashes) - chronic lymphocytic leukaemia (increased risk of erythematous rashes) - cytomegalovirus infection (increased risk of erythematous rashes) - glandular fever (erythematous rashes common) - maintain adequate hydration with high doses (particularly during parenteral therapy)

  **Specific Cautions**

  - With intravenous use Accumulation of sodium can occur with high parenteral doses

- **Side-Effects**

  - **Common or very common** Nausea - vomiting

  **Side-Effects, Further Information**

  Rash If rash occurs, discontinue treatment.

- **Pregnancy** Not known to be harmful.

- **Breast Feeding** Trace amount in milk, but appropriate to use.

- **Renal Impairment** Reduce dose in severe impairment; rashes more common. Risk of crystalluria with high doses (particularly during parenteral therapy). With intravenous use Accumulation of sodium from injection can occur in patients with renal failure.

- **Directions for Administration** For intravenous infusion (Amoxil®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes or give via drip tubing in Glucose 5% or Sodium chloride 0.9%; continuous infusion not usually recommended.

- **Prescribing and Dispensing Information** Flavours of oral liquid formulations and sachets may include peach, strawberry, or lemon.

- **Patient and Carer Advice**

  Patient counselling is advised for Amoxicillin (Amoxil®) paediatric suspension (use of pipette).

  Medicines for Children Leaflet: Amoxicillin for bacterial infections www.medicinesforchildren.org.uk/amoxicillin-bacterial-infections-0

- **Profession Specific Information**

  Dental practitioners' formulary

  Amoxicillin capsules may be prescribed. Amoxicillin sachets may be prescribed as Amoxicillin Oral Powder. Amoxicillin Oral Suspension may be prescribed.

- **Medicinal Forms**

  There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**Cautionary and Advisory Labels**

- **Amoxicillin (Non-proprietary)**

  Amoxicillin (as Amoxicillin trihydrate) 250 mg Amoxicillin 250mg capsules | 15 capsule [PO] £5.00 DT price = £0.77 | 21 capsule [PO] £5.00 DT price = £1.08 | 500 capsule [PO] £120.00

  Amoxicillin (as Amoxicillin trihydrate) 500 mg Amoxicillin 500mg capsules | 15 capsule [PO] £7.50 DT price = £0.90 | 21 capsule [PO] £15.00 DT price = £1.26 | 100 capsule [PO] £75.00
Ampicillin

**INDICATIONS AND DOSE**

Susceptible infections (including bronchitis, urinary-tract infections, otitis media, sinusitis, uncomplicated community-acquired pneumonia, salmonellosis)

- **By mouth**
  - Child 1–11 months: 125 mg 4 times a day; increased if necessary up to 30 mg/kg 4 times a day
  - Child 1–4 years: 250 mg 4 times a day; increased if necessary up to 30 mg/kg 4 times a day
  - Child 5–11 years: 500 mg 4 times a day; increased if necessary up to 30 mg/kg 4 times a day (max. per dose 1 g)
  - Child 12–17 years: 500 mg 4 times a day; increased if necessary to 1 g 4 times a day, use increased dose in severe infection
  - Adult: 0.5–1 g every 6 hours
  - **By intravenous injection, or by intravenous infusion**
  - Adult: 500 mg every 4–6 hours
  - **By intramuscular injection**
  - Adult: 500 mg every 4–6 hours

**Endocarditis** (in combination with another antibiotic if necessary) | **Listerial meningitis** (in combination with another antibiotic)

- **By intravenous infusion**
  - Adult: 2 g every 4 hours

- **UNLICENSED USE** Ampicillin doses in BNF may differ from those in product literature.

**CAUTIONS**

**GENERAL CAUTIONS**

Acute lymphocytic leukaemia (increased risk of erythematous rashes) • chronic lymphocytic leukaemia (increased risk of erythematous rashes) • cytomegalovirus infection (increased risk of erythematous rashes) • glandular fever (erythematous rashes common)

**SPECIFIC CAUTIONS**

- With intravenous use: Accumulation of electrolytes contained in parenteral preparations can occur with high doses

**SIDE-EFFECTS**

- Common or very common: Nausea, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Rash: If rash occurs, discontinue treatment

**PREGNANCY** Not known to be harmful

**RENAL IMPAIRMENT**

- In adults: Reduce dose if eGFR less than 10 mL/minute/1.73 m²; rashes more common
- In children: If estimated glomerular filtration rate less than 10 mL/minute/1.73 m² reduce dose or frequency; rashes more common
- With intravenous use: Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use: Administer at least 30 minutes before food
- With intravenous use: For intravenous infusion (Penbritin®), give intermittently in glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes via drip tubing in glucose 5% or Sodium chloride 0.9%. Continuous infusion not usually recommended.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Ampicillin for bacterial infection www.medicinesforchildren.org.uk/ampicillin-bacterial-infection

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 9, 23
- **Ampicillin (Non-proprietary)**
  - Ampicillin 250 mg | 28 capsule POM £0.92 DT price = £1.08
  - Ampicillin 500 mg | 28 capsule POM £0.92 DT price = £1.26

**Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS** 9, 23
- **Ampicillin (Non-proprietary)**
  - Ampicillin 25 mg per 1 ml | 100 mL POM £29.86 DT price = £29.86
  - Ampicillin 50 mg per 1 ml | 100 mL POM £38.86 DT price = £38.86

**Powder for solution for injection**

- **Ampicillin (Non-proprietary)**
  - Ampicillin (as Ampicillin sodium) 500 mg | 10 vial POM £78.30 DT price = £78.30

**Infection**

BY INTRAMUSCULAR INJECTION

- Amoxicillin (as Amoxicillin trihydrate) 250 mg | 21 capsule POM £0.92 DT price = £1.08
- Amoxicillin (as Amoxicillin trihydrate) 500 mg | 21 capsule POM £0.92 DT price = £1.26

**Oral suspension**

- CAUTIONARY AND ADVISORY LABELS 9
- EXCIPIENTS: May contain Sucrose

- **Ampicillin (Non-proprietary)**
  - Amoxicillin (as Amoxicillin trihydrate) 25 mg per 1 ml | 1 vial POM £1.92
  - Amoxicillin (as Amoxicillin trihydrate) 50 mg per 1 ml | 1 vial POM £4.65
  - Amoxicillin (as Amoxicillin trihydrate) 100 mg per 1 ml | 1 vial POM £8.55

**Powder for solution for injection**

- ELECTROLYTES: May contain Sodium

- **Ampicillin (Non-proprietary)**
  - Amoxicillin (as Ampicillin sodium) 1 gram | 1 vial POM £16.50 DT price = £10.96
  - Amoxicillin (as Ampicillin sodium) 250 mg | 10 vial POM £4.65
  - Amoxicillin (as Ampicillin sodium) 500 mg | 10 vial POM £8.55

**SUGGESTED VOLUME**

- In adults: 500–1000 mL given over 60–90 minutes via drip tubing in glucose 5% or Sodium chloride 0.9%.

**DRUG-INTERACTIONS**

- May increase plasma concentration of other drugs

**PRESENTATION**

- Capsule
- Oral suspension
- Powder for solution for injection

**BNF**

503
Co-fluampicil

**INDICATIONS AND DOSE**

**Mixed infections involving beta-lactamase-producing staphylococci**

- **By mouth**
  - Child 1 month–9 years: 125/250 mg every 6 hours
  - Child 10–17 years: 250/500 mg every 6 hours
  - Adult: 500/500 mg every 6 hours
- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
  - Adult: 250/250 mg every 6 hours

**Severe mixed infections involving beta-lactamase-producing staphylococci**

- **By mouth**
  - Child 1 month–9 years: 250/250 mg every 6 hours
  - Adult: 500/500 mg every 6 hours
- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
  - Adult: 500/500 mg every 6 hours

**INDICATIONS AND DOSE**

- **Co-fluampicil**
  - Mixed infections involving beta-lactamase-producing staphylococci
  - Severe mixed infections involving beta-lactamase-producing staphylococci

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Magnapen®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes. Via drip tubing in Glucose 5% or Sodium chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION**

Dose expressed as a combination of equal parts by mass of flucloxacillin and ampicillin.

**INDICATIONS AND DOSE**

**Flucloxacillin**

**Mixed infections involving beta-lactamase-producing staphylococci**

- **By mouth**
  - Child 1 month–9 years: 125/250 mg every 6 hours
  - Child 10–17 years: 250/500 mg every 6 hours
  - Adult: 500/500 mg every 6 hours
- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
  - Adult: 250/250 mg every 6 hours

**Severe mixed infections involving beta-lactamase-producing staphylococci**

- **By mouth**
  - Child 1 month–9 years: 250/250 mg every 6 hours
  - Adult: 500/500 mg every 6 hours
- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
  - Adult: 500/500 mg every 6 hours

**IMPORTANT SAFETY INFORMATION**

**HEPATIC DISORDERS**

Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Healthcare professionals are reminded that:

- flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin;
- flucloxacillin should be used with caution in patients with hepatic impairment;
- careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials.

**CAUTIONS**

**GENERAL CAUTIONS**

Acute lymphocytic leukaemia (increased risk of erythematous rashes) - chronic lymphocytic leukaemia (increased risk of erythematous rashes) - cytomegalovirus infection (increased risk of erythematous rashes) - glandular fever (erythematous rashes common)

**SPECIFIC CAUTIONS**

- With intravenous use accumulation of electrolytes contained in parenteral preparations can occur with high doses

**SIDE-EFFECTS**

- Common or very common Gastro-intestinal disturbances - nausea - vomiting
- Very rare Cholestatic jaundice - hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Rash If rash occurs, discontinue treatment.
- PREGNANCY Not known to be harmful.
- BREAST FEEDING Trace amount in milk, but appropriate to use.

**HEPATIC IMPAIRMENT** Use with caution.

**RENAL IMPAIRMENT**

- **In adults** Reduce dose if eGFR less than 10 mL/minute/1.73 m²; rashes more common.
- **In children** Reduce dose or frequency if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²; rashes more common.

- With intravenous use Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

**EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).

**ANTIBACTERIALS **

**PENICILLINS, BROAD-SPECTRUM WITH BETA-LACTAMASE INHIBITOR**

**Co-amoxiclav**

**INDICATIONS AND DOSE**

**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate), including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites**

- **By mouth using tablets**
  - Child 12–17 years: 250/125 mg every 8 hours; increased to 500/250 mg every 8 hours, increased dose used for severe infection
  - Adult: 250/125 mg every 8 hours; increased to 500/250 mg every 8 hours, increased dose used for severe infection
- **By intravenous injection, or by intravenous infusion**
  - Child 2–3 months: 30 mg/kg every 12 hours
  - Child 3 months–17 years: 30 mg/kg every 8 hours (max. per dose 1.2 g every 8 hours)
  - Adult: 1.2 g every 8 hours

**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites (doses for 125/31 suspension)**

- **By mouth using oral suspension**
  - Child 1–11 months: 0.25 mL/kg/3 times a day, dose doubled in severe infection
  - Child 1–5 years: 0.25 mL/kg/3 times a day, alternatively 5 mL 3 times a day, dose doubled in severe infection

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Magnapen®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes. Via drip tubing in Glucose 5% or Sodium chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION**

Dose expressed as a combination of equal parts by mass of flucloxacillin and ampicillin.

**INDICATIONS AND DOSE**

- **Co-amoxiclav**
  - (Non-proprietary)
    - Ampicillin (as Amoxicillin trihydrate) 25 mg per 1 mL, Flucloxacillin (as Flucloxacillin sodium) 250 mg Co-fluampicil
  - 250 mg Co-fluampicil 250mg/250mg capsules [28 capsule (£10.31 DT price = £2.06] 100 capsule (£9.47–£42.99

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 9, 22

- **Co-amoxiclav** (Non-proprietary)
  - Ampicillin (as Amoxicillin trihydrate) 25 mg per 1 mL, Flucloxacillin (as Flucloxacillin sodium magnesium) 25 mg per 1 mL Co-fluampicil
  - 125mg/125mg/5ml oral suspension | 100 ml (£23.93 DT price = £23.93

**Powder for solution for injection**

**ELECTROLYTES: May contain Sodium**

- **Co-amoxiclav** (Non-proprietary)
  - Ampicillin (as Amoxicillin sodium) 250 mg, Flucloxacillin (Flucloxacillin sodium) 250 mg Co-fluampicil 250mg/250mg powder for solution for injection vials | 10 vial (£13.33

**ANTIBACTERIALS**

**PENICILLINS, BROAD-SPECTRUM WITH BETA-LACTAMASE INHIBITOR**

**Co-amoxiclav**

**INDICATIONS AND DOSE**

**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate), including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites**

- **By mouth using tablets**
  - Child 12–17 years: 250/125 mg every 8 hours; increased to 500/250 mg every 8 hours, increased dose used for severe infection
  - Adult: 250/125 mg every 8 hours; increased to 500/250 mg every 8 hours, increased dose used for severe infection
- **By intravenous injection, or by intravenous infusion**
  - Child 2–3 months: 30 mg/kg every 12 hours
  - Child 3 months–17 years: 30 mg/kg every 8 hours (max. per dose 1.2 g every 8 hours)
  - Adult: 1.2 g every 8 hours

**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites (doses for 125/31 suspension)**

- **By mouth using oral suspension**
  - Child 1–11 months: 0.25 mL/kg/3 times a day, dose doubled in severe infection
  - Child 1–5 years: 0.25 mL/kg/3 times a day, alternatively 5 mL 3 times a day, dose doubled in severe infection

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Magnapen®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes. Via drip tubing in Glucose 5% or Sodium chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION**

Dose expressed as a combination of equal parts by mass of flucloxacillin and ampicillin.
Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, bone and joint infections, genitourinary and abdominal infections, cellulitis, animal bites (doses for 250/62 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 6–11 years: 0.15 mL/kilogram 3 times a day, alternatively 5 mL 3 times a day, dose doubled in severe infection
  - Child 2 months–1 year: 0.15 mL/kilogram twice daily, doubled in severe infection
  - Child 2–6 years (body-weight 13–21 kg): 2.5 mL twice daily, doubled in severe infection
  - Child 7–12 years (body-weight 22–40 kg): 5 mL twice daily, doubled in severe infection
  - Child 12–17 years (body-weight 41 kg and above): 10 mL twice daily; increased if necessary to 10 mL 3 times a day, increased frequency to be used in severe infection
  - Adult: 10 mL twice daily; increased if necessary to 10 mL 3 times a day, increased frequency to be used in severe infection

**Severe dental infection with spreading cellulitis** | **Dental infection not responding to first-line antibacterial**

- **BY MOUTH USING TABLETS**
  - Child 12–17 years: 250/125 mg every 8 hours for 5 days
  - Adult: 250/125 mg every 8 hours for 5 days

**Surgical prophylaxis**

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 1.2 g, to be administered up to 30 minutes before the procedure, then 1.2 g every 8 hours for up to 2–3 further doses in high risk procedures

**DOSE EQUIVALENCE AND CONVERSION**

- Doses are expressed as co-amoxiclav.
- A mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively.

- **CONTRA-INDICATIONS** History of co-amoxiclav–associated jaundice or hepatic dysfunction
- **CAUTIONS**
  - **GENERAL CAUTIONS** Acute lymphocytic leukaemia (increased risk of erythematous rashes) · chronic lymphocytic leukaemia (increased risk of erythematous rashes) · cytomegalovirus infection (increased risk of erythematous rashes) · glandular fever (erythematous rashes common) · maintain adequate hydration with high doses (particularly during parenteral therapy)
  - **SPECIFIC CAUTIONS**
  - With intravenous use Accumulation of electrolytes contained in parenteral preparations can occur with high doses

- **CAUTIONS, FURTHER INFORMATION** Cholestatic jaundice Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days.

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common Cholestatic jaundice · hepatitis · nausea · vomiting
    - Rare Dizziness · headache · prolongation of bleeding time
    - Frequency not known Exfoliative dermatitis · Steven–Johnson syndrome · toxic epidermal necrolysis · vasculitis
  - **SPECIFIC SIDE-EFFECTS**
    - Rash If rash occurs, discontinue treatment.
    - **PREGNANCY** Not known to be harmful.
    - **BREAST FEEDING** Trace amount in milk, but appropriate to use.
  - **HEPATIC IMPAIRMENT** Monitor liver function in liver disease.
  - **RENAL IMPAIRMENT** Risk of crystalluria with high doses (particularly during parenteral therapy).
    - With oral use in adults Co-amoxiclav 250/125 tablets or 500/125 tablets: if eGFR 10–30 mL/minute/1.73 m², one 250/125 strength tablet every 12 hours or one 500/125 strength tablet every 12 hours; if eGFR less than 10 mL/minute/1.73 m², one 250/125 strength tablet every 24 hours or one 500/125 strength tablet every 24 hours.
    - Co-amoxiclav 400/57 suspension: avoid if eGFR less than 30 mL/minute/1.73 m².
    - With intravenous use Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.
    - With intravenous use in adults Co-amoxiclav injection (expressed as co-amoxiclav): if eGFR 10–30 mL/minute/1.73 m², 1.2 g initially, then 600 mg every 12 hours; if eGFR less than 10 mL/minute/1.73 m², 1.2 g initially, then 600 mg every 24 hours.
    - With oral use in children Co-amoxiclav 125/31 suspension, 250/62 suspension, 250/125 tablets, or 500/125 tablets: use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Use the normal dose recommended for mild or moderate infections every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².
    - Co-amoxiclav 400/57 suspension: avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².
    - With intravenous use in children Co-amoxiclav injection: use normal initial dose and then use half normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; use normal initial dose and then use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children For intravenous infusion, dilute reconstituted solution to a concentration of 10 mg/mL with Sodium Chloride 0.9%; give intermittently over 30–40 minutes. For intravenous injection, administer over 3–4 minutes.
  - With intravenous use in adults For intravenous infusion (Augmentin®), give intermittently in Sodium chloride 0.9%. Reconstitute 600 mg initially with 10 mL water for injections, then dilute with 50 mL infusion fluid; reconstitute 1.2 g initially with 20 mL water for injections, then dilute with 100 mL infusion fluid; give over 30–40 minutes. For intravenous injection, administer over 3–4 minutes. Via drip tubing in Sodium chloride 0.9%.
  - **PRESCRIBING AND DISPENSING INFORMATION** Doses are expressed as co-amoxiclav: a mixture of amoxicillin (as the
trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively.

- With oral use Flavours of oral liquid formulations may include raspberry and orange.

- **PATIENT AND CARER ADVICE**
  Medicines for Children leaflet: Co-amoxiclav for bacterial infections [www.medicinesforchildren.org.uk/co-amoxiclav-bacterial-infections-0](http://www.medicinesforchildren.org.uk/co-amoxiclav-bacterial-infections-0)

### MEDICINAL FORMS

#### With oral use

- **Augmentin-Duo**
- **EXCIPIENTS:** May contain Aspartame

- **CAUTIONARY AND ADVISORY LABELS**
  - Oral suspension
  - **Augmentin**
  - **Co-amoxiclav (Non-proprietary)**

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Co-amoxiclav 250/125 Tablets may be prescribed.
  - Co-amoxiclav 125/31 Suspension may be prescribed.
  - Co-amoxiclav 250/62 Suspension may be prescribed.

- **MEDICINAL FORMS**

  There can be variation in the licensing of the same medicines containing the same drug. Forms available from special-order manufacturers include: infusion

### Tablet

**CAUTIONARY AND ADVISORY LABELS 9**

- **Co-amoxiclav (Non-proprietary)**
  - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 250 mg Co-amoxiclav 250mg/125mg tablets | 21 tablet [Pom] £6.00 DT price = £2.03 | 100 tablet [Pom] no price available
  - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 500 mg Co-amoxiclav 500mg/125mg tablets | 21 tablet [Pom] £12.00 DT price = £1.98
  - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 875 mg Co-amoxiclav 875mg/125mg tablets | 14 tablet [Pom] £18.00 DT price = £8.60
  - **Augmentin** (GlaxoSmithKline UK Ltd)
    - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 250 mg Augmentin 375mg tablets | 21 tablet [Pom] £5.03 DT price = £2.03
    - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 500 mg Augmentin 625mg tablets | 21 tablet [Pom] £9.60 DT price = £1.98

- **Oral suspension**

  **CAUTIONARY AND ADVISORY LABELS 9**

  - **Co-amoxiclav (Non-proprietary)**
    - Clavulanic acid (as Potassium clavulanate) 6.25 mg per 1 ml, Amoxicillin (as Amoxicillin trihydrate) 25 mg per 1 ml Co-amoxiclav 250mg/5ml oral suspension | 100 ml [Ps] £5.00 DT price = £5.00
    - Clavulanic acid (as Potassium clavulanate) 12.5 mg per 1 ml, Amoxicillin (as Amoxicillin trihydrate) 50 mg per 1 ml Co-amoxiclav 500mg/5ml oral suspension | 100 ml [Ps] £10.00 DT price = £5.00
    - Clavulanic acid (as Potassium clavulanate) 200 mg, Amoxicillin (as Amoxicillin trihydrate) 600 mg Co-amoxiclav 600mg/5ml oral suspension | 100 ml [Ps] £20.00 DT price = £5.00
    - **Augmentin** (GlaxoSmithKline UK Ltd)
      - Clavulanic acid (as Potassium clavulanate) 1.14 mg per 1 ml, Amoxicillin (as Amoxicillin trihydrate) 8.75 mg per 1 ml Augmentin 8.75mg tablets | 50 tablet [Ps] £1.14 DT price = £0.29
      - Clavulanic acid (as Potassium clavulanate) 2.20 mg per 1 ml, Amoxicillin (as Amoxicillin trihydrate) 17.5 mg per 1 ml Augmentin 17.5mg tablets | 50 tablet [Pom] £2.20 DT price = £0.29

### Powder for solution for injection

**ELECTROLYTES:** May contain Potassium, sodium

- **Co-amoxiclav (Non-proprietary)**
  - Clavulanic acid (as Potassium clavulanate) 100 mg, Amoxicillin (as Amoxicillin trihydrate) 500 mg Co-amoxiclav 500mg/100mg powder for solution for injection vials | 10 vial [Pom] £11.39–£14.90
  - Clavulanic acid (as Potassium clavulanate) 200 mg, Amoxicillin (as Amoxicillin sodium) 1000 mg Co-amoxiclav 1000mg/200mg powder for solution for injection vials | 10 vial [Pom] £29.70

- **Augmentin Intravenous** (GlaxoSmithKline UK Ltd)
  - Clavulanic acid (as Potassium clavulanate) 100 mg, Amoxicillin (as Amoxicillin sodium) 500 mg Augmentin Intravenous 600mg powder for solution for injection vials | 10 vial [Pom] £10.60
  - Clavulanic acid (as Potassium clavulanate) 200 mg, Amoxicillin (as Amoxicillin sodium) 1000 mg Augmentin Intravenous 1.2g powder for solution for injection vials | 10 vial [Pom] £10.60

## Pivmecillinam hydrochloride

### INDICATIONS AND DOSE

**Acute uncomplicated cystitis**

- **BY MOUTH**
  - Child (body-weight 40 kg and above): Initially 400 mg for 1 dose, then 200 mg every 8 hours for 3 days
  - Adult (body-weight 40 kg and above): Initially 400 mg for 1 dose, then 200 mg every 8 hours for 3 days

**Chronic or recurrent bacteriuria**

- **BY MOUTH**
  - Child (body-weight 40 kg and above): 400 mg every 6–8 hours
  - Adult (body-weight 40 kg and above): 400 mg every 6–8 hours

**Urinary-tract infections**

- **BY MOUTH**
  - Child (body-weight up to 40 kg): 5–10 mg/kg every 6 hours, alternatively 20–40 mg/kg daily in 3 divided doses

### UNLICENSED USE

Not licensed for use in children under 3 months.

### CONTRA-INDICATIONS

- Carnitine deficiency - gastrointestinal obstruction - infants under 3 months - oesophageal strictures

### CAUTIONS

- Avoid in acute porphyrias p. 930

### SIDE-EFFECTS

- **Common or very common** Abdominal pain - dizziness - headache - nausea - vomiting

- **Frequency not known** Mouth ulcers - oesophagitis - reduced serum and total body carnitine (especially with long-term or repeated use)

### PREGNANCY

- Not known to be harmful, but manufacturer advises avoid.

### BREAST FEEDING

- Trace amount in milk, but inappropriate to use.

### MONITORING REQUIREMENTS

- Liver and renal function tests required in long-term use.

### EFFECT ON LABORATORY TESTS

- False-positive urinary glucose (if tested for reducing substances).

### DIRECTIONS FOR ADMINISTRATION

- Tablets should be swallowed whole with plenty of fluid during meals while sitting or standing.

- **PATIENT AND CARER ADVICE** Patient counselling is advised on administration of pivmecillinam hydrochloride tablets (posture).
Flucloxacillin

**INDICATIONS AND DOSE**

Infections due to beta-lactamase-producing staphylococci including otitis externa | Adjunct in pneumonia | Adjunct in impetigo | Adjunct in cellulitis

- **BY MOUTH**
  - Child 1 month-1 year: 62.5–125 mg 4 times a day
  - Child 2–9 years: 125–250 mg 4 times a day
  - Child 10–17 years: 250–500 mg 4 times a day
  - Adult: 250–500 mg 4 times a day

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 250–500 mg every 6 hours

- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 0.25–2 g every 6 hours

Endocarditis (in combination with other antibiotic if necessary)

- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 85 kg): 8 g daily in 4 divided doses
  - Adult (body-weight 85 kg and above): 12 g daily in 6 divided doses

Osteomyelitis

- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Up to 8 g daily in 3–4 divided doses

Surgical prophylaxis

- **INITIALLY BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 1–2 g, to be administered up to 30 minutes before the procedure, then (by mouth or by intramuscular injection or by slow intravenous injection or by intravenous infusion) 500 mg every 6 hours if required for up to 4 further doses in high risk procedures

Staphylococcal lung infection in cystic fibrosis

- **BY MOUTH**
  - Child: 25 mg/kg 4 times a day (max. per dose 1 g), alternatively 100 mg/kg daily in 3 divided doses; maximum 4 g per day

Prevention of *Staphylococcus aureus* lung infection in cystic fibrosis—primary prevention

- **BY MOUTH**
  - Child 1 month-3 years: 125 mg twice daily

Prevention of *Staphylococcus aureus* lung infection in cystic fibrosis—secondary prevention

- **BY MOUTH**
  - Child: 50 mg/kg twice daily (max. per dose 1 g twice daily)

**UNLICENSED USE** Flucloxacillin doses in the BNF may differ from those in product literature.

**SIDE-EFFECTS**

- Common or very common: Gastrointestinal disturbances
- Very rare: Cholestatic jaundice - hepatitis
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Trace amounts in milk, but appropriate to use.

**HEPATIC IMPAIRMENT** Use with caution.

**RENAL IMPAIRMENT**

- In adults: Reduce dose if eGFR less than 10 mL/minute/1.73 m².
- In children: Use normal dose every 8 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².
- With intravenous use: Accumulation of electrolytes can occur in patients with renal failure.

**EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (FloxaPen®), give intermittently in Glucose 5% or Sodium chloride 0.9%; suggested volume 100 mL given over 30–60 minutes. via drip tubing in Glucose 5% or Sodium chloride 0.9%; continuous infusion not usually recommended.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Flucloxacillin for bacterial infections www.medicinesforchildren.org.uk/flucloxacillin-for-bacterial-infections

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

**Capsule**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage</th>
<th>Price</th>
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<tbody>
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<td>Flucloxacillin sodium 250 mg</td>
<td>20 capsule (PO)</td>
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<tr>
<td>Flucloxacillin sodium 500 mg</td>
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**Oral solution**

<table>
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<th>Formulation</th>
<th>Dosage</th>
<th>Price</th>
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</thead>
<tbody>
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<td>Flucloxacillin sodium 25 mg</td>
<td>1 ml</td>
<td>£20.99</td>
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<tr>
<td>Flucloxacillin sodium 50 mg</td>
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<td>£38.94</td>
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</table>

**Powder for solution for injection**

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<th>Formulation</th>
<th>Dosage</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin sodium 250 mg</td>
<td>10 vial (PO)</td>
<td>£10.43</td>
</tr>
</tbody>
</table>
Flucloxacillin (as Flucloxacillin sodium) 500 mg

Flucloxacillin 500mg powder for solution for injection vials | 10 vial £20.85–£24.50

Flucloxacillin (as Flucloxacillin sodium) 1 gram

Flucloxacillin 1g powder for solution for injection vials | 10 vial £41.75–£49.00

### Temocillin

- **INDICATIONS AND DOSE**
  - Septicaemia | Urinary-tract infections | Lower respiratory-tract infections caused by susceptible Gram-negative bacteria
  - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 1–2 g every 12 hours, give over 3–4 minutes when administered by intravenous injection

- **CAUTIONS** Accumulation of sodium from injection can occur with high doses
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Trace amounts in milk.
- **RENAI IMPAIRMENT** 1 g every 12 hours if eGFR 30–60 mL/minute/1.73 m², 1 g every 24 hours if eGFR 10–30 mL/minute/1.73 m², 1 g every 48 hours or 500 mg every 24 hours if eGFR less than 10 mL/minute/1.73 m². Accumulation of sodium from injection can occur in patients with renal failure.

### DIRECTIONS FOR ADMINISTRATION

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- Adult: 1–2 g every 12 hours, give over 3–4 minutes when administered by intravenous injection

- **EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Negaban®), give intermittently in Glucose 5% or 10% or Sodium chloride 0.9%. Reconstitute 1 g with 10 mL water for injections then dilute with 50–150 mL infusion fluid; give over 30–40 minutes.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for injection**
    - ELECTROLYTES: May contain Sodium
    - **Negaban** (Eumedica Pharmaceuticals)
      - Temocillin (as Temocillin sodium) 1 gram
        - Negaban 1g powder for solution for injection vials | 1 vial £25.45

### ANTIBACTERIALS

- **Colistimethate sodium** (Colistin sulphomethate sodium)
  - **DRUG ACTION** The polymyxin antibiotic, colistimethate sodium (colistin sulphomethate sodium), is active against Gram-negative organisms including *Pseudomonas aeruginosa, Acinetobacter baumanii*, and *Klebsiella pneumoniae*. It is not absorbed by mouth and thus needs to be given by injection for a systemic effect.

  - **INDICATIONS AND DOSE**
    - Gram-negative infections resistant to other antibacterials, including those caused by *Pseudomonas aeruginosa, Acinetobacter baumanii* and *Klebsiella pneumoniae*
    - **BY INTRAVENOUS INFUSION**
      - Adult (body-weight up to 60 kg): 50 000–75 000 units/kg daily in 3 divided doses, to be administered into a totally implantable venous access device when giving via slow intravenous injection
      - Adult (body-weight 60 kg and above): 1–2 million units every 8 hours, to be administered into a totally implantable venous access device when giving via slow intravenous injection; maximum 6 million units per day

  - **CONTRA-INDICATIONS** Myasthenia gravis
  - **CAUTIONS**
    - Acute porphyrias p. 930
  - **SPECIFIC CAUTIONS**
    - When used by inhalation Severe haemoptysis—risk of further haemorrhage
  - **INTERACTIONS** → Appendix 1 (polymyxins).
  - **SIDE-EFFECTS**
    - Common or very common
    - When used by inhalation Bronchospasm · cough · dysphonia · nausea · sore mouth · Sore throat · taste disturbances · vomiting
    - Uncommon
      - When used by inhalation Hypersalivation · thirst
    - Rare
      - With intravenous use Vasomotor instability
    - Frequency not known
      - With intravenous use Apnoea · confusion · headache · muscle weakness · nephrotoxicity · neurotoxicity reported especially with excessive doses · perioral paraesthesia · peripheral paraesthesia · psychosis · rash · slurred speech · vertigo · visual disturbances
  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Dose-related side-effects The major adverse effects are dose-related neurotoxicity and nephrotoxicity.
  - **PREGNANCY**
    - When used by inhalation Clinical use suggests probably safe.
    - With intravenous use Use only if potential benefit outweighs risk.
  - **BREAST FEEDING** Present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk).

### Adjunct to standard antibacterial therapy for *Pseudomonas aeruginosa* infection in cystic fibrosis

- **BY INHALATION OF NEBULISED SOLUTION**
  - Adult: 1–2 million units twice daily, adjusted according to response, increased to 2 million units 3 times daily for subsequent respiratory isolates of *Pseudomonas aeruginosa*

- **BY INHALATION OF POWDER**
  - Adult: 1.66 million units twice daily

### PROMIXIN® INJECTION

- **Gram-negative infections resistant to other antibacterials, including those caused by *Pseudomonas aeruginosa, Acinetobacter baumanii*, and *Klebsiella pneumoniae***
  - **BY SLOW INTRAVENOUS INFUSION, OR BY INTRAVENOUS INFUSION**
  - Adult: 9 million units daily in 2–3 divided doses, to be administered into a totally implantable venous access device when giving via slow intravenous injection, an initial loading dose of 9 million units (up to max. 12 million units, if adequate renal function) should be used in those who are critically ill, consult product literature for details

### PROMIXIN® NEBULISER SOLUTION

- **Management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis**
  - **BY INHALATION OF NEBULISED SOLUTION**
    - Child 2-17 years: 1–2 million units 2–3 times a day, for specific advice on administration using nebulisers—consult product literature; maximum 6 million units per day
    - Adult: 1–2 million units 2–3 times a day, for specific advice on administration using nebulisers—consult product literature; maximum 6 million units per day
RENAL IMPAIRMENT

- With intravenous use: Reduce dose. Monitor plasma colistimethate sodium concentration during parenteral treatment—consult product literature. Recommended ‘peak’ plasma colistimethate sodium concentration (approx. 1 hour after intravenous injection or infusion) 5–15 mg/litre; pre-dose (‘trough’) concentration 2–6 mg/litre.

MONITORING REQUIREMENTS

- With intravenous use: Monitor renal function.
- When used by inhalation: Measure lung function before and after initial dose of colistimethate sodium and monitor for bronchospasm; if bronchospasm occurs in a patient not using a bronchodilator, repeat test using a bronchodilator before the dose of colistimethate sodium.

DIRECTIONS FOR ADMINISTRATION

- When used by inhalation: Other inhaled drugs should be administered before colistimethate sodium. For nebulisation: Administer required dose in 2–4 mL of sodium chloride 0.9% (or water for injections) or a 1:1 mixture of sodium chloride 0.9% and water for injection.
- With intravenous use: For intravenous infusion (Colomycin®, Promixin®), give intermittently in Sodium chloride 0.9% (or Glucose 5% for Promixin® brand only); dilute with 50 mL infusion fluid and give over 30 minutes.

COLOMYCIN® Injection may be used for nebulisation; administer required dose in 2–4 mL of sodium chloride 0.9%, (or water for injections) or a 1:1 mixture of sodium chloride 0.9% and water for injection.

PRESCRIBING AND DISPENSING INFORMATION

Colistimethate sodium is included in some preparations for topical application.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness, confusion and visual disturbances.

- When used by inhalation: Patient should be advised to rinse mouth with water after each dose of dry powder inhalation. Patients or carers should be given advice on how to administer colistimethate sodium; first dose should be given under medical supervision.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Colistimethate sodium by dry powder inhalation for pseudomonal lung infection in cystic fibrosis (March 2013)

NICE TA276

Colistimethate sodium dry powder for inhalation is recommended for chronic pulmonary infection caused by Pseudomonas aeruginosa in patients with cystic fibrosis who would benefit from continued treatment, but do not tolerate the drug in its nebulised form. The manufacturer must provide colistimethate sodium dry powder for inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS. Patients currently receiving colistimethate sodium dry powder for inhalation can continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA276

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Colomycin® (Forest Laboratories UK Ltd)
  Colistin sulfate IS000000 unit Colomycin 1.5 million unit tablets | 50 tablet (P) £55.00

Powder for solution for injection

ELECTROLYTES: May contain Sodium

- Colistimethate sodium (Non-proprietary)
  Colistimethate sodium 1000000 unit Colistimethate sodium 1 million unit powder for solution for injection vials | 10 vial (P) £15.75 | 10 vial (P) £16.79 (Hospital only)
  Colomycin® (Teva UK Ltd)
  Colistimethate sodium 1000000 unit Colomycin 1 million unit powder for solution for injection vials | 10 vial (P) £18.00
  Colistimethate sodium 2000000 unit Colomycin 2 million unit powder for solution for injection vials | 10 vial (P) £22.46
  Promixin® (Profile Pharma Ltd)
  Colistimethate sodium 1000000 unit Promixin 1 million unit powder for solution for injection vials | 10 vial (P) £30.00 (Hospital only)

Powder for nebuliser solution

- ColFin® (Pari Medical Ltd)
  Colimistatum 1 millio unit Colistat 1 million unit powder for nebuliser solution for injection vials | 56 unit dose (P) £180.53
  Colmistatum 2 million unit Colimistat 2 million unit powder for nebuliser solution for injection vials | 56 unit dose (P) £261.72
  Promixin® (Profile Pharma Ltd)
  Colimistatum 1 million unit Promixin 1 million unit powder for nebuliser solution unit dose vials | 30 unit dose (P) £168.00 DT price = £168.00

ANTIBACTERIALS > QUINOLONES

Quinolones

Overview

Nalidixic acid p. 517 and norfloxacin p. 517 are effective in uncomplicated urinary-tract infections.

Ciprofloxacin p. 514 is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as Streptococcus pneumoniae and Enterococcus faecalis; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), urinary-tract infections, infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.

Ofloxacin p. 517 is used for urinary-tract infections, lower respiratory-tract infections, gonorrhoea, and nongonococcal urethritis and cervicitis.

Levofloxacin p. 515 is active against Gram-positive and Gram-negative organisms. It has greater activity against pneumococci than ciprofloxacin. Levofloxacin is licensed for the treatment of acute sinusitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia, but it should only be considered for these infections when first-line treatment cannot be used or is ineffective. Levofloxacin is also licensed for the treatment of urinary-tract infections.

Although ciprofloxacin, levofloxacin, moxifloxacin p. 516, and ofloxacin are licensed for skin and soft-tissue infections, many staphylococci are resistant to the quinolones and their use should be avoided in MRSA infections.

Moxifloxacin should be reserved for the treatment of sinusitis, community-acquired pneumonia, exacerbations of chronic bronchitis, mild to moderate pelvic inflammatory disease, or complicated skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials. It has been associated with QT interval prolongation and life-threatening threatening hepatotoxicity. Moxifloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against Gram-positive organisms, including pneumococci, than ciprofloxacin. Moxifloxacin is not active
Quinolones

**IMPORTANT SAFETY INFORMATION**

The CSM has warned that quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them.

**TENDON DAMAGE**

Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping a quinolone. Healthcare professionals are reminded that:

- quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
- patients over 60 years of age are more prone to tendon damage;
- the risk of tendon damage is increased by the concomitant use of corticosteroids;
- if tendinitis is suspected, the quinolone should be discontinued immediately.

**CONTRA-INDICATIONS**  History of tendon disorders related to quinolone use

**CAUTIONS**  Can prolong the QT interval - children or adolescents (arthropathy has developed in weight-bearing joints in young animals) - conditions that predispose to seizures - exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs) - G6PD deficiency - history of epilepsy - myasthenia gravis (risk of exacerbation)

**CAUTIONS, FURTHER INFORMATION**

- **in children**  Quinolones cause arthropathy in the weight-bearing joints of immature animals and are therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of either ciprofloxacin or nalidixic acid may be justified in children.

**INTERACTIONS**  Appendix 1 (quinolones).

**SIDE-EFFECTS**

- **Common or very common**  Diarrhoea - dizziness - headache - nausea - vomiting
- **Uncommon**  Abdominal pain - anorexia - anxiety - arthralgia - asthenia - blood disorders - confusion - depression - disturbances in taste - disturbances in vision - dyspepsia - eosinophilia - hallucinations - leucopenia - myalgia - rash - sleep disturbances - thrombocytopenia - tremor
- **Rare**  Antibiotic-associated colitis - convulsions - disturbances in hearing - disturbances in smell - dyspnoea - hepatic dysfunction - hepatitis - hypotension - interstitial nephritis - jaundice - photosensitivity - psychoses - renal failure - symptoms of peripheral neuropathy (sometimes irreversible) - tendon damage - tendon inflammation - vasculitis
- **Very rare**  Stevens-Johnson syndrome - toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

The drug should be discontinued if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.

**ALLERGY AND CROSS-SENSITIVITY**  Use of quinolones contra-indicated in quinolone hypersensitivity.

**PREGNANCY**  Avoid in pregnancy—shown to cause arthropathy in animal studies; safer alternatives are available.

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**Ciprofloxacin**

**INDICATIONS AND DOSE**

**Fistulating Crohn’s disease**

- **BY MOUTH**
  - Adult: 500 mg twice daily

**Respiratory-tract infections**

- **BY MOUTH**
  - Adult: 500–750 mg twice daily
  - **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Pseudomonal lower respiratory-tract infection in cystic fibrosis**

- **BY MOUTH**
  - Adult: 750 mg twice daily

**Urinary-tract infections**

- **BY MOUTH**
  - Adult: 250–750 mg twice daily
  - **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Acute uncomplicated cystitis in women**

- **BY MOUTH**
  - Adult: 250 mg twice daily for 3 days

**Acute or chronic prostatitis**

- **BY MOUTH**
  - Adult: 500 mg twice daily for 28 days
  - **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Gonorrhoea**

- **BY MOUTH**
  - Adult: 500 mg for 1 dose

**Most other infections**

- **BY MOUTH**
  - Adult: Initially 500 mg twice daily; increased to 750 mg twice daily, in severe or deep-seated infection
  - **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Surgical prophylaxis**

- **BY MOUTH**
  - Adult: 750 mg, to be taken 60 minutes before procedure

**Anthrax (treatment and post-exposure prophylaxis)**

- **BY MOUTH**
  - Adult: 500 mg twice daily
  - **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 12 hours, to be given over 60 minutes

**Prevention of secondary case of meningococcal meningitis**

- **BY MOUTH**
  - Child 1 month–4 years: 30 mg/kg (max. per dose 125 mg) for 1 dose
  - Child 5–11 years: 250 mg for 1 dose
  - Child 12–17 years: 500 mg for 1 dose
  - Adult: 500 mg for 1 dose

**UNLICENSED USE**


**CAUTIONS**  Acute myocardial infarction (risk factor for QT interval prolongation) - avoid excessive alkalinity of urine (risk of crystalluria) - bradycardia (risk factor for QT interval prolongation) - congenital long QT syndrome (risk factor for QT interval prolongation) - electrolyte disturbances (risk factor for QT interval prolongation) - ensure adequate fluid intake (risk of crystalluria) - heart
failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) - history of symptomatic arrhythmias (risk factor for QT interval prolongation)

- INTERACTIONS Caution if concomitant use with other drugs known to prolong the QT interval.

- SIDE-EFFECTS
  - Common or very common Flatulence
  - Rare Abnormal dreams - chest pain - dysphagia - dyspnoea - erythema nodosum - hot flushes - hyperglycaemia - hypoglycaemia - oedema - pancreatitis - sweating - syncope - tachycardia
  - Very rare Intracranial hypertension - movement disorders - tenosynovitis - tinnitus - vasculitis (in children)

- EFFECTS on the FLUID ELECTROLYTES: May contain Sodium

- PREGNANCY A single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis.

- BREAST FEEDING Amount too small to be harmful but manufacturer advises avoid.

- RECURRENT IMPAIRMENT
  - With oral use in adults Give 250–500 mg every 12 hours if eGFR 30–60 mL/minute/1.73 m² (every 24 hours if eGFR less than 30 mL/minute/1.73 m²).
  - With intravenous use in adults Give (200 mg over 30 minutes), 200–400 mg every 12 hours if eGFR 30–60 mL/minute/1.73 m² (every 24 hours if eGFR less than 30 mL/minute/1.73 m²).
  - In children Reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m² — consult product literature.

- PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include strawberry.

- PATIENT AND CARER ADVICE

  - Driving and skilled tasks May impair performance of skilled tasks (e.g. driving); effects enhanced by alcohol.
  - Medicines for Children leaflet: Ciprofloxacin for bacterial infections www.medicinesforchildren.org.uk/ciprofloxacin-bacterial-infection

- MEDICINAL FORMS

  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Table

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<tbody>
<tr>
<td>CAUTIONARY AND ADVISORY LABELS 7, 9, 25</td>
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<tr>
<td>Ciprofloxacin (Non-proprietary)</td>
</tr>
<tr>
<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 100 mg Ciprofloxacin 100mg tablets</td>
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<tr>
<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 250 mg Ciprofloxacin 250mg tablets</td>
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<tr>
<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 500 mg Ciprofloxacin 500mg tablets</td>
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<tr>
<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 750 mg Ciprofloxacin 750mg tablets</td>
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<tr>
<td>Ciproxin (Bayer Plc)</td>
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<tr>
<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 250 mg Ciproxin 250mg tablets</td>
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<tr>
<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 500 mg Ciproxin 500mg tablets</td>
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<td>Ciprofloxacin (as Ciprofloxacin hydrochloride) 750 mg Ciproxin 750mg tablets</td>
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| Oral suspension |
| CAUTIONARY AND ADVISORY LABELS 7, 9, 25 |
| Ciproxin (Bayer Plc) |
| Ciprofloxacin 50 mg per 1 ml Ciproxin 250mg/5ml oral suspension | 100 ml | P40 | £19.80 DT price = £19.80 |

| Infusion |
| Ciprofloxacin (Non-proprietary) |
| Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciprofloxacin 200mg/100ml solution for infusion vials | 1 vial | P40 | £14.45 |
| Ciprofloxacin 200mg/100ml solution for infusion vials | 10 bottle | P40 | £14.45 |
| Ciprofloxacin 100mg/50ml solution for infusion vials | 1 vial | P40 | £7.57 |
| Ciprofloxacin 200mg/200ml solution for infusion vials | 5 bottle | P40 | £19.59 |
| Ciprofloxacin 200mg/200ml solution for infusion vials | 1 vial | P40 | £19.79 (Hospital only) |
| Ciproxin (Bayer Plc) |
| Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciproxin Infusion 100mg/50ml solution for infusion vials | 1 bottle | P30 | £7.61 (Hospital only) |
| Ciprofloxacin 200mg/200ml solution for infusion vials | 5 bottle | P30 | £122.23 (Hospital only) |
| Ciprofloxacin 200mg/100ml solution for infusion vials | 5 bottle | P40 | £75.06 (Hospital only) |

Levofloxacin

- INDICATIONS AND DOSE

  - Acute sinusitis
    - BY MOUTH
      - Adult: 500 mg once daily for 10–14 days
  - Acute exacerbation of chronic bronchitis
    - BY MOUTH
      - Adult: 500 mg once daily for 7–10 days
  - Community-acquired pneumonia
    - BY MOUTH
      - Adult: 500 mg 1–2 times a day for 7–14 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes
  - Urinary-tract infections
    - BY MOUTH
      - Adult: 500 mg once daily for 7–14 days
  - Urinary-tract infections (uncomplicated infection)
    - BY MOUTH
      - Adult: 250 mg once daily for 3 days
  - Complicated urinary-tract infections
    - BY INTRAVENOUS INFUSION
      - Adult: 500 mg once daily, to be given over at least 60 minutes
  - Chronic prostatitis
    - BY MOUTH
      - Adult: 500 mg once daily for 28 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg once daily, to be given over at least 60 minutes
  - Complicated skin infections | Complicated soft-tissue infections
    - BY MOUTH
      - Adult: 500 mg 1–2 times a day for 7–14 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes
Inhalation of anthrax (treatment and post-exposure prophylaxis)

- **BY MOUTH**
- Adult: 500 mg once daily for 8 weeks
- **BY INTRAVENOUS INFUSION**
- Adult: 500 mg once daily, to be given over at least 60 minutes

- **CAUTIONS**
  - Acute myocardial infarction (risk factor for QT interval prolongation)
  - Bradycardia (risk factor for QT interval prolongation)
  - Congenital long QT syndrome (risk factor for QT interval prolongation)
  - Electrolyte disturbances (risk factor for QT interval prolongation)
  - Heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation)
  - History of psychiatric illness
  - History of symptomatic arrhythmias
  - Hypersensitivity

- **SIDE-EFFECTS**
  - Abnormal dreams
  - Constipation
  - Flatulence
  - Hyperhidrosis
  - Frequency not known
  - Local reactions
  - Transient hypotension

- **INTERACTIONS**
  - Caution if concomitant use with other drugs known to prolong the QT interval.

- **BREAST FEEDING**
  - Manufacturer advises avoid.

- **RENAI IMPAIRMENT**
  - Usual initial dose, then use half normal dose if eGFR 20–50 mL/minute/1.73 m²; consult product literature if eGFR less than 20 mL/minute/1.73 m².

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

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<td>Evoxil (Beacon Pharmaceuticals Ltd)</td>
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</table>

**Infusion**

- **Levofloxacin (Non-proprietary)**
- Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml
  - Levofloxacin 500 mg/100 ml infusion bags | 20 | Bag | £52.00

**Solution for infusion**

- **ELECTROLYTES**: May contain Sodium
- **Levofloxacin (Non-proprietary)**
- Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml
  - Levofloxacin 500 mg/100 ml solution for infusion bottles | 10 bottle | £26.40
- **Evoxil (Beacon Pharmaceuticals Ltd)**
- Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml
  - Evoxil 500 mg/100 ml solution for infusion vials | 1 vial | £26.40

**Moxifloxacin**

- **INDICATIONS AND DOSE**
  - **Sinusitis**
    - Adult: 400 mg once daily for 7 days
  - **Community-acquired pneumonia**
    - **BY MOUTH**
      - Adult: 400 mg once daily for 7–14 days
      - **BY INTRAVENOUS INFUSION**
        - Adult: 400 mg once daily for 7–14 days, to be given over 60 minutes
  - **Exacerbations of chronic bronchitis**
    - **BY MOUTH**
      - Adult: 400 mg once daily for 5–10 days
    - **Mild to moderate pelvic inflammatory disease**
      - **BY MOUTH**
        - Adult: 400 mg once daily for 7–21 days
      - **BY INTRAVENOUS INFUSION**
        - Adult: 400 mg once daily for 7–21 days, to be given over 60 minutes
  - **Complicated skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials**
    - **BY MOUTH**
      - Adult: 400 mg once daily for 7–21 days
    - **BY INTRAVENOUS INFUSION**
      - Adult: 400 mg once daily for 7–21 days, to be given over 60 minutes

- **CONTRA-INDICATIONS**
  - Acute myocardial infarction (risk factor for QT interval prolongation)
  - Bradycardia (risk factor for QT interval prolongation)
  - Congenital long QT syndrome (risk factor for QT interval prolongation)
  - Electrolyte disturbances (risk factor for QT interval prolongation)
  - History of psychiatric illness
  - History of symptomatic arrhythmias

- **SIDE-EFFECTS**
  - **Common or very common**
    - Angina
    - Arrhythmias
    - Constipation
    - Flatulence
    - Gastritis
    - Hyperlipidaemia
    - Palpitation
    - Sweating
    - Vasodilatation
  - **Uncommon**
    - Dyspnoea
    - Abnormal dreams
    - Hypersensitivity
    - Hyperuricaemia
    - Hypertension
    - Hyperuricaemia
    - Incoordination
    - Myopathy
    - Oedema
    - Peripheral neuropathy
    - Stomatitis
    - Syncope
  - **Very rare**
    - Potentially life-threatening hepatic failure
    - Rhabdomyolysis

- **Frequency not known**
  - With intravenous use
    - Pain at injection site
    - Phlebitis at injection site

- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in severe impairment.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks**
    - May impair performance of skilled tasks (e.g. driving).
Norfloxacin

**INDICATIONS AND DOSE**

**Lower urinary-tract infections**

- **BY MOUTH**
  - Adult: 400 mg twice daily for 7–10 days (for 3 days for uncomplicated infections in women)

**Chronic relapsing lower urinary-tract infections**

- **BY MOUTH**
  - Adult: 400 mg twice daily for up to 12 weeks; reduced to 400 mg once daily, if adequate suppression within first 4 weeks

**Chronic prostatitis**

- **BY MOUTH**
  - Adult: 400 mg twice daily for 28 days

**CAUTIONS**

- Acute myocardial infarction (risk factor for QT interval prolongation) • bradycardia (risk factor for QT interval prolongation) • congenital long QT syndrome (risk factor for QT interval prolongation) • electrolyte disturbances (risk factor for QT interval prolongation) • heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) • history of symptomatic arrhythmias (risk factor for QT interval prolongation)

**INTERACTIONS**

- Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**

- Common or very common • Epiphora • tinnitus
- Rare • Pancreatitis
- Very rare • Arrhythmias
- Frequency not known • Exfoliative dermatitis • polyneuropathy

**BREAST FEEDING**

- No information available—manufacturer advises avoid.

**RENAI IMPAIRMENT**

- Use 400 mg once daily if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks
  - May impair performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 7, 9, 23
  - Norfloxacin (Non-proprietary)

- **Norfloxacin 400 mg** Norfloxacin 400mg tablets | 14 tablet [POM] no price available

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Ofloxacin

**INDICATIONS AND DOSE**

**Urinary-tract infections**

- **BY MOUTH**
  - Adult: 200–400 mg daily, preferably taken in the morning; increased if necessary to 400 mg twice daily, in upper urinary tract infections

**Complicated urinary-tract infection**

- **BY INTRAVENOUS INFUSION**
  - Adult: 200 mg daily, increased if necessary to 400 mg twice daily, dose increased for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

**Acute or chronic prostatitis**

- **BY MOUTH**
  - Adult: 200 mg twice daily for 28 days

---

**Nalidixic acid**

**INDICATIONS AND DOSE**

**Urinary-tract infections**

- **BY MOUTH**
  - Adult: 900 mg every 6 hours for 7 days, then reduced to 600 mg every 6 hours for prolonged therapy in chronic infections

**CAUTIONS**

- Acute myocardial infarction (risk factor for QT interval prolongation) • avoid in Acute porphyrias p. 930 • bradycardia (risk factor for QT interval prolongation) • congenital long QT syndrome (risk factor for QT interval prolongation) • electrolyte disturbances (risk factor for QT interval prolongation) • heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) • history of symptomatic arrhythmias (risk factor for QT interval prolongation)

**INTERACTIONS**

- Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**

- Cranial nerve palsy • increased intracranial pressure • metabolic acidosis • peripheral neuropathy • toxic psychosis

**BREAST FEEDING**

- Risk to infant very small but one case of haemolytic anaemia reported.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in liver disease.

**RENAI IMPAIRMENT**

- Use with caution; avoid if eGFR less than 20 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Monitor blood counts, renal and liver function if treatment exceeds 2 weeks.

**EFFECT ON LABORATORY TESTS**

- False positive urinary glucose (if tested for reducing substances).

**PRESCRIBING AND DISPENSING INFORMATION**

- Flavours of oral liquid formulations may include raspberry and strawberry.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

- No licensed medicines identified.
Lower respiratory-tract infections
- **BY MOUTH**
  - Adult: 400 mg daily, dose preferably taken in the morning, then increased if necessary to 400 mg twice daily
- **BY INTRAVENOUS INFUSION**
  - Adult: 200 mg twice daily, increased to 400 mg twice daily, dose to be increased for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

Skin and soft-tissue infections
- **BY MOUTH**
  - Adult: 400 mg twice daily
  - **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg twice daily, to be given over at least 30 minutes for each 200 mg

Uncomplicated gonorrhoea
- **BY MOUTH**
  - Adult: 400 mg as a single dose

Uncomplicated genital chlamydial infection | Non-gonococcal urethritis
- **BY MOUTH**
  - Adult: 400 mg daily for 7 days, dose may be taken as a single daily dose or in divided doses

Pelvic inflammatory disease
- **BY MOUTH**
  - Adult: 400 mg twice daily for 14 days

Septicaemia
- **BY INTRAVENOUS INFUSION**
  - Adult: 200 mg twice daily, increased if necessary to 400 mg twice daily, dose to be increased for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

**CAUTIONS** Acute myocardial infarction (risk factor for QT interval prolongation); bradycardia (risk factor for QT interval prolongation); congenital long QT syndrome (risk factor for QT interval prolongation); electrolyte disturbances (risk factor for QT interval prolongation); heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation); history of psychiatric illness; history of symptomatic arrhythmias (risk factor for QT interval prolongation)

**INTERACTIONS** Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**
- Common or very common Cough; eye irritation; nasopharyngitis
- Rare Abnormal dreams; arrhythmias; bronchospasm; dyspnoea; hot flushes; hyperhidrosis
- Very rare Extrapyramidal symptoms; neuropathy; tinnitus
- Frequency not known
- With intravenous use Hypotension; local reactions; thrombophlebitis
- With intravenous use or oral use Changes in blood sugar; myopathy; pneumonitis; rhabdomyolysis

**BREAST FEEDING** Amount probably too small to be harmful but manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Use with caution; elimination may be reduced in severe impairment.

**RENAL IMPAIRMENT** Usual initial dose, then use half normal dose if eGFR 20–50 mL/minute/1.73 m²; 100 mg every 24 hours if eGFR less than 20 mL/minute/1.73 m²

**PATIENT AND CARER ADVICE**
- Driving and skilled tasks
  - May affect performance of skilled tasks (e.g. driving); effects enhanced by alcohol.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 6, 9, 11
- **Ofloxacin** (Non-proprietary)
  - **Ofloxacin 200 mg** Ofloxacin 200 mg tablets | 10 tablet [Pot] £6.75
  - **DT price** = £6.68
  - **Ofloxacin 400 mg** Ofloxacin 400 mg tablets | 5 tablet [Pot] £12.80
  - **DT price** = £12.52
- **Tarivid** (Sandofi)
  - **Tarivid 200 mg** Tarivid 200 mg tablets | 10 tablet [Pot] £7.53
  - **DT price** = £6.68
  - **Tarivid 400 mg** Tarivid 400 mg tablets | 5 tablet [Pot] £15.05
  - **DT price** = £12.52

**Solution for infusion**
- **Tarivid** (Sandofi)
  - Ofloxacin (as Ofloxacin hydrochloride) 2 mg per 1 ml Tarivid 200 mg/100 ml solution for infusion bottles | 1 bottle [Pot] £16.16

**ANTIBACTERIALS › SULFONAMIDES**

**Co-trimoxazole**
- **DRUG ACTION** Sulfamethoxazole and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity (the importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic).

**INDICATIONS AND DOSE**
- **Treatment of susceptible infections**
  - **BY MOUTH**
    - Child 6 weeks–5 months: 120 mg twice daily, alternatively 24 mg/kg twice daily
    - Child 6 months–5 years: 240 mg twice daily, alternatively 24 mg/kg twice daily
    - Child 6–11 years: 480 mg twice daily, alternatively 24 mg/kg twice daily
    - Child 12–17 years: 960 mg twice daily
    - Adult: 960 mg twice daily
  - **BY INTRAVENOUS INFUSION**
    - Adult: 960 mg every 12 hours, increased to 1.44 g every 12 hours, increased dose used in severe infection

**Treatment of Pneumocystis jirovecii (Pneumocystis carinii) infections (undertaken where facilities for appropriate monitoring available—consult microbiologist and product literature)**
- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - Child: 120 mg/kg daily in 2–4 divided doses for 14–21 days, oral route preferred for children
  - Adult: 120 mg/kg daily in 2–4 divided doses for 14–21 days

**Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infections**
- **BY MOUTH**
  - Child: 450 mg/m² twice daily (max. per dose 960 mg twice daily) for 3 days of the week (either consecutively or on alternate days), dose regimens may vary, consult local guidelines
  - Adult: 960 mg once daily, reduced if not tolerated to 480 mg once daily, alternatively 960 mg once daily on alternate days, alternate day dose to be given 3 times weekly, alternatively 960 mg twice a day on alternate days, alternate day dose to be given 3 times weekly

**DOSE EQUIVALENCE AND CONVERSION**
- 480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg.
**SIDE-EFFECTS**

- **Common or very common** Diarrhoea • headache • hyponatraemia • myalgia • myelitis • phototoxicity • pulmonary infiltrates • renal disorders • shortness of breath • Stevens-Johnson syndrome • stomatitis • systemic lupus erythematosus • thrombocytopenia • tinnitus • toxic epidermal necrolysis • uveitis • vasculitis • vertigo

- **Frequency not known** Rhabdomyolysis reported in HIV-infected patients

**SIDE-EFFECTS, FURTHER INFORMATION**

- Blood disorders or rash • Co-trimoxazole is associated with rare but serious side effects. Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity) develop.

- **PREGNANCY** Teratogenic risk in first trimester (trimethoprim a folate antagonist). Neonatal haemolysis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.

- **BREAST FEEDING** Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole).

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe liver disease.


**IMPORTANT SAFETY INFORMATION**

**RESTRICTIONS ON THE USE OF CO-TRIMOXAZOLE**

Co-trimoxazole is the drug of choice in the prophylaxis and treatment of *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia; it is also indicated for nocardiosis, *Stenotrophomonas maltophilia* infection [unlicensed indication], and toxoplasmosis. It should only be considered for use in acute exacerbations of chronic bronchitis and infections of the urinary tract when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it. Co-trimoxazole is also used for the treatment of infections caused by *Burkholderia cepacia* in cystic fibrosis [unlicensed indication].

**CONTRA-INDICATIONS** Acute porphyrias p. 930

**CAUTIONS** Asthma • avoidance in blood disorders (unless under specialist supervision) • avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) because of the risk of kernicterus • elderly (increased risk of serious side-effects) • G6PD deficiency (risk of haemolytic anaemia) • maintain adequate fluid intake • predisposition to folate deficiency • predisposition to hyperkalaemia (in adults)

**INTERACTIONS** → Appendix 1 (trimethoprim, sulfamethoxazole).

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea • headache • hyponatraemia • nausea • rash

- **Uncommon** Vomiting

- **Rare** Agranulocytosis • bone marrow depression

- **Very rare** Anorexia • antibiotic-associated colitis • arthralgia • asptic menigitis • ataxia • blood disorders • convulsions • cough • depression • eosinophilia • glossitis • hallucinations • hepatic necrosis • hypoglycaemia • hyponatraemia • interstitial nephritis • jaundice • leucopenia • liver damage • megaloblastic anaemia • myalgia • myocardiitis • pancreatitis • peripheral neuropathy • photosensitivity • pulmonary infiltrates • renal disorders • shortness of breath • Stevens-Johnson syndrome • stomatitis • systemic lupus erythematosus • thrombocytopenia • tinnitus • toxic epidermal necrolysis • uveitis • vasculitis • vertigo

- **Frequency not known** Rhabdomyolysis reported in HIV-infected patients

**DIRECTIONS FOR ADMINISTRATION**

- **In children** Recommended dose: 100 or 200 mg twice daily (trimethoprim, sulfamethoxazole) in a single dose. In children, monitor blood counts on prolonged treatment.

**PRESCRIBING AND DISPENSING INFORMATION**

Co-trimoxazole is a mixture of trimethoprim and sulfamethoxazole (sulphamethoxazole) in the proportions of 1 part to 5 parts.

*Flavours of oral liquid formulations may include banana, or vanilla.*

**RENAL IMPAIRMENT**

- **In adults** Use half normal dose if eGFR 15–30 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored.

- **In children** Use half normal dose if estimated glomerular filtration rate 15–30 mL/minute/1.73 m². Avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored.

**MONITORING REQUIREMENTS**

- **In children** Plasma concentration monitoring may be required with high doses; seek expert advice.

- **Monitor blood counts on prolonged treatment.**

**PRECAUTIONS**

- With intravenous use in children For intermittent intravenous infusion, may be further diluted in glucose 5% and 10% or sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and the required dose infused over max. 60 minutes; check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

- With intravenous use in adults For intravenous infusion (Septrin® for infusion), give intermittently in Glucose 5% or 10% or Sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and infused over max. 60 minutes.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **Co-trimoxazole (Non-proprietary)**

- **Trimeprin® (80 mg, Sulfamethoxazole 400 mg)**

- **Co-trimoxazole 80mg/400mg tablets** | 100 tablet | £15.50 DT price + £2.29 | £13.21

- **Trimeprin® (160 mg, Sulfamethoxazole 800 mg)**

- **Co-trimoxazole 160mg/800mg tablets** | 100 tablet | £23.40–£24.00 DT price + £23.46

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS**

- **Co-trimoxazole (Non-proprietary)**

- **Trimeprin® (8 mg per 1 mL, Sulfamethoxazole 40 mg per 1 mL)**

- **Co-trimoxazole 40mg/200mg/5ml oral suspension sugar free**

- **Trimeprin® (16 mg per 1 mL, Sulfamethoxazole 80 mg per 1 mL)**

- **Co-trimoxazole 80mg/400mg/5ml oral suspension** | 100 ml | £9.95 DT price + £9.95

**Solution for infusion**

**EXCIPIENTS:** May contain Alcohol, propylene glycol, sulfites

**ELECTROLYTES:** May contain Sodium

- **Co-trimoxazole (Non-proprietary)**

- **Trimeprin® (16 mg per 1 mL, Sulfamethoxazole 80 mg per 1 mL)**

- **Co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules** | 10 ampoule | £35.00
Sulfadiazine ( Sulphadiazine )

**Drug action** Sulfadiazine is a short-acting sulphonamide with bacteriostatic action against a broad spectrum of organisms. The importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.

**Indications and dose** Prevention of rheumatic fever recurrence

- **By mouth**
  - Adult (body-weight up to 30 kg): 500 mg daily
  - Adult (body-weight 30 kg and above): 1 g daily

**Contra-indications** Acute porphyrias p. 930

**Caution** Asthma, avoid in blood disorders (unless under specialist supervision) - elderly - G6PD deficiency (risk of haemolytic anaemia) - maintain adequate fluid intake - predisposition to folate deficiency - predisposition to hyperkalaemia

**Interactions** → Appendix 1 (sulphonamides).

**Side-effects**
- Common or very common Diarrhoea - headache - hyperkalaemia - nausea - rash
- Uncommon Vomiting
- Rare Agranulocytosis - bone marrow depression
- Frequency not known Benign intracranial hypertension - hypothyroidism - optic neuropathy - oedema - pericarditis - photosensitivity - reported in HIV-infected patients

**Side-effects, further information**
- Blood disorders or rash Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity) develop.
- Pregnancy Risk of neonatal haemolysis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.
- Breast feeding Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants.
- Hepatic impairment Use with caution in mild to moderate impairment; avoid in severe impairment.
- Renal impairment Use with caution in mild to moderate impairment; avoid in severe impairment; high risk of crystalluria.
- Monitoring requirements Monitor blood counts on prolonged treatment.

**Medicinal forms**

- **Tablet**
  - Sulfadiazine (Non-proprietary)
  - Sulfadiazine 500 mg Sulfadiazine 500mg tablets | 56 tablet £138.62 DT price = £93.47

**Antibacterials** Tetracyclines and related drugs

**Tetracyclines**

**Overview** The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. They remain, however, the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever), brucella (doxycycline p. 521 with either streptomycin p. 480 or rifampicin p. 535), and the spirochaete, Borrelia burgdorferi (See Lyme disease). They are also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic bronchitis (because of their activity against Haemophilus influenzae), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin p. 497).

Tetracyclines have a role in the management of meticillin-resistant Staphylococcus aureus (MRSA) infection. Microbiologically, there is little to choose between the various tetracyclines, the only exception being minocycline p. 522 which has a broader spectrum; it is active against Neisseria meningitidis and has been used for meningococcal prophylaxis but is no longer recommended because of side-effects including dizziness and vertigo. Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation.

**Contra-indications** Children under 12 years (deposition in growing bone and teeth, by binding to calcium, causes staining and occasionally dental hypoplasia)

**Caution** Myasthenia gravis (muscle weakness may be increased) - systemic lupus erythematosus (may be exacerbated)

**Interactions** → Appendix 1 (tetracyclines).

Antacids, and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines. Use with caution in those receiving potentially hepatotoxic drugs.

**Side-effects**
- Rare Anaphylaxis - angioedema - blood disorders - exfoliative dermatitis - hepatotoxicity - hypersensitivity reactions - pancreatitis - pericarditis - photosensitivity (particularly with demeclocycline) - rash - Stevens-Johnson syndrome - urticaria
- Frequency not known Antibioc-associated colitis - benign intracranial hypertension - bulging fontanelles (in infants and in children) - diarrhoea - dysphagia - headache - nausea - oesophageal irritation - visual disturbances - vomiting

**Side-effects, further information**
- Benign intracranial hypertension Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment).
Demeclocycline hydrochloride

**INDICATIONS AND DOSE**
Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
- **BY MOUTH**
  - Adult: 150 mg 4 times a day, alternatively 300 mg twice daily

Treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable
- **BY MOUTH**
  - Adult: Initially 0.9–1.2 g daily in divided doses, maintenance 600–900 mg daily

**CAUTIONS**
Photosensitivity more common than with other tetracyclines

**INTERACTIONS**
Milk reduces absorption.

**SIDE-EFFECTS**
Acute renal failure - reversible nephrogenic diabetes insipidus

**HEPATIC IMPAIRMENT**
Max. 1 g daily in divided doses.

**RENAL IMPAIRMENT**
May exacerbate renal failure and should not be given to patients with renal impairment.

**PATIENT AND CARER ADVICE**
Patients should be advised to avoid exposure to sunlight or sun lamps.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Demeclocycline hydrochloride (Non-proprietary)
- Demeclocycline hydrochloride 150 mg
- Demeclocycline 150mg tablets | 100 tablet [PSt] no price available

**Capsule**
- CAUTIONARY AND ADVISORY LABELS 7, 9, 11, 23
- Demeclocycline hydrochloride (Non-proprietary)
- Demeclocycline hydrochloride 150 mg
- Demeclocycline 150mg capsules | 28 capsule [PSt] £160.89 DT price = £160.89
- Demeclocycline hydrochloride 300 mg
- Ledermycin 300mg capsules | 16 capsule [PSt] no price available

Doxycycline

**INDICATIONS AND DOSE**
Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: Initially 200 mg daily for 1 dose, then maintenance 100 mg once daily
  - Adult: Initially 200 mg daily for 1 dose, then maintenance 100 mg once daily

**SEVERE INFECTIONS (INCLUDING REFRACTORY URINARY-TRACT INFECTIONS)**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 200 mg daily
  - Adult: 200 mg once daily

**ACNE**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg once daily
  - Adult: 100 mg once daily

**ROSAEA**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 100 mg once daily

**PAPULOPUSTULAR FACIAL ROSacea (W/OUT OCULAR INVOLVEMENT)**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 200 mg twice daily for 28 days

**NEUROSYphilis**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 200 mg twice daily for 28 days

**UNCOMPLICATED GENITAL CHLAMYDIA | Non-gonococcal urethritis**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg twice daily for 7 days
  - Adult: 100 mg twice daily for 7 days

**PELVIC INFLAMMATORY DISEASE**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg twice daily for 14 days
  - Adult: 100 mg twice daily for 14 days

**LYME DISEASE (UNDER EXPERT SUPERVISION)**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg twice daily for 10–14 days (for 28 days in Lyme arthritis)
  - Adult: 100 mg twice daily for 10–14 days (for 28 days in Lyme arthritis)

**ANTHRAX (TREATMENT OR POST-EXPOSURE PROPHYLAXIS)**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg twice daily for 14 days
  - Adult: 100 mg twice daily for 14 days

**PROPHYLAXIS OF MALARIA**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving, can be used for up to 2 years
  - Adult: 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving, can be used for up to 2 years

**ADJUNCT TO QUININE IN TREATMENT OF Plasmodium falciparum MALARIA**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 200 mg daily for 7 days
  - Adult: 200 mg daily for 7 days

**PERIODONTITIS (AS AN ADJUNCT TO GINGIVAL SCALING AND ROOT PLANING)**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 20 mg twice daily for 3 months
  - Adult: 20 mg twice daily for 3 months

**UNLICENSED USE**
Not licensed for use in children under 12 years. Doxycycline doses in BNF Publications may differ from those in product literature. Not licensed for malaria
prophylaxis during pregnancy. Not licensed for treatment or post-exposure prophylaxis of anthrax.

- in adults Immediate-release doxycycline not licensed for treatment of rosacea.
- **CAUTIONS** Alcohol dependence
- **INTERACTIONS** The metabolism of doxycycline may be influenced by antiepileptics.
- **SIDE-EFFECTS** Anorexia · anxiety · dry mouth · flushing · fungal superinfection (when used for periodontitis) · tinnitus
- **PREGNANCY** When travel to malarious areas is unavoidable during pregnancy, doxycycline can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks’ gestation.
- **RENAI IMPAIRMENT** Use with caution (avoid excessive doses).
- **MONITORING REQUIREMENTS** When used for periodontitis, monitor for superficial fungal infection, particularly if predisposition to oral candidiasis.
- **DIRECTIONS FOR ADMINISTRATION** Capsules and Tablets should be swallowed whole with plenty of fluid, while sitting or standing. Capsules should be taken during meals.
- **PATIENT AND CARER ADVICE** Counselling on administration advised (posture). Photosensitivity Patients should be advised to avoid exposure to sunlight or sun lamps.
- **PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary
Doxycycline Capsules 100 mg may be prescribed. Dispersible tablets may be prescribed as Dispersible Doxycycline Tablets. Tablets may be prescribed as Doxycycline Tablets 20 mg.

- **MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

**CAUTIONARY AND ADVISORY LABELS** 6, 11, 27
- **Periostat** (Alliance Pharmaceuticals Ltd)
  - Doxycycline (as Doxycycline hyclate) 20 mg Periostat 20mg tablets | 56 tablet 8p £17.30 DT price = £17.30

### Dispersible tablet

**CAUTIONARY AND ADVISORY LABELS** 6, 9, 11, 13
- **Vibramycin-D** (Pfizer Ltd)
  - Doxycycline (as Doxycycline monohydrate) 100 mg Vibramycin-D 100mg dispersible tablets sugar-free | 8 tablet 8p £4.91 DT price = £4.91

### Capsule

**CAUTIONARY AND ADVISORY LABELS** 6, 9, 11, 12, 27
- **Doxycycline (Non-proprietary)**
  - Doxycycline (as Doxycycline hyclate) 50 mg Doxycycline 50mg capsules | 28 capsule 8p £2.26 DT price = £1.39
  - Doxycycline (as Doxycycline hyclate) 100 mg Doxycycline 100mg capsules | 5 capsule 8p £5.44

### Modified-release capsule

**CAUTIONARY AND ADVISORY LABELS** 6, 11, 27
- **Efracea** (Galderma (UK) Ltd)
  - Doxycycline (as Doxycycline monohydrate) 40 mg Efracea 40mg modified-release capsules | 14 capsule 8p £7.99 DT price = £7.99 | 56 capsule 8p £21.71

### Lymecycline

- **INDICATIONS AND DOSE**
  - Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
    - By mouth using immediate-release medicines
      - Child 12-17 years: 100 mg twice daily
      - Adult: 100 mg twice daily
    - Acne
      - By mouth using immediate-release medicines
      - Child 12-17 years: 100 mg once daily, alternatively 50 mg twice daily
      - Adult: 100 mg once daily, alternatively 50 mg twice daily
    - By mouth using modified-release medicines
      - Child 12-17 years: 100 mg daily
      - Adult: 100 mg daily

### Prophylaxis of asymptomatic meningococcal carrier state (but no longer recommended)

- By mouth using immediate-release medicines
  - Adult: 100 mg twice daily for 5 days, minocycline treatment is usually followed by administration of rifampicin

- **CAUTIONS** Systemic lupus erythematosus
- **SIDE-EFFECTS**
  - Rare Acute renal failure · alopecia · anorexia · hyperaesthesia · impaired hearing · paraesthesia · pigmentation (sometimes irreversible) · tinnitus
  - Very rare Discoloration of conjunctiva · discoloration of sweat · discoloration of tears · systemic lupus erythematosus
  - Frequency not known Dizziness (more common in women) · vertigo (more common in women)
- **RENAI IMPAIRMENT** Use with caution (avoid excessive doses).
- **MONITORING REQUIREMENTS** If treatment continued for longer than 6 months, monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus
erythematous—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens.

- **DIRECTIONS FOR ADMINISTRATION** Tablets or capsules should be swallowed whole with plenty of fluid while sitting or standing.

- **PATIENT AND CARER ADVICE** Counselling on administration advised (posture).

- **LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing (compared with other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome; it sometimes causes irreversible pigmentation).

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 7, 9, 23
  - Oxytetracycline (Non-proprietary) 50 mg 50mg tablets  | 28 tablet  price = £6.19
  - Oxytetracycline (as Oxytetracycline dihydrate) 100 mg 100mg tablets  | 28 tablet  price = £14.01

  **Capsule**
  CAUTIONARY AND ADVISORY LABELS 7, 9, 23
  - Aknemin (Almirall Ltd) 50 mg 56 capsule  price = £15.27
  - Aknemin (as Minocycline hydrochloride) 100 mg 100mg capsules  | 28 capsule  price = £13.09

  **Modified-release capsule**
  CAUTIONARY AND ADVISORY LABELS 6, 25
  - Minocycline (as Minocycline hydrochloride) 100 mg 100mg modified-release capsules  | 56 capsule  price = £20.08
  - Acmamino MR (Almus Pharmaceuticals Ltd, Dexcel-Pharma Ltd) 28 capsule

- **RENAL IMPAIRMENT** May exacerbate renal failure and should **not** be given to patients with renal impairment.

- **PROFESSION SPECIFIC INFORMATION**
  Dental practitioners’ formulary
  Oxytetracycline Tablets may be prescribed.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension.

  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 7, 9, 23
  - Oxytetracycline (Non-proprietary) 250 mg Oxytetracycline 250mg tablets  | 28 tablet  price = £3.45

**Tetracycline**

- **INDICATIONS AND DOSE**
  **Susceptible infections (e.g. chlamydia, rickettsia, mycoplasma)**
  - BY MOUTH
    - Child 12-17 years:  250–500 mg 4 times a day, increased if necessary to 500 mg 3–4 times a day, increased dose used in severe infections.
    - Adult:  250 mg 4 times a day, increased if necessary to 500 mg 3–4 times a day, increased dose used in severe infections.

- **Rosacea**
  - BY MOUTH
    - Adult:  500 mg twice daily usually for 6–12 weeks (course may be repeated intermittently)

- **Acne**
  - BY MOUTH
    - Adult:  500 mg twice daily usually for 6–12 weeks (course may be repeated intermittently)

- **Non-gonococcal urethritis**
  - BY MOUTH
    - Adult:  500 mg 4 times a day for 7–14 days (21 days if failure or relapse after first course)
    - Adult:  500 mg 4 times a day for 7–14 days (21 days if failure or relapse after first course)

- **Diabetic diarrhoea in autonomic neuropathy**
  - BY MOUTH
    - Adult:  250 mg for 2 or 3 doses

- **Helicobacter pylori eradication failure in combination with a proton pump inhibitor, tripotassium dicitratobismuthate, and metronidazole**
  - BY MOUTH
    - Adult:  500 mg 4 times a day for 2 weeks

- **UNLICENSED USE** Not licensed for treatment of diabetic diarrhoea in autonomic neuropathy.

- **INTERACTIONS** Milk reduces absorption.

- **SIDE-EFFECTS** Acute renal failure - skin discoloration

- **HEPATIC IMPAIRMENT** Max. 1 g daily in divided doses.

- **RENAL IMPAIRMENT** May exacerbate renal failure and should **not** be given to patients with renal impairment.
Tigecycline

**DRUG ACTION**  Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines. Tigecycline is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, but *Pseudomonas aeruginosa* and many strains of *Proteus spp* are resistant to tigecycline.

**INDICATIONS AND DOSE**  Treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used

- **BY INTRAVENOUS INFUSION**  
- **Adult:** Initially 100 mg, then 50 mg every 12 hours for 5–14 days, not recommended for the treatment of foot infections in patients with diabetes.

**CAUTIONS**  Cholestasis

**SIDE-EFFECTS**

- **Common or very common**  Abdominal pain, anorexia, bilirubinaemia, diarrhoea, dizziness, dyspepsia, headache, hypoglycaemia, injection-site reactions, nausea, prolonged activated partial thromboplastin time, prolonged prothrombin time, pruritus, rash, vomiting.
- **Uncommon**  Cholestatic jaundice, hypoproteinaemia, pancreatitis.
- **Frequency not known**  Antibiotic-associated colitis, hepatic failure, Stevens-Johnson syndrome, thrombocytopenia.

**SIDE-EFFECTS, FURTHER INFORMATION**

Side-effects similar to those of the tetracyclines can potentially occur.

**ALLERGY AND CROSS-SENSITIVITY**  Contra-indicated in patients hypersensitive to tetracyclines.

**PREGNANCY**  Tetracyclines should not be given to pregnant women; effects on skeletal development have been documented in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth, and maternal hepatotoxicity has been reported with large parenteral doses.

**BREAST FEEDING**  Manufacturer advises caution—present in milk in animal studies.

**HEPATIC IMPAIRMENT**  Initially 100 mg then 25 mg every 12 hours in severe hepatic impairment.

**DIRECTIONS FOR ADMINISTRATION**  For intravenous infusion (Tigacil®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute each vial with 5.3 mL infusion fluid to produce a 10 mg/mL solution; dilute requisite dose in 100 mL infusion fluid; give over 30–60 minutes.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- **Tygacil** (Pfizer Ltd)
  - Tigecycline 50 mg
  - Tigacil 50mg powder for solution for infusion vials 10 vial (POM) £323.10 (Hospital only)

**ANTIBACTERIALS > OTHER**

**Chloramphenicol**

**DRUG ACTION**  Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**  Life threatening infections particularly those caused by *Haemophilus influenzae* / Typhoid fever

- **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**  
  - Adult: 12.5 mg/kg every 6 hours, in exceptional cases dose can be doubled for severe infections such as septicaemia and meningitis, providing high doses reduced as soon as clinically indicated.

**CONTRA-INDICATIONS**  Acute porphyrias p. 930

**CAUTIONS**  Avoid repeated courses and prolonged treatment.

**INTERACTIONS**  → Appendix 1 (chloramphenicol).

**SIDE-EFFECTS**  Blood disorders, depression, diarrhoea, dry mouth, erythema multiforme, glossitis, headache, nausea, nocturnal haemoglobinuria, optic neuritis, peripheral neuritis, reversible and irreversible aplastic anaemia (with reports of resulting leukaemia); stomatitis; urticaria; vomiting.

**SIDE-EFFECTS, FURTHER INFORMATION**  Associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections.

**PREGNANCY**  Manufacturer advises avoid; neonatal ‘grey-baby syndrome’ if used in third trimester.

**BREAST FEEDING**  Manufacturer advises avoid; use another antibiotic may cause bone–marrow toxicity in infant; concentration in milk usually insufficient to cause ‘grey syndrome’.

**HEPATIC IMPAIRMENT**  Reduce dose. Avoid if possible—increased risk of bone–marrow depression. Monitor plasma–chloramphenicol concentration in hepatic impairment.

**RENAL IMPAIRMENT**  Avoid in severe renal impairment unless no alternative; dose–related depression of haematopoiesis.

**MONITORING REQUIREMENTS**

- Plasma concentration monitoring preferred in the elderly.
- Recommended peak plasma concentration (approx. 2 hours after administration by mouth, intravenous injection or infusion) 10–25 mg/litre; pre-dose (‘trough’) concentration should not exceed 15 mg/litre.
- Blood counts required before and periodically during treatment.

**DIRECTIONS FOR ADMINISTRATION**  For intravenous infusion (Kemicetine®), give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.
**Daptomycin**

**DRUG ACTION** Daptomycin is a lipopeptide antibacterial with a spectrum of activity similar to vancomycin but its efficacy against enterococci has not been established. It needs to be given with other antibacterials for mixed infections involving Gram-negative bacteria and some anaerobes.

**INDICATIONS AND DOSE**

Complicated skin and soft-tissue infections caused by Gram-positive bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA)

- By slow intravenous injection, or by intravenous infusion
- Adult: 4 mg/kg once daily; increased to 6 mg/kg once daily, increased dose only if associated with *Staphylococcus aureus* bacteraemia

*Staphylococcal endocarditis caused by organisms resistant to vancomycin or in patients intolerant of vancomycin (in combination with other antibacterials)*

- By slow intravenous injection, or by intravenous infusion
- Adult: 6 mg/kg once daily

**UNLICENSED USE** Not licensed for use in left-sided endocarditis.

**INTERACTIONS** → Appendix 1 (daptomycin).

Monitor creatine kinase more frequently than weekly during treatment if receiving another drug known to cause myopathy (preferably avoid concomitant use).

**SIDE-EFFECTS**

- Common or very common Abdominal pain · anaemia · anxiety · arthralgia · asthenia · constipation · diarrhoea · dizziness · flatulence · headache · hypertension · hypotension · injection-site reactions · insomnia · nausea · pruritus · rash · vomiting
- Uncommon Anorexia · arrhythmias · dyspepsia · electrolyte disturbances · esophagitis · flushing · glossitis · hyperglycaemia · muscle effects · muscle weakness · myalgia · myositis · paraesthesia · renal failure · taste disturbance · thrombocytopenia · tremor
- Rare Jaundice · rhombomylitis
- Frequency not known Antibiotic-associated colitis · elevated creatine kinase · eosinophilic pneumonia · peripheral neuropathy · syncope · wheezing

**SIDE-EFFECTS, FURTHER INFORMATION**

- Muscle effects If unexplained muscle pain, tenderness, weakness, or cramps develop during treatment, measure creatine kinase every 2 days; discontinue if unexplained muscular symptoms and creatine elevated markedly.
- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk—no information available.

**MEDICAL FORMS**

<table>
<thead>
<tr>
<th>Capsule</th>
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<tbody>
<tr>
<td>Chloramphenicol (Non-proprietary)</td>
</tr>
<tr>
<td>Chloramphenicol 250 mg</td>
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<tr>
<td>Chloramphenicol capsules 250 mg</td>
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<tr>
<td>Powder for solution for injection</td>
</tr>
<tr>
<td>ELECTROLYTES: May contain Sodium</td>
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<tr>
<td>Chloramphenicol (Non-proprietary)</td>
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<tr>
<td>Chloramphenicol (as Chloramphenicol sodium succinate)</td>
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<tr>
<td>1 gram Chloramphenicol 1g powder for solution for injection vials</td>
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<tr>
<td>1 vial Powder £22.00</td>
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<tr>
<td>Kemicetine (Pfizer Ltd)</td>
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<tr>
<td>Chloramphenicol (as Chloramphenicol sodium succinate)</td>
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<tr>
<td>1 gram Kemicetine 1g powder for solution for injection vials</td>
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<tr>
<td>1 vial Powder £1.39</td>
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**BREAST FEEDING** Present in milk in small amounts, but absorption from gastrointestinal tract negligible.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe hepatic impairment—no information available.

**RENAL IMPAIRMENT** Use normal dose every 48 hours if eGFR less than 30 mL/minute/1.73 m². If eGFR less than 80 mL/minute/1.73 m², monitor renal function, and monitor creatine kinase before treatment and then at least weekly during treatment.

**MONITORING REQUIREMENTS** Monitor creatine kinase before treatment and then weekly during treatment (more frequently if creatine kinase elevated more than 5 times upper limit of normal before treatment).

**EFFECT ON LABORATORY TESTS** Interference with assay for prothrombin time and INR—take blood sample immediately before daptomycin dose.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion *(Cubicin)*, give intermittently in Sodium chloride 0.9%; reconstitute with sodium chloride 0.9% (350 mg in 7 mL, 500 mg in 10 mL); gently rotate vial without shaking; allow to stand for at least 10 minutes then rotate gently to dissolve; dilute requisite dose in 50 mL infusion fluid and give over 30 minutes. For intravenous injection, give over 2 minutes.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2008) that daptomycin *(Cubicin)* is accepted for restricted use within NHS Scotland for the treatment of MRSA bacteraemia associated with right-sided endocarditis or with complicated skin and soft-tissue infections.

**MEDICAL FORMS**

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<tbody>
<tr>
<td>Chloramphenicol (as Chloramphenicol sodium succinate)</td>
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<tr>
<td>Chloramphenicol 250 mg Capsule</td>
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<tr>
<td>Powder for solution for infusion</td>
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<tr>
<td>ELECTROLYTES: May contain Sodium</td>
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<tr>
<td>Chloramphenicol (as Chloramphenicol sodium succinate)</td>
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<tr>
<td>1 gram Chloramphenicol 1g powder for solution for injection vials</td>
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<tr>
<td>1 vial Powder £22.00</td>
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<td>Kemicetine (Pfizer Ltd)</td>
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<tr>
<td>Chloramphenicol (as Chloramphenicol sodium succinate)</td>
</tr>
<tr>
<td>1 gram Kemicetine 1g powder for solution for injection vials</td>
</tr>
<tr>
<td>1 vial Powder £1.39</td>
</tr>
</tbody>
</table>

**Fidaxomicin**

**DRUG ACTION** Fidaxomicin is a macrocyclic antibacterial that is poorly absorbed from the gastro-intestinal tract, and, therefore, it should not be used to treat systemic infections.

**INDICATIONS AND DOSE**

*Clostridium difficile* infection

- By mouth
- Adult: 200 mg every 12 hours for 10 days, limited clinical data is available on the use of fidaxomicin in severe or life-threatening *Clostridium difficile* infection

**CAUTIONS** Inflammatory bowel disease · severe or life-threatening *C. difficile* infection

**INTERACTIONS** → Appendix 1 (fidaxomicin).

**SIDE-EFFECTS**

- Common or very common Constipation · nausea · vomiting
- Uncommon Abdominal distension · decreased appetite · dizziness · dry mouth · flatulence · headache · taste disturbance

**ALLERGY AND CROSS-SENSITIVITY** Use with caution in macrolide hypersensitivity.

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.
Infection

Frequency not known

Common or very common

RENAL IMPAIRMENT  Manufacturer advises caution in severe impairment—no information available.

With intravenous use

CAUTIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (June 2012) that fidaxomicin (Dificlir®) is accepted for restricted use within NHS Scotland to treat the first recurrence of C. difficile infection, on the advice of a microbiologist or specialist in infectious diseases.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 9

Dificlir (Astellas Pharma Ltd)

Fidaxomicin 200 mg Dificlir 200mg tablets | 20 tablet £1,350.00

Indications and Dose

Acute uncomplicated lower urinary-tract infections

BY MOUTH USING GRANULES

Adult: 3 g for 1 dose

Prophylaxis of urinary-tract infections in transurethral surgical procedures

BY MOUTH USING GRANULES

Adult: 3 g, to be given 3 hours before surgery. Dose may be repeated once, 24 hours after surgery

Osteomyelitis when first-line treatments are inappropriate or ineffective

Hospital-acquired lower respiratory-tract infections when first-line treatments are inappropriate or ineffective

BY INTRAVENOUS INFUSION

Adult: 12–24 g daily in 2–3 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

Complicated urinary-tract infections when first-line treatment ineffective or inappropriate

BY INTRAVENOUS INFUSION

Adult: 12–16 g daily in 2–3 divided doses (max. per dose 8 g)

Bacterial meningitis when first-line treatment ineffective or inappropriate

BY INTRAVENOUS INFUSION

Adult: 16–24 g daily in 3–4 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

CAUTIONS

With intravenous use Cardiac insufficiency · elderly (high doses) · hyperaldosteronism · hypernatraemia · hypertension · pulmonary oedema

INTERACTIONS  Appendix 1 (fosfomycin).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Gastro-intestinal disturbances

Uncommon Diarrhoea · nausea · rash · vomiting

Frequency not known Abdominal pain · antibiotic-associated colitis

SPECIFIC SIDE-EFFECTS

Common or very common

With oral use Diarrhoea · dizziness · headache

Uncommon

With intravenous use Decreased appetite · dyspnoea · fatigue · headache · hypernatraemia · hypokalaemia · taste disturbances · vertigo

Rare

With intravenous use Aplastic anaemia · blood disorders · eosinophilia

Very rare

With intravenous use Fatty liver · visual impairment

Frequency not known

With intravenous use Bronchospasm · confusion · hepatitis · jaundice · tachycardia

PREGNANCY  Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING  Manufacturer advises use only if potential benefit outweighs risk—present in milk.

RENAL IMPAIRMENT

With oral use Avoid oral treatment if eGFR less than 10 mL/minute/1.73 m².

With intravenous use Use intravenous treatment with caution if eGFR 40–80 mL/minute/1.73 m² and consult product literature for dose if eGFR less than 40 mL/minute/1.73 m².

MONITORING REQUIREMENTS

With intravenous use Monitor electrolytes and fluid balance.

DIRECTIONS FOR ADMINISTRATION

With intravenous use For Intravenous infusion (Fomicyt®), give intermittently in Glucose 5% or 10% or Water for Injections; reconstitute each 2-g vial with 50 mL infusion fluid; give 2 g over 15 minutes.

With oral use Manufacturer advises granules should be taken on an empty stomach (about 2–3 hours before or after a meal), preferably before bedtime and after emptying the bladder. The granules should be dissolved into a glass of water and taken immediately.

PRESCRIBING AND DISPENSING INFORMATION  Doses expressed as fosfomycin base.

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2015) that Fosfomycin (Fomicyt®) is accepted for restricted use within NHS Scotland; initiation should be restricted to microbiologists or infectious disease specialists.

MEDIcular FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule Granules

CAUTIONARY AND ADVISORY LABELS 9, 13, 23

EXCIPIENTS: May contain Sucrose

Fosfomycin (Non-proprietary)

Fosfomycin (as Fosfomycin trometamol) 3 gram Monurol 3g granules sachets | 1 sachet £0.45

Fosfomycin 3g granules sachets | 1 sachet £75.45

Monuril (Zambon S.p.A.)

Fosfomycin (as Fosfomycin trometamol) 3 gram Monuril 3g granules sachets | 1 sachet £4.86

Powder for solution for infusion

ELECTROLYTES: May contain Sodium

Fomicyt (Nordic Pharma Ltd)

Fosfomycin (as Fosfomycin sodium) 2 gram Fomicyt 2g powder for solution for infusion vials | 10 vial £150.00

Fosfomycin (as Fosfomycin sodium) 4 gram Fomicyt 4g powder for solution for infusion vials | 10 vial £300.00

Fosfomycin 12-Dec-2016

Drug Action

Fosfomycin, a phosphonic acid antibacterial, is active against a range of Gram-positive and Gram-negative bacteria including Staphylococcus aureus and Enterobacteriaceae.
Fusidic acid

- **DRUG ACTION** Fusidic acid and its salts are narrow-spectrum antibiotics used for staphylococcal infections.

### INDICATIONS AND DOSE

#### Staphylococcal skin infection
- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 250 mg every 12 hours for 5-10 days
  - Adult: 250 mg every 12 hours for 5-10 days
- **TO THE SKIN**
  - Child: Apply 3–4 times a day usually for 7 days
  - Adult: Apply 3–4 times a day

**Penicillin-resistant staphylococcal infection including osteomyelitis | Staphylococcal endocarditis in combination with other antibacterials**
- **BY MOUTH USING ORAL SUSPENSION**
  - Child 1-11 months: 15 mg/kg 3 times a day
  - Child 1-4 years: 250 mg 3 times a day
  - Child 5-11 years: 500 mg 3 times a day
  - Child 12-17 years: 750 mg 3 times a day
  - Adult: 750 mg 3 times a day
- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 500 mg every 8 hours, increased to 1 g every 8 hours, increased dose can be used for severe infections
  - Adult: 500 mg every 8 hours, increased to 1 g every 8 hours, increased dose can be used for severe infections

**DOSE EQUIVALENCE AND CONVERSION**
- **With oral use**
  - Fusidic acid is incompletely absorbed and doses recommended for suspension are proportionately higher than those for sodium fusidate tablets.

### CAUTIONS
- With topical use Avoid contact of cream or ointment with eyes.

**CAUTIONS, FURTHER INFORMATION**
- **Avoiding resistance** To avoid the development of resistance, fusidic acid should not be used for longer than 10 days and local microbiology advice should be sought before using it in hospital.

### INTERACTIONS
- **Appendix 1 (fusidic acid).**

### SIDE-EFFECTS
- **Common or very common**
  - With oral use Abdominal pain · diarrhoea · dizziness · drowsiness · dyspepsia · nausea · vomiting
  - **Uncommon**
  - With oral use Anorexia · headache · malaise · pruritus · rash
  - **Rare**
  - With topical use Hypersensitivity reactions
  - **Frequency not known**
  - With oral use Acute renal failure (usually with jaundice) · blood disorders · reversible jaundice especially after high dosage (withdraw therapy if persistent)

### PREGNANCY
- With oral use Not known to be harmful; manufacturer advises use only if potential benefit outweighs risk.

### BREAST FEEDING
- With oral use Present in milk—manufacturer advises caution.

### HEPATIC IMPAIRMENT
- With oral use Impaired biliary excretion; possibly increased risk of hepatotoxicity; avoid or reduce dose.
  - Elimination may be reduced in hepatic impairment or biliary disease or biliary obstruction.
  - Monitor liver function in hepatic impairment.

### MONITORING REQUIREMENTS
- With oral use Monitor liver function with high doses or on prolonged therapy.

### PRESCRIBING AND DISPENSING INFORMATION
- Flavours of oral liquid formulations may include banana and orange.

### PROFESSION SPECIFIC INFORMATION
- Dental practitioners' formulary
  - May be prescribed as Sodium Fusidate ointment.

### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

#### Tablet
- **CAUTIONARY AND ADVISORY LABELS**
  - **Fucidin (Sodium fusidate)** (LEO Pharma)
    - Sodium fusidate 250 mg Fucidin 250mg tablets | 10 tablet £6.02 DT price = £6.02 | 100 tablet £54.99

#### Oral suspension
- **CAUTIONARY AND ADVISORY LABELS**
  - **Fucidin (Fusidic acid)** (LEO Pharma)
    - Fusidic acid 50 mg per 1 ml Fucidin 250mg/5ml oral suspension | 50 ml £6.73 DT price = £6.73

#### Cream
- **EXCIPIENTS:** May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol)
  - **Fucidic acid (Non-proprietary)**
    - Fusidic acid 20 mg per 1 g Fusidic acid 2% cream | 15 gram £1.92 DT price = £1.77 | 30 gram £3.62 DT price = £3.54
  - **Fucidin (Fusidic acid)** (LEO Pharma)
    - Fusidic acid 20 mg per 1 g Fucidin 20mg/g cream | 15 gram £1.92 DT price = £1.77 | 30 gram £3.59 DT price = £3.54

#### Ointment
- **EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), wool fat and related substances including lanolin
  - **Fucidin (Sodium fusidate)** (LEO Pharma)
    - Sodium fusidate 20 mg per 1 g Fucidin 20mg/g ointment | 15 gram £2.68 DT price = £2.68 | 30 gram £4.55 DT price = £4.55

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**Linezolid**

- **DRUG ACTION** Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including meticillin-resistant *Staphylococcus aureus* (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.

### INDICATIONS AND DOSE

**Pneumonia (when other antibacterials e.g. a glycopeptide, such as vancomycin, cannot be used) (initiated under specialist supervision)**
- **Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)**
  - **BY MOUTH**
    - Adult: 600 mg every 12 hours usually for 10–14 days (maximum duration of treatment 28 days)
  - **BY INTRAVENOUS INFUSION**
    - Adult: 600 mg every 12 hours

### IMPORTANT SAFETY INFORMATION

**CHM ADVICE (OPTIC NEUROPATHY)**
- Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:
  - patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately;
patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;

visual function should be monitored regularly if treatment is required for longer than 28 days.

BLOOD DISORDERS
Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

- receive treatment for more than 10–14 days;
- have pre-existing myelosuppression;
- are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function;
- have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

CAUTIONS
Acute confusional states, bipolar depression, carcinoid tumour, elderly (increased risk of blood disorders), history of seizures, phaeochromocytoma, schizophreneia, thyrotoxicosis, uncontrolled hypertension

CAUTIONS, FURTHER INFORMATION

Close observation. Unless close observation and blood pressure monitoring possible, linezolid should be avoided in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states.

INTERACTIONS → Appendix 1 (MAOIs).

Monoamine oxidase inhibition Linezolid is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, 5HT, agonists (‘triptans’), tricyclic antidepressants, sympathomimetics, dopaminergics, bupivacaine, and possibly other opioid analgesics.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Diarrhoea, eosinophilia, headache, nausea, taste disturbances, vomiting

Uncommon Abdominal pain, blurred vision, constipation, diaphoresis, dizziness, dry mouth, dyspepsia, electrolyte disturbances, fatigue, fever, gastricul, glossitis, hypertension, hypoaesthesia, insomnia, leucopenia, pancreatitis, paraesthesia, polyuria, pruritus, rash, stomatitis, thirst, thrombocytopenia, tinnitus, tongue discoloration

Rare Renal failure, tachycardia, transient ischaemic attacks

Frequency not known Anaemia, antibiotic-associated colitis, convulsions, hypotension, lactic acidosis, optic neuropathy reported on prolonged therapy, pancytopenia, peripheral neuropathy reported on prolonged therapy, Stevens-Johnson syndrome, tooth discoloration, toxic epidermal necrolysis

SPECIFIC SIDE-EFFECTS

Uncommon

With intravenous use Injection-site reactions

PREGNANCY

Manufacturer advises use only if potential benefit outweighs risk—no information available.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

In severe hepatic impairment manufacturer advises use only if potential benefit outweighs risk.

RENAL IMPAIRMENT

Manufacturer advises metabolites may accumulate if eGFR less than 30 ml/minute/1.73 m².

MONITORING REQUIREMENTS

Monitor full blood count (including platelet count) weekly.

DIRECTIONS FOR ADMINISTRATION

Infusion to be administered over 30–120 minutes.

PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include orange.

PATIENT AND CARER ADVICE

Patients should be advised to read the patient information leaflet given with linezolid.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 9, 10

Linezolid (Non-proprietary)

Linezolid 600 mg Linezolid 600mg tablets | 10 tablet £228.86–£445.00 DT price = £392.86

Zyvox (Pfizer Ltd)

Linezolid 600 mg Zyvox 600mg tablets | 10 tablet £445.00 DT price = £392.86

Oral suspension

CAUTIONARY AND ADVISORY LABELS 9, 10

EXCIPIENTS: May contain Aspartame

Zyvox (Pfizer Ltd)

Linezolid 20 mg per 1 ml 200mg/5ml granules for oral suspension | 150 ml £222.90

Infusion

EXCIPIENTS: May contain Glucose

ELECTROLYTES: May contain Sodium

Linezolid (Non-proprietary)

Linezolid 2 mg per 1 ml Linezolid 600mg/300ml infusion bags | 10 bag £445.00 (Hospital only)

Zyvox (Pfizer Ltd)

Linezolid 2 mg per 1 ml Zyvox 600mg/300ml infusion bags | 10 bag £445.00

Tedizolid

26-Sep-2016

DRUG ACTION

Tedizolid is an oxazolidinone antibacterial, which inhibits bacterial protein synthesis.

INDICATIONS AND DOSE

Treatment of acute bacterial skin and skin structure infections

BY INTRAVENOUS INFUSION, OR BY MOUTH

Adult: 200 mg once daily for 6 days, patients should be switched from the intravenous to the oral route when clinically appropriate

CAUTIONS

Neutropenia—limited clinical experience. Patients aged 75 years and over—limited clinical experience

INTERACTIONS → Appendix 1 (MAOIs).

Monoamine-oxidase inhibition Tedizolid is a reversible, non-selective monoamine-oxidase inhibitor (MAOI). Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, tedizolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, 5HT, agonists (‘triptans’), tricyclic antidepressants, sympathomimetics, dopaminergics, bupivacaine, and possibly other opioid analgesics.
Trimethoprim

**INDICATIONS AND DOSE**

**Urinary-tract infections**  
**Respiratory tract infections**

- **BY MOUTH**
  - Child 4–5 weeks: 4 mg/kg twice daily (max. per dose 200 mg)
  - Child 6 weeks–5 months: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 25 mg twice daily
  - Child 6 months–5 years: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 50 mg twice daily
  - Child 6–11 years: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 100 mg twice daily
  - Child 12–17 years: 200 mg twice daily
  - Adult: 200 mg twice daily

**Prophylaxis of urinary-tract infection** (considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage)

- **BY MOUTH**
  - Child 4–5 weeks: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night
  - Child 6 weeks–5 months: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 12.5 mg once daily, dose to be taken at night
  - Child 6 months–5 years: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 25 mg once daily, dose to be taken at night
  - Child 6–11 years: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 50 mg once daily, dose to be taken at night
  - Child 12–17 years: 100 mg once daily, dose to be taken at night
  - Adult: 100 mg once daily, dose to be taken at night

**Treatment of mild to moderate Pneumocystis jirovecii (Pneumocystis carinii) pneumonia in patients who cannot tolerate co-trimoxazole (in combination with dapsone)**

- **BY MOUTH**
  - Child: 5 mg/kg every 6–8 hours
  - Adult: 5 mg/kg every 6–8 hours

**Acne resistant to other antibacterials**

- **BY MOUTH**
  - Adult: 300 mg twice daily

**Prostatitis**

- **BY MOUTH**
  - Adult: (consult product literature)

**Shigellosis | Invasive salmonella infection**

- **BY MOUTH**
  - Adult: (consult product literature)

**UNLICENSED USE**


**CONTRA-INDICATIONS**

- Blood dyscrasias

**CAUTIONS**

- Elderly · acute porphyrinas p. 930 · predisposition to folate deficiency

**INTERACTIONS**

- Appendix 1 (trimethoprim).

**SIDE-EFFECTS**

- Rare Allergic reactions · anaphylaxis · angioedema · erythema multiforme · photosensitivity · toxic epidermal necrolysis

- Frequency not known Aseptic meningitis · depression of haematopoiesis · gastro-intestinal disturbances · hyperkalaemia · nausea · pruritus · rashes · uvetitis (in adults) · vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Trimethoprim has side-effects similar to co-trimoxazole but they are less severe and occur less frequently.
\* **PREGNANCY** Teratogenic risk in first trimester (folate antagonist). Manufacturers advise avoid during pregnancy.

\* **BREAST FEEDING** Present in milk—short-term use not known to be harmful.

\* **RENAL IMPAIRMENT**
  - In adults Use half normal dose after 3 days if eGFR 15–30 mL/minute/1.73 m². Use half normal dose if eGFR less than 15 mL/minute/1.73 m².
  - In children Use half normal dose after 3 days if estimated glomerular filtration rate 15–30 mL/minute/1.73 m². Use half normal dose if estimated glomerular filtration rate less than 15 mL/minute/1.73 m². Monitor plasma-trimethoprim concentration if eGFR less than 10 mL/minute/1.73 m².

\* **MONITORING REQUIREMENTS** Manufacturer recommends blood counts on long-term therapy (but evidence of practical value unsatisfactory).

\* **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Trimethoprim for bacterial infections www.medicinesforchildren.org.uk/trimethoprim-for-bacterial-infections

Blood disorders On long-term treatment, patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

\* **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
- **CAUTIONARY AND ADVISORY LABELS 9**
  - **Trimethoprim (Non-proprietary)**
    - **Trimethoprim 100 mg** Trimethoprim 100mg tablets | 28 tablet (PO) £9.99 DT price = £1.27
    - **Trimethoprim 200 mg** Trimethoprim 200mg tablets | 6 tablet (PO) £2.15 DT price = £0.73 | 14 tablet (PO) £9.99 DT price = £1.71

Oral suspension
- **CAUTIONARY AND ADVISORY LABELS 9**
  - **Trimethoprim (Non-proprietary)**
    - **Trimethoprim 10 mg per 1 ml** Trimethoprim 50mg/5ml oral suspension sugar-free | 100 ml (PO) £2.03 DT price = £2.00
    - **Monotrim** (Chemidex Pharma Ltd)
      - **Trimethoprim 10 mg per 1 ml** Monotrim 50mg/5ml oral suspension sugar-free | 100 ml (PO) £1.77 DT price = £2.00

\* **ANTIMYCOBACTERIALS › RIFAMYCINS**

\* **Rifabutin**

\* **INDICATIONS AND DOSE**
  - **Prophylaxis of Mycobacterium avium complex infections in immunosuppressed patients with low CD4 count**
    - **BY MOUTH**
    - Adult: 300 mg once daily, also consult product literature
  - **Treatment of non-tuberculous mycobacterial disease, in combination with other drugs**
    - **BY MOUTH**
    - Adult: 450–600 mg once daily for up to 6 months after cultures negative
  - **Treatment of pulmonary tuberculosis, in combination with other drugs**
    - **BY MOUTH**
    - Adult: 150–450 mg once daily for at least 6 months

\* **CAUTIONS** Acute porphyrias p. 930. discosolurs soft contact lenses

\* **INTERACTIONS** → Appendix 1 (rifamycins).

\* **SIDE-EFFECTS**
  - **Common or very common** Anaemia · blood disorders · leucopenia · malabsorption · myalgia · nausea · pyrexia · rash · thrombocytopenia
  - **Uncommon** Arthralgia · body secretions coloured orange-red · bronchospasm · congeal deposits · eosinophilia · hypersensitivity reactions · jaundice · raised liver enzymes · saliva coloured orange-red · skin coloured orange-red · urinary orange-red · urethritis (especially following high doses or concomitant use with drugs that increase plasma concentration) · vomiting
  - **Rare** Haemolysis
  - **Frequency not known** Chest pain · dyspnoea · hepatitis · influenza-like symptoms

\* **SIDE-EFFECTS, FURTHER INFORMATION** Discontinue permanently if serious side-effects develop.

\* **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with rifamycin hypersensitivity.

\* **CONCEPTION AND CONTRACEPTION** Important Rifabutin induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced; alternative family planning advice should be offered.

\* **PREGNANCY** Manufacturer advises avoid—no information available.

\* **BREAST FEEDING** Manufacturer advises avoid—no information available.

\* **HEPATIC IMPAIRMENT** Reduce dose in severe impairment. In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months; blood counts should also be monitored in these patients.

\* **RENAL IMPAIRMENT** Use half normal dose if eGFR less than 30 mL/minute/1.73 m².

\* **MONITORING REQUIREMENTS**
  - **Renal function** should be checked before treatment.
  - **Hepatic function** should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However, hepatic function should be monitored on prolonged therapy.
  - Blood counts should be monitored on prolonged therapy.
  - Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months. Blood counts should also be monitored in these patients.

\* **PRESCRIBING AND DISPENSING INFORMATION** If treatment interruption occurs, re-introduce with low dosage and increase gradually.

\* **PATIENT AND CARER ADVICE**
  - Soft contact lenses Patients or their carers should be advised that rifabutin discoulours soft contact lenses. Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

\* **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Capsule
- **CAUTIONARY AND ADVISORY LABELS 8, 14**
  - **Mycobutin** (Pfizer Ltd)
    - **Rifabutin 150 mg** Mycobutin 150mg capsules | 30 capsule (PO) £90.38
**Rifaximin**

- **DRUG ACTION** Rifaximin is a rifamycin that is poorly absorbed from the gastro-intestinal tract, and, therefore, should not be used to treat systemic infections.

- **INDICATIONS AND DOSE**

  **Travellers’ diarrhoea that is not associated with fever, bloody diarrhoea, blood or leucocytes in the stool, or 8 or more unformed stools in the previous 24 hours**
  - **BY MOUTH**
    - Adult: 200 mg every 8 hours for 3 days

- **Reduction in recurrence of hepatic encephalopathy**
  - **BY MOUTH**
    - Adult: 550 mg twice daily

- **CONTRA-INDICATIONS** Intestinal obstruction

- **INTERACTIONS** → Appendix 1 (rifaximin).

  Rifamycins interactions in Appendix 1 do not apply to rifaximin.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain • depression • diarrhoea • dizziness • dysphoria • flatulence • headache • muscle spasm • nausea • pruritus • rash • vomiting
  - **Uncommon** Anorexia • antibiotic-associated colitis • anxiety • blood disorders • convulsions • dry mouth • dysuria • glycosuria • hyperkalaemia • hypoesthesia • influenza-like symptoms • memory impairment • paraesthesia • peripheral oedema • polyneuropathy • polyuria • sleep disturbances • taste disturbances
  - **Rare** Blood pressure changes • constipation
  - **Frequency not known** Syncope

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of rifamycin hypersensitivity.

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Unlikely to be present in milk in significant amounts, but manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution when used for hepatic encephalopathy in patients with severe hepatic impairment.

- **PRESCRIBING AND DISPENSING INFORMATION**

  Not recommended for diarrhoea associated with invasive organisms such as *Campylobacter* and *Shigella*.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**

  - Rifaximin for preventing episodes of overt hepatic encephalopathy (March 2015) NICE TA337

    Rifaximin is recommended, within its marketing authorisation, as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in adults.

    www.nice.org.uk/TA337

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - **CAUTIONARY AND ADVISORY LABELS** 14 (Targaxan® brand only), 9 (Xifaxan® brand only)
    - **Targaxan** (Norgine Pharmaceuticals Ltd)
      - Rifaximin 550 mg: Targaxan 550mg tablets | 56 tablet | £250.23 DT price = £259.23
    - **Xifaxan®** (Norgine Pharmaceuticals Ltd)
      - Rifaximin 200 mg: Xifaxan® 200mg tablets | 9 tablet | £15.15 DT price = £15.15

  **Oral suspension**

  - **Rifaximin (Non-proprietary)**
    - Rifaximin 20 mg per 1 ml: Normix 100mg/5ml granules for oral suspension | 100 ml | no price available

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**2.1 Anthrax**

**Anthrax**

**Treatment and post-exposure prophylaxis**

*Inhalation* or *gastro-intestinal anthrax* should be treated initially with either ciprofloxacin p. 514 or, in patients over 12 years, doxycycline p. 521 [unlicensed indication] combined with one or two other antibacterials (such as amoxicillin p. 506, benzylpenicillin sodium p. 504, chloramphenicol p. 524, clarithromycin p. 496, clindamycin p. 493, imipenem with cilastatin p. 482, rifampicin p. 535 [unlicensed indication], and vancomycin p. 492). When the condition improves and the sensitivity of the *Bacillus anthracis* strain is known, treatment may be switched to a single antibacterial. Treatment should continue for 60 days because germination may be delayed.

Cutaneous anthrax should be treated with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] for 7 days. Treatment may be switched to amoxicillin if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck.

Ciprofloxacin or doxycycline may be given for *post-exposure prophylaxis*. If exposure is confirmed, antibacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin after 10–14 days if the strain of *B. anthracis* is susceptible. Vaccination against anthrax may allow the duration of antibacterial prophylaxis to be shortened.

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**2.2 Leprosy**

**Leprosy**

**Management**

Advice from a member of the Panel of Leprosy Opinion is essential for the treatment of leprosy (Hansen’s disease).

Details can be obtained from the Hospital for Tropical Diseases, London (telephone (020) 3456 7890).

The World Health Organization has made recommendations to overcome the problem of dapsone resistance and to prevent the emergence of resistance to other antileprotic drugs. Drugs recommended are dapsone p. 532, rifampicin p. 535, and clofazimine p. 532. Other drugs with significant activity against *Mycobacterium leprae* include ofloxacin p. 517, minocycline p. 522 and clarithromycin p. 496, but none of these are as active as rifampicin; at present they should be reserved as second-line drugs for leprosy.

A three-drug regimen is recommended for *multibacillary* leprosy (lepromatous, borderline-lepromatous, and borderline leprosy) and a two-drug regimen for *paucibacillary leprosy* (borderline-tuberculoid, tuberculoid, and indeterminate).

Multibacillary leprosy should be treated with a combination of rifampicin, dapsone and clofazimine for at least 2 years. Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum leprosum) reactions. During reversal reactions neuritic pain or weakness can herald the rapid onset of permanent nerve damage. Treatment with prednisolone p. 622 should be instituted at once. Mild type II reactions may respond to aspirin. Severe type II reactions may require corticosteroids; thalidomide p. 856 [unlicensed] is also useful in patients who

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have become corticosteroid dependent, but it should be used only under specialist supervision. Thalidomide is teratogenic and, therefore, contra-indicated in pregnancy; it must not be given to women of child-bearing potential unless they comply with a pregnancy prevention programme. Increased doses of clofazimine are also useful.

Paucibacillary leprosy should be treated with rifampicin and dapsone for 6 months. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course.

Neither the multibacillary nor the paucibacillary antileprosy regimen is sufficient to treat tuberculosis.

**ANTIMYCOBACTERIALS**

**Clofazimine**

- **INDICATIONS AND DOSE**

  Multibacillary leprosy in combination with rifampicin and dapsone (3-drug regimen) (administered on expert advice)
  - **BY MOUTH**
  - Adult: 300 mg once a month, to be administered under supervision and 50 mg daily, to be self-administered, alternatively 300 mg once a month, to be administered under supervision and 100 mg once daily on alternate days, to be self-administered

  Lepromatous lepra reactions (administered on expert advice)
  - **BY MOUTH**
  - Adult: 300 mg daily for max. 3 months
  - Severe type II (erythema nodosum leprosum) reactions (administered on expert advice)
  - **BY MOUTH**
  - Adult: 100 mg 3 times a day for one month, subsequent dose reductions are required, may take 4–6 weeks to attain full effect

- **CAUTIONS**

  Avoid if persistent abdominal pain and diarrhoea · may discolour soft contact lenses

- **SIDE-EFFECTS**

  Abdominal pain · acne-like eruptions · anorexia · bowel obstruction · brownish-black discoloration of lesions and skin including areas exposed to light · dimmed vision · dry eyes · dry skin · elevation of blood sugar · eosinophilic enteropathy · headache · lymphadenopathy · macular corneal pigmentation · nausea · photosensitivity · pruritus · rash · red discoloration of body fluids · red discoloration of faeces · red discoloration of urine · reversible hair discoloration · splenic infarction · subepithelial corneal pigmentation · tiredness · vomiting (hospitalise if persistent) · weight loss

- **PREGNANCY**

  Use with caution.

- **BREAST FEEDING**

  May alter colour of milk; skin discoloration of infant.

- **HEPATIC IMPAIRMENT**

  Use with caution.

- **RENAL IMPAIRMENT**

  Use with caution.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

  - **Capsule**
    - CAUTIONARY AND ADVISORY LABELS 8, 14, 21
    - Clofazimine (Non-proprietary)
      - Clofazimine 50 mg Lamprene 50mg capsules | 100 capsule [POM]
        - no price available

**Dapsone**

- **INDICATIONS AND DOSE**

  Multibacillary leprosy in combination with rifampicin and clofazimine (3-drug regimen) · Paucibacillary leprosy in combination with rifampicin (2-drug regimen)
  - **BY MOUTH**
  - Adult (body-weight up to 35 kg): 50 mg daily, alternatively 1–2 mg/kg daily, may be self-administered
  - Adult (body-weight 35 kg and above): 100 mg daily, may be self-administered

  **Dermatitis herpetiformis**
  - **BY MOUTH**
  - Adult: (consult product literature or local protocols)

  **Treatment of mild to moderate Pneumocystis jirovecii (Pneumocystis carinii) pneumonia (in combination with trimethoprim)**
  - **BY MOUTH**
  - Adult: 100 mg once daily

  **Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia**
  - **BY MOUTH**
  - Adult: 100 mg daily

- **UNLICENSED USE**

  Not licensed for treatment of pneumocystis (P. jirovecii) pneumonia.

- **CAUTIONS**

  Anaemia (treat severe anaemia before starting) · avoid in acute porphyrias p. 930 · cardiac disease · G6PD deficiency · pulmonary disease · susceptibility to haemolysis

- **INTERACTIONS**

  → Appendix 1 (dapsone).

- **SIDE-EFFECTS**

  Rare Stevens-Johnson syndrome · toxic epidermal necrolysis

- **Frequency not known**

  Agranulocytosis · allergic dermatitis · anorexia · dapsone syndrome · haemolysis · headache · hepatitis · insomnia · methaemoglobinemia · nausea · neuropathy · psychosis · tachycardia · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**

  Dapsone syndrome If dapsone syndrome occurs (rash with photosensitivity) → consult product literature or local protocols

- **Frequency not known**

  Agranulocytosis · allergic dermatitis · anorexia · dapsone syndrome · haemolysis · headache · hepatitis · insomnia · methaemoglobinemia · nausea · neuropathy · psychosis · tachycardia · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**

  Dapsone syndrome If dapsone syndrome occurs (rash with photosensitivity) → consult product literature or local protocols

- **Frequency not known**

  Agranulocytosis · allergic dermatitis · anorexia · dapsone syndrome · haemolysis · headache · hepatitis · insomnia · methaemoglobinemia · nausea · neuropathy · psychosis · tachycardia · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**

  Dapsone syndrome If dapsone syndrome occurs (rash with photosensitivity) → consult product literature or local protocols

- **Frequency not known**

  Agranulocytosis · allergic dermatitis · anorexia · dapsone syndrome · haemolysis · headache · hepatitis · insomnia · methaemoglobinemia · nausea · neuropathy · psychosis · tachycardia · vomiting

- **PREGNANCY**

  Folic acid p. 989 (higher dose) should be given to mother throughout pregnancy; neonatal haemolysis and methaemoglobinemia reported in third trimester.

- **BREAST FEEDING**

  Haemolytic anaemia; although significant amount in milk, risk to infant very small unless infant is G6PD deficient.

- **PATIENT AND CARER ADVICE**

  Blood disorders On long-term treatment, patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Tablet**

  - CAUTIONARY AND ADVISORY LABELS 8
  - Dapsone (Non-proprietary)
    - Dapsone 50 mg Dapsone 50mg tablets | 28 tablet [POM] £58.89 DT price = £32.68
    - Dapsone 100 mg Dapsone 100mg tablets | 28 tablet [POM] £117.80 DT price = £105.07
2.3 Lyme disease

Lyme disease

Treatment

Lyme disease should generally be treated by those experienced in its management. Doxycycline p. 521, amoxicillin p. 506 [unlicensed indication] or cefuroxime p. 486 (as cefuroxime axetil) are the antibacterials of choice for early Lyme disease or Lyme arthritis. If these antibacterials are contra-indicated, a macrolide (e.g. clarithromycin p. 496) can be used for early Lyme disease. Intravenous administration of ceftriaxone p. 489, cefotaxime p. 487, or benzylpenicillin sodium p. 504 is recommended for Lyme disease associated with cardiac or neurological complications. The duration of treatment is usually 2–4 weeks; Lyme arthritis may require further treatment.

2.4 Methicillin-resistant staphylococcus aureus

MRSA

Management

Infection from *Staphylococcus aureus* strains resistant to meticillin [now discontinued] (meticillin-resistant *Staph. aureus*, MRSA) and to flucloxacillin p. 511 can be difficult to manage. Treatment is guided by the sensitivity of the infecting strain.

Rifampicin p. 535 or fusidic acid p. 527 should not be used alone because resistance may develop rapidly. A tetracycline alone or a combination of rifampicin and fusidic acid can be used for skin and soft-tissue infections caused by MRSA; clindamycin p. 493 alone is an alternative. A glycopeptide (e.g. vancomycin p. 492) can be used for severe skin and soft-tissue infections associated with MRSA; if a glycopeptide is unsuitable, linezolid p. 527 can be used on expert advice. As linezolid is not active against Gram-negative organisms, it can be used for mixed skin and soft-tissue infections only when other treatments are not available; linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. A combination of a glycopeptide and fusidic acid or a glycopeptide and rifampicin can be considered for skin and soft-tissue infections that have failed to respond to a single antibacterial.

Tigecycline p. 524 and daptomycin p. 525 are licensed for the treatment of complicated skin and soft-tissue infections involving MRSA.

A tetracycline or clindamycin can be used for *bronchiectasis* caused by MRSA. A glycopeptide can be used for *pneumonia* associated with MRSA; if a glycopeptide is unsuitable, linezolid can be used on expert advice. Linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms.

A tetracycline can be used for *urinary-tract infections* caused by MRSA; trimethoprim p. 529 or nitrofurantoin p. 544 are alternatives. A glycopeptide can be used for urinary-tract infections that are severe or resistant to other antibacterials.

A glycopeptide can be used for *septicaemia* associated with MRSA.

See the management of *endocarditis*, *osteomyelitis*, or *septic arthritis* associated with MRSA.

Prophylaxis with vancomycin or teicoplanin p. 491 (alone or in combination with another antibacterial active against other pathogens) is appropriate for patients undergoing surgery if:

- there is a history of MRSA colonisation or infection without documented eradication;
- there is a risk that the patient’s MRSA carriage has recurred;
- the patient comes from an area with a high prevalence of MRSA.

See eradication of nasal carriage of MRSA in *Nose* p. 1055.

2.5 Tuberculosis

Tuberculosis

Treatment phases, overview

Tuberculosis is treated in two phases—an initial phase using 4 drugs and a continuation phase using 2 drugs in fully sensitive cases. Treatment requires specialised knowledge and supervision, particularly where the disease involves resistant organisms or non-respiratory organs.

There are two regimens recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen should be used; the two regimens should not be used concurrently. Compliance with therapy is a major determinant of its success.

Initial phase

The concurrent use of 4 drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as combination preparations unless one of the components cannot be given because of resistance or intolerance. The treatment of choice for the initial phase is the daily use of isoniazid p. 541, rifampicin p. 535, pyrazinamide p. 542 and ethambutol hydrochloride p. 540. Treatment should be started without waiting for culture results if clinical features or histology results are consistent with tuberculosis; treatment should be continued even if initial culture results are negative. The initial phase drugs should be continued for 2 months. Where a positive culture for *M. tuberculosis* has been obtained, but susceptibility results are not available after 2 months, treatment with rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride should be continued until full susceptibility is confirmed, even if this is for longer than 2 months.

Streptomycin p. 480 is rarely used in the UK but it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced.

Continuation phase

After the initial phase, treatment is continued for a further 4 months with rifampicin with isoniazid p. 537 (preferably given as a combination preparation). Longer treatment is necessary for meningitis, direct spinal cord involvement, and for resistant organisms which may also require modification of the regimen.

Unsupervised treatment

The unsupervised treatment regimen should be used for patients who are likely to take antituberculous drugs reliably without supervision. Patients who are unlikely to comply with daily administration of antituberculous drugs should be treated with the regimen described under Supervised Treatment.
### Recommended dosage for standard unsupervised 6-month treatment

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Adult:</th>
<th>Child:</th>
</tr>
</thead>
</table>
| **Rifampicin with isoniazid and** pyrazinamide | - body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 40–49 kg: 4 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 50–64 kg: 5 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast | - body-weight up to 50 kg: 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 450 mg per day  
- body-weight 50 kg and above: 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 600 mg per day  
- body-weight up to 50 kg: 35 mg/kg once daily for 2 months (initial phase); maximum 1.5 g per day  
- body-weight 50 kg and above: 35 mg/kg once daily for 2 months (initial phase); maximum 2 g per day |
| **Ethambutol hydrochloride**     | Adult: 15 mg/kg once daily for 2 months (initial phase)                                     | Child: 20 mg/kg once daily for 2 months (initial phase)                                       |
| **Rifampicin**                   | Adult:                                                                                   | Adult: 30 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases) |
|                                 | - body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 40–49 kg: 4 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 50–64 kg: 5 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast | - body-weight up to 50 kg: 15 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase);  
- body-weight 50 kg and above: 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)  
- body-weight up to 50 kg: 2 g 3 times a week for 2 months (initial phase);  
- body-weight 50 kg and above: 2.5 g 3 times a week for 2 months (initial phase) |
| **Pyrazinamide**                 | Adult: 600–900 mg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases) | Child:                                                                                     |
|                                 | - body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 40–49 kg: 4 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 50–64 kg: 5 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast | - body-weight up to 50 kg: 35 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase);  
- body-weight 50 kg and above: 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)  
- body-weight up to 50 kg: 2 g 3 times a week for 2 months (initial phase);  
- body-weight 50 kg and above: 2.5 g 3 times a week for 2 months (initial phase) |
| **Ethambutol hydrochloride**     | Adult: 15 mg/kg once daily for 2 months (initial phase)                                     | Adult: 30 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases) |

### Recommended dosage for intermittent supervised 6-month treatment

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Adult:</th>
<th>Child:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Adult: 30 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)</td>
<td>Child: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)</td>
</tr>
</tbody>
</table>
|                                 | - body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 40–49 kg: 4 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 50–64 kg: 5 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast | - body-weight up to 50 kg: 15 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase);  
- body-weight 50 kg and above: 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)  
- body-weight up to 50 kg: 2 g 3 times a week for 2 months (initial phase);  
- body-weight 50 kg and above: 2.5 g 3 times a week for 2 months (initial phase) |
| **Rifampicin**                   | Adult: 600–900 mg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases) | Child:                                                                                     |
|                                 | - body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 40–49 kg: 4 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 50–64 kg: 5 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast | - body-weight up to 50 kg: 35 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase);  
- body-weight 50 kg and above: 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)  
- body-weight up to 50 kg: 2 g 3 times a week for 2 months (initial phase);  
- body-weight 50 kg and above: 2.5 g 3 times a week for 2 months (initial phase) |
| **Pyrazinamide**                 | Adult: 600–900 mg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases) | Child:                                                                                     |
|                                 | - body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 40–49 kg: 4 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 50–64 kg: 5 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast;  
- body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use Rifater\textsuperscript{®} Tablets, preferably taken before breakfast | - body-weight up to 50 kg: 35 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase);  
- body-weight 50 kg and above: 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)  
- body-weight up to 50 kg: 2 g 3 times a week for 2 months (initial phase);  
- body-weight 50 kg and above: 2.5 g 3 times a week for 2 months (initial phase) |
Pregnancy and breast-feeding
The standard unsupervised 6-month treatment regimen may be used during pregnancy. Streptomycin should not be given in pregnancy.

The standard unsupervised 6-month treatment regimen may be used during breast-feeding.

Supervised treatment
Drug administration needs to be fully supervised (directly observed therapy, DOT) in patients who cannot comply reliably with the treatment regimen. These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol hydrochloride (or streptomycin) 3 times a week under supervision for the first 2 months followed by isoniazid and rifampicin 3 times a week for a further 4 months.

Immunocompromised patients
Multi-resistant Mycobacterium tuberculosis may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity. Conflated M. tuberculosis infection sensitive to first-line drugs should be treated with a standard 6-month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms, and specialist advice is needed.

Corticosteroids
In meningeal or pericardial tuberculosis, a corticosteroid should be started at the same time as antituberculosis therapy.

Prevention of tuberculosis
Some individuals may develop tuberculosis owing to reactivation of previously latent disease. Chemoprophylaxis may be required in those who have evidence of latent tuberculosis and are receiving treatment with immunosuppressants (including cytotoxics and possibly long-term treatment with systemic corticosteroids). In these cases, chemoprophylaxis involves use of either isoniazid alone for 6 months or of isoniazid and rifampicin for 3 months; longer chemoprophylaxis is not recommended.

Corticosteroids
In meningeal or pericardial tuberculosis, a corticosteroid should be started at the same time as antituberculosis therapy.

Indications and use of rifampicin in children
Children are given isoniazid p. 541, rifampicin below, pyrazinamide p. 542, and ethambutol hydrochloride p. 540 for the first 2 months followed by isoniazid and rifampicin during the next 4 months. However, care is needed in young children receiving ethambutol hydrochloride because of the difficulty in testing eyesight and in obtaining reports of visual symptoms.

Antimycobacteria > rifamycins
Rifampicin

- Indications and dose
  Brucellosis in combination with other antibiotics | Legionnaires disease in combination with other antibiotics | Serious staphylococcal infections in combination with other antibiotics
  - By mouth, or by intravenous infusion
  - Child 1–11 months: 5–10 mg/kg twice daily
  - Child 1–17 years: 10 mg/kg twice daily (max. per dose 600 mg)
  - Adult: 0.6–1.2 g daily in 2–4 divided doses

Endocarditis in combination with other drugs
  - By mouth, or by intravenous infusion
  - Adult: 0.6–1.2 g daily in 2–4 divided doses

Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)
  - By mouth
  - Child: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)
  - Adult: 600–900 mg 3 times a week for 6 months (initial and continuation phases)
Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)
- **BY MOUTH**
  - Child (body-weight up to 50 kg): 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 450 mg per day
  - Child (body-weight 50 kg and above): 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 600 mg per day
  - Adult (body-weight up to 50 kg): 450 mg once daily for 6 months (initial and continuation phases)

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, in combination with isoniazid
- **BY MOUTH**
  - Child 1 month–11 years (body-weight up to 50 kg): 15 mg/kg daily for 3 months; maximum 450 mg per day
  - Child 1 month–11 years (body-weight 50 kg and above): 15 mg/kg daily for 3 months; maximum 600 mg per day
  - Child 12–17 years (body-weight up to 50 kg): 450 mg daily for 3 months
  - Child 12–17 years (body-weight 50 kg and above): 600 mg daily for 3 months
  - Adult (body-weight up to 50 kg): 450 mg daily for 6 months
  - Adult (body-weight 50 kg and above): 600 mg daily for 6 months

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, who are isoniazid-resistant
- **BY MOUTH**
  - Child 1 month–11 years (body-weight up to 50 kg): 15 mg/kg daily for 6 months; maximum 450 mg per day
  - Child 1 month–11 years (body-weight 50 kg and above): 15 mg/kg daily for 6 months; maximum 600 mg per day
  - Child 12–17 years (body-weight up to 50 kg): 450 mg daily for 6 months
  - Child 12–17 years (body-weight 50 kg and above): 600 mg daily for 6 months

Prevention of secondary case of *Haemophilus influenzae* type b disease
- **BY MOUTH**
  - Child 1–2 months: 10 mg/kg once daily for 4 days
  - Child 3 months–11 years: 20 mg/kg once daily (max. per dose 600 mg) for 4 days
  - Child 12–17 years: 600 mg once daily for 4 days
  - Adult: 600 mg once daily for 4 days

Prevention of secondary case of meningococcal meningitis
- **BY MOUTH**
  - Child 1–11 months: 5 mg/kg every 12 hours for 2 days
  - Child 1–11 years: 10 mg/kg every 12 hours (max. per dose 600 mg) for 2 days
  - Child 12–17 years: 600 mg every 12 hours for 2 days
  - Adult: 600 mg every 12 hours for 2 days

**Multibacillary leprosy in combination with dapsone and clofazimine (3-drug regimen)**
- **BY MOUTH**
  - Adult (body-weight up to 35 kg): 450 mg once a month, supervised administration
  - Adult (body-weight 35 kg and above): 600 mg once a month, supervised administration

- **UNLICENSED USE** Not licensed for use in children for pruritus due to cholestasis.
- **CONTRA-INDICATIONS** Acute porphyrias p. 930 - jaundice
- **CAUTIONS** Discourages soft contact lenses
- **INTERACTIONS** → Appendix 1 (rifamycins). Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulfonylureas, and anticoagulants.

**SIDE-EFFECTS**

### GENERAL SIDE-EFFECTS


**SPECIFIC SIDE-EFFECTS**

*With intravenous use* Thrombophlebitis reported if infusion used for prolonged period

### SED-EFFECTS, FURTHER INFORMATION

Discontinue permanently if serious side-effects develop.

- **Intermittent therapy** Side-effects that mainly occur with intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, thrombocytopenic purpura, disseminated intravascular coagulation, and acute renal failure

### ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in patients with rifamycin hypersensitivity.

### CONCEPTION AND CONTRACEPTION

Important. Effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered.

### PREGNANCY

Manufacturers advise very high doses teratogenic in *animal* studies in first trimester; risk of neonatal bleeding may be increased in third trimester.

### BREAST FEEDING

Amount too small to be harmful.

### HEPATIC IMPAIRMENT

Avoid or do not exceed 8 mg/kg daily. Impaired elimination. In patients with pre-existing liver disease or hepatic impairment, monitor liver function regularly and particularly frequently in the first 2 months; blood counts should also be monitored in these patients.

### RENAL IMPAIRMENT

- In children Use with caution if doses above 10 mg/kg daily.
- In adults Use with caution if dose above 600 mg daily.

### MONITORING REQUIREMENTS

* Renal function should be checked before treatment.
* Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary
MEDICINAL FORMS

PATIENT AND CARER ADVICE

▷ Blood counts should be monitored in patients on prolonged therapy.
▷ In adults Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months. Blood counts should also be monitored in these patients.

DIRECTIONS FOR ADMINISTRATION

▷ With oral use in children
▷ With intravenous use in adults

DIRECTIONS FOR ADMINISTRATION

▷ In adults

Blood counts should be monitored in patients on Rifampicin (Non-proprietary), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute with solvent provided then dilute with 500 mL infusion fluid; give over 2–3 hours.

▷ With intravenous use in children Displacement value may be significant, consult local reconstitution guidelines; reconstitute with solvent provided. May be further diluted with Glucose 5% or Sodium chloride 0.9% to a final concentration of 1.2 mg/mL. Infuse over 2–3 hours.

PRESCRIBING AND DISPENSING INFORMATION

If treatment interruption occurs, re-introduce with low dosage and increase gradually. Flavours of syrup may include raspberry.

▷ With oral use in children In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. Doses may also need to be recalculated to allow for weight gain in younger children.

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Rifampicin for meningococcal prophylaxis www.medicinesforchildren.org.uk/ rifampicin-for-meninococcal-prophylaxis


Soft contact lenses Patients or their carers should be advised that rifampicin discoulers soft contact lenses.

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

INDICATIONS AND DOSE

Initial treatment of tuberculosis

▷ By mouth
▷ Adult (body-weight 30–39 kg): 2 tablets daily for 2 months (initial phase)
▷ Adult (body-weight 40–54 kg): 3 tablets daily for 2 months (initial phase)
▷ Adult (body-weight 55–69 kg): 4 tablets daily for 2 months (initial phase)
▷ Adult (body-weight 70 kg and above): 5 tablets daily for 2 months (initial phase)

DOSE EQUIVALENCE AND CONVERSION

Tablet quantities refer to the number of Voractiv ® Tablets which should be taken. Each Voractiv ® Tablet contains ethambutol hydrochloride 275 mg, isoniazid 75 mg, pyrazinamide 400 mg and rifampicin 150 mg.

CAUTIONS

CAUTIONS, FURTHER INFORMATION

Peripheral neuropathy The risk of peripheral neuropathy may be increased by high doses of isoniazid; pyridoxine should, therefore, be considered for those receiving Voractiv ® 5 tablets daily.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Capsule

CAUTIONARY AND ADVISORY LABELS 8, 14, 23

▷ Rifampicin (Non-proprietary)
  Rifampicin 150 mg Rifampicin 150mg capsules | 100 capsule £44.84 DT price = £44.65
  Rifampicin 300 mg Rifampicin 300mg capsules | 100 capsule £103.25 DT price = £102.77
  Rifadin (Sanofi)
  Rifampicin 150 mg Rifadin 150mg capsules | 100 capsule £18.32 DT price = £44.65
  Rifampicin 300 mg Rifadin 300mg capsules | 100 capsule £36.63 DT price = £102.77
  Rimactane (Sandoz Ltd)
  Rifampicin 300 mg Rimactane 300mg capsules | 60 capsule £21.98

Oral suspension

CAUTIONARY AND ADVISORY LABELS 8, 14, 23

EXCIPIENTS: May contain Sucrose

▷ Rifadin (Sanofi)
  Rifampicin 20 mg per 1 ml Rifadin 100mg/5ml syrup | 120 ml £4.27

Powder and solvent for solution for injection

▷ Rifampicin (Non-proprietary)
  Rifampicin 300 mg RIFA parenteral 300mg powder and solvent for solution for injection vials | 1 vial no price available

If the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However, liver function should be monitored on prolonged therapy.

Rifampicin with ethambutol, isoniazid and pyrazinamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, rifampicin p. 535, ethambutol hydrochloride p. 540, isoniazid p. 541, pyrazinamide p. 542.

INDICATIONS AND DOSE

Treatment of tuberculosis (continuation phase)

▷ By mouth
▷ Adult (body-weight up to 50 kg): 450/300 mg daily for 4 months (continuation phase after 2-month initial phase), use Rifinah ® 150/100 Tablets, preferably taken before breakfast.
▷ Adult (body-weight 50 kg and above): 600/300 mg daily for 4 months (continuation phase after 2-month initial phase), use Rifinah ® 300/150 Tablets, preferably taken before breakfast.

DOSE EQUIVALENCE AND CONVERSION

▷ Rifinah ® Tablets contain rifampicin and isoniazid; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of rifampicin and isoniazid respectively.
Infection

**583 Bacterial infection**

- Each Rifater® 150/100 Tablet contains rifampicin 150 mg and isoniazid 100 mg.
- Each Rifinah® 300/150 Tablet contains rifampicin 300 mg and isoniazid 150 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

*CAUTIONARY AND ADVISORY LABELS* 8, 14, 23

<table>
<thead>
<tr>
<th>Product name</th>
<th>Dose</th>
<th>Price £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifinah®</td>
<td>150 mg/100 mg</td>
<td>£19.09</td>
</tr>
<tr>
<td>Rifater®</td>
<td>300 mg/150 mg</td>
<td>£25.22</td>
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</table>

**Rifampicin with isoniazid and pyrazinamide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, rifampicin p. 535, isoniazid p. 541, pyrazinamide p. 542.

**INDICATIONS AND DOSE**

Initial unsupervised treatment of tuberculosis (in combination with ethambutol)

- **BY MOUTH**
  - Adult (body-weight up to 40 kg): 3 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.
  - Adult (body-weight 40–49 kg): 4 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.
  - Adult (body-weight 50–64 kg): 5 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.
  - Adult (body-weight 65 kg and above): 6 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.

**DOSE EQUVALENCE AND CONVERSION**

Tablet quantities refer to the number of Rifater® Tablets which should be taken. Each Rifater® Tablet contains isoniazid 50 mg, pyrazinamide 300 mg and rifampicin 120 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

*CAUTIONARY AND ADVISORY LABELS* 8, 14, 22

<table>
<thead>
<tr>
<th>Product name</th>
<th>Dose</th>
<th>Price £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granupas gastro-resistant granules</td>
<td>4g sachets sugar-free</td>
<td>£331.00</td>
</tr>
</tbody>
</table>

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · bloating · diarrhea · nausea · rash · vestibular syndrome · vomiting
- **Uncommon** Anorexia
- **Rare** Gastrointestinal bleeding · hypothyroidism · jaundice · malabsorption syndrome · metallic taste · peptic ulcer · urticaria
- **Very rare** Agranulocytosis · anaemia · crystalluria · dizziness · headache · hypoglycaemia · leucopenia · methemoglobinemia · peripheral neuropathy · purpura · tendon pain · thrombocytopenia · visual abnormalities · weight loss
- **Frequency not known** Hepatitis · hypersensitivity

**PREGNANCY**

Manufacturer advises avoid unless essential—toxicity in animal studies (highest risk during first trimester).

**BREAST FEEDING**

Present in milk—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Use with caution.

**RENAL IMPAIRMENT**

Use with caution in mild to moderate impairment. Avoid in severe impairment due to accumulation of inactive metabolites.

**MONITORING REQUIREMENTS**

- Monitor for hypersensitivity reaction during the first 3 months of treatment— for desensitisation dosing regimen consult product literature.
- Monitor liver function—discontinue immediately if signs or symptoms of hepatic toxicity (including rash, fever and gastrointestinal disturbance).

**DIRECTIONS FOR ADMINISTRATION**

Disperse granules in orange or tomato juice and take immediately (granules will not dissolve, ensure all granules are swallowed). Granules can be sprinkled on apple sauce or yoghurt for administration.

**PATIENT AND CARER ADVICE**

Patients should be advised that the skeletons of the granules may be seen in the stools. Counselling advised on administration.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant granules**

*CAUTIONARY AND ADVISORY LABELS* 9, 25

<table>
<thead>
<tr>
<th>Product name</th>
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</table>

**Antimycobacterials**

**Aminosalicylic acid**

**INDICATIONS AND DOSE**

Multiple-drug resistant tuberculosis, in combination with other drugs

- **BY MOUTH**
  - Adult: 4 g every 8 hours for a usual treatment duration of 24 months; maximum 12 g per day
- **Desensitisation regimen**
  - **BY MOUTH**
  - Adult: (consult product literature)

**CAUTIONS**

Peptic ulcer

**Bedaquiline**

**INDICATIONS AND DOSE**

Multiple-drug resistant pulmonary tuberculosis, in combination with other drugs

- **BY MOUTH**
  - Adult: Initially 400 mg once daily for 2 weeks, then 200 mg 3 times a week for 22 weeks, intervals of at least 48 hours between each dose, continue appropriate combination therapy after bedaquiline

**CONTRA-INDICATIONS**

- QTc interval more than 500 milliseconds (derived using Fridericia’s formula) · ventricular arrhythmia

**CAUTIONS**

Hypothyroidism · QTc interval (derived using Fridericia’s formula) 450–500 milliseconds—discontinue if QTc interval more than 500 milliseconds · risk factors for QT interval prolongation (e.g. electrolyte disturbances, heart failure with reduced left ventricular ejection fraction, history of symptomatic arrhythmias (avoid if ventricular arrhythmia present), bradycardia, congenital long QT syndrome)
**INTERACTIONS** → Appendix 1 (bedaquiline).
Caution with concomitant use of hepatotoxic drugs.

**SIDE-EFFECTS** Arthralgia - diarrhoea - dizziness - headache - myalgia - nausea - QT interval prolongation - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Syncope if syncope occurs, obtain ECG.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risks.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment; avoid in severe impairment—no information available. Avoid concomitant use of hepatotoxic drugs unless essential.

**RENAL IMPAIRMENT** Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**
- Determine serum potassium, calcium, and magnesium before starting treatment (correct if abnormal)—remeasure if QT prolongation occurs during treatment.
- Obtain ECG before starting treatment, and then at least monthly during treatment or more frequently if concomitant use with other drugs known to prolong the QT interval.
- Monitor liver function before starting treatment and then at least monthly during treatment—discontinue treatment if severe abnormalities in liver function tests.

**PATIENT AND CARER ADVICE**
- Missed doses
  If a dose is missed during the first two weeks of treatment, the missed dose should not be taken and the next dose should be taken at the usual time; if a dose is missed during weeks 3–24 of treatment, the missed dose should be taken as soon as possible and then the usual regimen resumed.
- Driving and skilled tasks
  Dizziness may affect performance of skilled tasks (e.g. driving)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cycloserine**

**INDICATIONS AND DOSE**
Tuberculosis resistant to first-line drugs, in combination with other drugs

**BY MOUTH**
- Adult: Initially 250 mg every 12 hours for 2 weeks, then increased if necessary up to 500 mg every 12 hours, dose to be increased according to blood concentration and response

**PHARMACOKINETICS**
Cycloserine penetrates the CNS.

**CONTRA-INDICATIONS**
- Alcohol dependence · depression · epilepsy · psychotic states · severe anxiety

**INTERACTIONS** → Appendix 1 (cycloserine).

**SIDE-EFFECTS** Allergic dermatitis · changes in liver function tests · confusion · convulsions · depression · dizziness · drowsiness · headache · heart failure at high doses · megaloblastic anaemia · psychosis · rashes · tremor · vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**
- CNS toxicity Discontinue or reduce dose if symptoms of CNS toxicity occur.
- Rashes or allergic dermatitis Discontinue or reduce dose if rashes or allergic dermatitis develops.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—crosses the placenta.

**BREAST FEEDING** Present in milk—amount too small to be harmful.

**RENAL IMPAIRMENT** Increase interval between doses if creatinine clearance less than 50 mL/minute. Monitor blood-cycloserine concentration if creatinine clearance less than 50 mL/minute.

**MONITORING REQUIREMENTS**
- Blood concentration monitoring required especially in renal impairment or if dose exceeds 500 mg daily or if signs of toxicity; blood concentration should not exceed 30 mg/litre.
- Monitor haematological, renal, and hepatic function.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capreomycin**

**INDICATIONS AND DOSE**
Tuberculosis resistant to first-line drugs, in combination with other drugs

**BY DEEP INTRAMUSCULAR INJECTION**
- Adult: 1 g daily (max. per dose 20 mg/kg) for 2–4 months, then reduced to 1 g 2–3 times a week

**CAUTIONS** Auditory impairment

**INTERACTIONS** → Appendix 1 (capreomycin).

**SIDE-EFFECTS** Induration at injection site · changes in liver function tests · electrolyte disturbances · hearing loss with tinnitus and vertigo · hypersensitivity reactions · leucocytosis · leucopenia · nephrotoxicity · neuromuscular block after large doses · pain at injection site · rashes · thrombocytopenia · urticaria

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—teratogenic in animal studies.

**BREAST FEEDING** Manufacturer advises caution—no information available.

**HEPATIC IMPAIRMENT** Use with caution.

**RENAL IMPAIRMENT** Reduce dose—consult product literature. Nephrotoxic · ototoxic.

**MONITORING REQUIREMENTS** Monitor renal, hepatic, auditory, and vestibular function and electrolytes.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Capreomycin (Non-proprietary)
  Capreomycin (as Capreomycin sulfate) 1 gram
  Capreomycin 1g powder for solution for injection vials  | 1 vial [POM] £28.61

**BNF 73**

**Tuberculosis 539**
Delamanid

**INDICATIONS AND DOSE**
Multiple-drug resistant pulmonary tuberculosis, in combination with other drugs

- **BY MOUTH**
  - Adult: 100 mg twice daily for 24 weeks, continue appropriate combination therapy after delamanid

- **CONTRA-INDICATIONS** QTc interval more than 500 milliseconds (derived using Fridericia’s formula) - serum albumin less than 28 g/litre

- **CAUTIONS** Risk factors for QT interval prolongation (e.g. electrolyte disturbances, acute myocardial infarction, heart failure with reduced left ventricular ejection fraction, severe hypertension, left ventricular hypertrophy, bradycardia, congenital long QT syndrome, history of symptomatic arrhythmias)

- **INTERACTIONS** → Appendix 1 (delamanid).

  Caution when concomitant use with other drugs known to prolong the QT interval. Contra-indicated with concomitant use of potent CYP3A4 inducers.

- **SIDE-EFFECTS**
  - Uncommon Arrhythmias - balance disorder - dehydration - dysphagia - herpes zoster - hypocalcaemia - leucopenia - nocturia - renal impairment - retinopathy - vomiting

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in moderate to severe impairment.

- **RENAL IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor serum albumin and electrolytes before starting treatment and then during treatment—discontinue treatment if serum albumin less than 28 g/litre.
  - Obtain ECG before starting treatment and then monthly during treatment (more frequently if serum albumin 28–34 g/litre, or if concomitant use of potent CYP3A4 inhibitors, or if risk factors for QT interval prolongation, or if QTc interval 450–500 milliseconds in men or 470–500 milliseconds in women)—discontinue treatment if QTc interval more than 500 milliseconds (derived using Fridericia’s formula).

- **HANDLING AND STORAGE** Dispense in original container (contains desiccant).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 8, 21
  - **Deltyba** (Otsuka Novel Products GmbH) ▼
    - Delamanid 50 mg Deltyba 50mg tablets | 48 tablet [Pack] £1,250.00

Ethambutol hydrochloride

**INDICATIONS AND DOSE**
Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)

- **BY MOUTH**
  - Child: 20 mg/kg once daily for 2 months (initial phase)
  - Adult: 15 mg/kg once daily for 2 months (initial phase)

Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)

- **BY MOUTH**
  - Child: 30 mg/kg 3 times a week for 2 months (initial phase)
  - Adult: 30 mg/kg 3 times a week for 2 months (initial phase)

- **CONTRA-INDICATIONS** Optic neuritis - poor vision

- **CAUTIONS** Elderly - young children

- **INTERACTIONS**
  - **FURTHER INFORMATION**
    - Understand warnings Patients who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.

- **SIDE-EFFECTS**
  - Rare Pruritus - rash - thrombocytopenia - urticaria
  - **Frequency not known** Colour blindness - loss of visual acuity - optic neuritis - peripheral neuritis - red/green colour blindness - restriction of visual fields - visual disturbances

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Ocular toxicity Ocular toxicity is more common where excessive dosage is used or if the patient’s renal function is impaired. Early discontinuation of the drug is almost always followed by recovery of eyesight.

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Amount too small to be harmful.

- **RENAL IMPAIRMENT** Risk of optic nerve damage. Should preferably be avoided in patients with renal impairment. If creatinine clearance less than 30 mL/minute, monitor plasma-ethambutol concentration.
  - In adults If creatinine clearance less than 30 mL/minute, use 15–25 mg/kg (max. 2.5 g) 3 times a week.
  - In children If creatinine clearance less than 30 mL/minute/1.73 m², use 15–25 mg/kg (max. 2.5 g) 3 times a week.

- **MONITORING REQUIREMENTS**
  - “Peak” concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); “trough” (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre).
  - Renal function should be checked before treatment.
  - Visual acuity should be tested by Snellen chart before treatment with ethambutol.
  - In children In young children, routine ophthalmological monitoring recommended.

- **PATIENT AND CARER ADVICE**
  - Ocular toxicity The earliest features of ocular toxicity are subjective and patients should be advised to discontinue therapy immediately if they develop deterioration in vision and promptly seek further advice.

INTERACTIONS  
Peripheral neuropathy

INDICATIONS AND DOSE
Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)

PATIENT AND CARER ADVICE
Hepatic disorders  Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise, jaundice or unexplained deterioration during treatment.

PRESCRIBING AND DISPENSING INFORMATION
With oral use in children  In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet.

PATIENT AND CARER ADVICE
Hepatic disorders  Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise, jaundice or unexplained deterioration during treatment.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS
Hepatitis  Hepatitis more common in those aged over 35 years.

PREGNANCY
Not known to be harmful; prophylactic pyridoxine recommended.

BREAST FEEDING
Theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother. In breast-feeding, monitor infant for possible toxicity.

HEPATIC IMPAIRMENT
Use with caution. In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months.

RENAL IMPAIRMENT
Risk of ototoxicity and peripheral neuropathy; prophylactic pyridoxine hydrochloride p. 950 recommended.

MONITORING REQUIREMENTS
Renal function should be checked before treatment.

Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment.

In adults  Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months.

CONTRA-INDICATIONS
Drug-induced liver disease

CAUTIONS
Acute porphyrias p. 930  alcohol dependence  diabetes mellitus  epilepsy  history of psychosis  HIV infection  malnutrition  slow acetylator status (increased risk of side-effects).

CAUTIONS, FURTHER INFORMATION
Peripheral neuropathy  Peripheral neuropathy is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, pregnancy, malnutrition and HIV infection. In patients at increased risk of peripheral neuropathy, pyridoxine hydrochloride p. 950 should be given prophylactically from the start of treatment.

INTERACTIONS
  ➔ Appendix 1 (isoniazid).
When used with tyramine or histamine rich foods, tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating reported.

SIDE-EFFECTS
  ➔ Common or very common  Peripheral neuropathy
  ➔ Rare  Hepatitis  psychotic episodes
  ➔ Frequency not known  Agranulocytosis  aplastic anaemia  blood disorders  constipation  convulsions  difficulty with

CAUTIONARY AND ADVISORY LABELS
Hepatitis  Hepatitis more common in those aged over 35 years.

PREGNANCY
Not known to be harmful; prophylactic pyridoxine recommended.

BREAST FEEDING
Theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother. In breast-feeding, monitor infant for possible toxicity.

HEPATIC IMPAIRMENT
Use with caution. In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months.

RENAL IMPAIRMENT
Risk of ototoxicity and peripheral neuropathy; prophylactic pyridoxine hydrochloride p. 950 recommended.

MONITORING REQUIREMENTS
Renal function should be checked before treatment.

Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment.

In adults  Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months.

CONTRA-INDICATIONS
Drug-induced liver disease

CAUTIONS
Acute porphyrias p. 930  alcohol dependence  diabetes mellitus  epilepsy  history of psychosis  HIV infection  malnutrition  slow acetylator status (increased risk of side-effects).

CAUTIONS, FURTHER INFORMATION
Peripheral neuropathy  Peripheral neuropathy is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, pregnancy, malnutrition and HIV infection. In patients at increased risk of peripheral neuropathy, pyridoxine hydrochloride p. 950 should be given prophylactically from the start of treatment.

INTERACTIONS
  ➔ Appendix 1 (isoniazid).
When used with tyramine or histamine rich foods, tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating reported.

SIDE-EFFECTS
  ➔ Common or very common  Peripheral neuropathy
  ➔ Rare  Hepatitis  psychotic episodes
  ➔ Frequency not known  Agranulocytosis  aplastic anaemia  blood disorders  constipation  convulsions  difficulty with

CAUTIONARY AND ADVISORY LABELS
Hepatitis  Hepatitis more common in those aged over 35 years.

PREGNANCY
Not known to be harmful; prophylactic pyridoxine recommended.

BREAST FEEDING
Theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother. In breast-feeding, monitor infant for possible toxicity.

HEPATIC IMPAIRMENT
Use with caution. In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months.

RENAL IMPAIRMENT
Risk of ototoxicity and peripheral neuropathy; prophylactic pyridoxine hydrochloride p. 950 recommended.

MONITORING REQUIREMENTS
Renal function should be checked before treatment.

Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment.

In adults  Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months.

CONTRA-INDICATIONS
Drug-induced liver disease

CAUTIONS
Acute porphyrias p. 930  alcohol dependence  diabetes mellitus  epilepsy  history of psychosis  HIV infection  malnutrition  slow acetylator status (increased risk of side-effects).

CAUTIONS, FURTHER INFORMATION
Peripheral neuropathy  Peripheral neuropathy is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, pregnancy, malnutrition and HIV infection. In patients at increased risk of peripheral neuropathy, pyridoxine hydrochloride p. 950 should be given prophylactically from the start of treatment.

INTERACTIONS
  ➔ Appendix 1 (isoniazid).
When used with tyramine or histamine rich foods, tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating reported.

SIDE-EFFECTS
  ➔ Common or very common  Peripheral neuropathy
  ➔ Rare  Hepatitis  psychotic episodes
  ➔ Frequency not known  Agranulocytosis  aplastic anaemia  blood disorders  constipation  convulsions  difficulty with
Solution for injection
- Isoniazid (Non-proprietary)
  Isoniazid 20 mg per 1 ml Tebesium-S 100mg/5ml solution for injection ampoules | 2 ampoule Pack, no price available
  Isoniazid 25 mg per 1 ml Tebesium-S 50mg/2ml solution for injection ampoules | 10 ampoule Pack, £329.08

Combinations available: Rifampicin with ethambutol, isoniazid and pyrazinamide, p. 537 · Rifampicin with isoniazid, p. 537 · Rifampicin with isoniazid and pyrazinamide, p. 538

Pyrazinamide

INDICATIONS AND DOSE
Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)
- BY MOUTH
  - Child (body-weight up to 50 kg): 35 mg/kg once daily for 2 months (initial phase); maximum 1.5 g per day
  - Child (body-weight 50 kg and above): 35 mg/kg once daily for 2 months (initial phase); maximum 2 g per day
  - Adult (body-weight up to 50 kg): 1.5 g once daily for 2 months (initial phase)
  - Adult (body-weight 50 kg and above): 2 g once daily for 2 months (initial phase)

Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)
- BY MOUTH
  - Child (body-weight up to 50 kg): 50 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase)
  - Child (body-weight 50 kg and above): 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)
  - Adult (body-weight up to 50 kg): 2 g 3 times a week for 2 months (initial phase)
  - Adult (body-weight 50 kg and above): 2.5 g 3 times a week for 2 months (initial phase)

PRESCRIBING AND DISPENSING INFORMATION
- In children, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. Doses may also need to be recalculated to allow for weight gain in younger children.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Pyrazinamide for treatment of tuberculosis www.medicinesforchildren.org.uk/pyrazinamide-for-tuberculosis

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 8
- Pyrazinamide (Non-proprietary)
  Pyrazinamide 500 mg Pyrazinamide 500mg tablets | 30 tablet Pack, £31.35-£38.34 | 50 tablet Pack, £52.25
  Zinamide (Thornton & Ross Ltd)
  Pyrazinamide 500 mg Zinamide 500mg tablets | 30 tablet Pack, £31.35

Combinations available: Rifampicin with ethambutol, isoniazid and pyrazinamide, p. 537 · Rifampicin with isoniazid and pyrazinamide, p. 538

2.6 Urinary tract infections

Urinary-tract infections

Overview
Urinary-tract infection is more common in women than in men; when it occurs in men there is frequently an underlying abnormality of the renal tract. Recurrent episodes of infection are an indication for radiological investigation especially in children in whom untreated pyelonephritis may lead to permanent kidney damage.

Escherichia coli is the most common cause of urinary-tract infection; Staphylococcus saprophyticus is also common in sexually active young women. Less common causes include Proteus and Klebsiella spp. Pseudomonas aeruginosa infections usually occur in the hospital setting and may be associated with functional or anatomical abnormalities of the renal tract. Staphylococcus epidermidis and Enterococcus faecalis infection may complicate catheterisation or instrumentation.

A specimen of urine should be collected for culture and sensitivity testing before starting antibacterial therapy;
- in men;
- in pregnant women;
- in children under 3 years of age;
- in patients with suspected upper urinary-tract infection;
- complicated infection, or recurrent infection;
- if resistant organisms are suspected;
- if urine dipstick testing gives a single positive result for leucocyte esterase or nitrite;
- if clinical symptoms are not consistent with results of dipstick testing.

Treatment should not be delayed while waiting for results. The antibacterial chosen should reflect current local bacterial sensitivity to antibacterials.
Antibacterial therapy for lower urinary-tract infections

Uncomplicated lower urinary-tract infections often respond to trimethoprim p. 529 or nitrofurantoin p. 544, or alternatively, amoxicillin p. 506, ampicillin p. 507 or oral cephalosporin.

Suggested duration of treatment is 7 days, but a short course (e.g. 3 days) is usually adequate for uncomplicated urinary-tract infections in women.

Infections caused by fully sensitive bacteria respond to amoxicillin.

Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav p. 508 (amoxicillin with clavulanic acid), an oral cephalosporin, nitrofurantoin, pivmecillinam hydrochloride p. 510, or a quinolone.

Fosfomycin [unlicensed] can be used, on the advice of a microbiologist, for the treatment of uncomplicated lower urinary-tract infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used.

Long-term low dose therapy may be required in selected patients to prevent recurrence of infection; indications include frequent relapses and significant kidney damage. Trimethoprim, nitrofurantoin and cefalexin p. 485 have been recommended for long-term therapy.

Methenamine hippurate below (hexamine hippurate) should not generally be used because it requires an acidic urine for its antimicrobial activity and it is ineffective for upper urinary-tract infections; it may, however, have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower urinary-tract infections.

Antibacterial therapy for upper urinary-tract infections

Acute pyelonephritis can lead to septicemia and is treated initially by injection of a broad-spectrum antibacterial such as a cephalosporin (e.g. cefuroxime p. 486) or a quinolone if the patient is severely ill; gentamicin p. 479 can also be used.

Suggested duration of treatment is 10–14 days (longer treatment may be necessary in complicated pyelonephritis).

Prostatitis can be difficult to cure and requires treatment for several weeks with an antibacterial which penetrates prostatic tissue such as some of the quinolones (ciprofloxacin p. 514 or ofloxacin p. 517), or alternatively, trimethoprim.

Suggested duration of treatment is 28 days.

Where infection is localised and associated with an indwelling catheter, a bladder instillation is often effective.

Pregnancy

Urinary-tract infection in pregnancy may be asymptomatic and requires prompt treatment to prevent progression to acute pyelonephritis. Penicillins and cephalosporins are suitable for treating urinary-tract infection during pregnancy. Nitrofurantoin may also be used but it should be avoided at term. Sulfonamides and quinolones should be avoided during pregnancy; trimethoprim should also preferably be avoided particularly in the first trimester.

Renal impairment

In renal failure antibacterials normally excreted by the kidney accumulate with resultant toxicity unless the dose is reduced. This applies especially to the aminoglycosides which should be used with great caution; tetracyclines, methenamine hippurate, and nitrofurantoin should be avoided altogether.

Urinary-tract infections in children

Urinary-tract infections in children require prompt antibacterial treatment to minimise the risk of renal scarring. Uncomplicated 'lower' urinary-tract infections in children over 3 months of age can be treated with trimethoprim, nitrofurantoin, a first generation cephalosporin (e.g. cefalexin), or amoxicillin for 3 days; children should be reassessed if they continue to be unwell 24–48 hours after the initial assessment. Amoxicillin should only be used if the organism causing the infection is sensitive to it.

Acute pyelonephritis in children over 3 months of age can be treated with a first generation cephalosporin or co-amoxiclav for 7–10 days. If the patient is severely ill, then the infection is best treated initially by injection of a broad-spectrum antibacterial such as cefotaxime p. 487 or co-amoxiclav; gentamicin is an alternative.

Children under 3 months of age should be transferred to hospital and treated initially with intravenous antibacterial drugs such as ampicillin with gentamicin, or cefotaxime alone, until the infection responds; full doses of oral antibacterials are then given for a further period.

Recurrent episodes of infection are an indication for imaging tests. Antibacterial prophylaxis with low doses of trimethoprim or nitrofurantoin may be considered for children with recurrent infection, significant urinary-tract anomalies, or significant kidney damage.

ANTIBACTERIALS

Methenamine hippurate

(Hexamine hippurate)

- INDICATIONS AND DOSE
  - **Prophylaxis and long-term treatment of chronic or recurrent uncomplicated lower urinary-tract infections**
    - **BY MOUTH**
      - Adult: 1 g every 12 hours
  - **Prophylaxis and long-term treatment of chronic or recurrent uncomplicated lower urinary-tract infections in patients with catheters**
    - **BY MOUTH**
      - Adult: 1 g every 8–12 hours

- CONTRA-INDICATIONS
  - Gout · metabolic acidosis · severe dehydration

- INTERACTIONS
  - Appendix 1 (methenamine). Caution—avoid concurrent administration with sulfonamides (risk of crystalluria) or urinary alkalinising agents.

- SIDE-EFFECTS
  - Bladder irritation · gastro-intestinal disturbances · rash

- PREGNANCY
  - Use with caution.

- BREAST FEEDING
  - Amount too small to be harmful.

- HEPATIC IMPAIRMENT
  - Avoid.

- RENAL IMPAIRMENT
  - Avoid if eGFR less than 10 mL/minute/1.73 m²—risk of hippurate crystalluria.

- LESS SUITABLE FOR PRESCRIBING
  - Methenamine (hexamine) hippurate should not generally be used because it requires an acidic urine for its antimicrobial activity and it is ineffective for upper urinary-tract infections; it may, however, have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower urinary-tract infections. It is considered less suitable for prescribing.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 9

- Hiprex (Meda Pharmaceuticals Ltd)
  - Methenamine hippurate 1 gram Hiprex 1g tablets | 60 tablet £19.74 DT price + £19.74
Nitrofurantoin

**INDICATIONS AND DOSE**

**Acute uncomplicated urinary-tract infections**
- **By mouth using immediate-release medicines**
  - Child 3 months–11 years: 750 micrograms/kg 4 times a day for 3–7 days
  - Child 12–17 years: 50 mg 4 times a day for 3–7 days
  - Adult: 50 mg 4 times a day for 3–7 days, dose to be taken with food
- **By mouth using modified-release medicines**
  - Child 12–17 years: 100 mg twice daily, dose to be taken with food
  - Adult: 100 mg twice daily, dose to be taken with food

**Severe chronic recurrent urinary-tract infections**
- **By mouth using immediate-release medicines**
  - Child 12–17 years: 100 mg 4 times a day for 3–7 days
  - Adult: 100 mg 4 times a day for 7 days, dose to be taken with food, reduce dose or discontinue treatment if severe nausea occurs

**Prophylaxis of urinary-tract infection (considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage)**
- **By mouth using immediate-release medicines**
  - Child 3 months–11 years: 1 mg/kg once daily, dose to be taken at night
  - Child 12–17 years: 50–100 mg once daily, dose to be taken at night
  - Adult: 50–100 mg once daily, dose to be taken at night

**Genito-urinary surgical prophylaxis**
- **By mouth using modified-release medicines**
  - Adult: 100 mg twice daily on day of procedure and for 3 days after

**CONTRA-INDICATIONS**
- Acute porphyrias p. 390 - G6PD deficiency - infants less than 3 months old

**CAUTIONS**
- Anaemia - diabetes mellitus - electrolyte imbalance - folate deficiency - pulmonary disease - susceptibility to peripheral neuropathy - urination may be coloured yellow or brown - vitamin B deficiency

**INTERACTIONS**
- Appendix 1 (nitrofurantoin).

**SIDE-EFFECTS**
- Rare: Agranulocytosis - aplastic anaemia - arthralgia - benign intracranial hypertension - blood disorders - cholestatic jaundice - erythema multiforme - exfoliative dermatitis - hepatitis - pancreatitis - thrombocytopenia - transient alopecia
- Frequency not known: Acute pulmonary reactions - anaphylaxis - angioedema - anorexia - chronic pulmonary reactions (pulmonary fibrosis reported; possible association with lupus erythematosus-like syndrome) - diarrhoea - hypersensitivity reactions - nausea - peripheral neuropathy - pruritus - rash - sialadenitis - urticaria - vomiting

**PREGNANCY**
- Avoid at term—may produce neonatal haemolysis.

**BREAST FEEDING**
- Avoid; only small amounts in milk but enough to produce haemolysis in G6PD-deficient infants.

**HEPATIC IMPAIRMENT**
- Use with caution; cholestatic jaundice and chronic active hepatitis reported.

**RENAL IMPAIRMENT**
- Risk of peripheral neuropathy; antibacterial efficacy depends on renal secretion of the drug into urinary tract.
  - In adults: Avoid if eGFR less than 45 mL/minute/1.73 m²; may be used with caution if eGFR 30–44 mL/minute/1.73 m² as a short-course only (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk.
  - In children: Avoid if estimated glomerular filtration rate less than 45 mL/minute/1.73 m²; may be used with caution if estimated glomerular filtration rate 30–44 mL/minute/1.73 m² as a short-course only (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk.

**MONITORING REQUIREMENTS**
- On long-term therapy, monitor liver function and monitor for pulmonary symptoms, especially in the elderly (discontinue if deterioration in lung function).

**EFFECT ON LABORATORY TESTS**
- False positive urinary glucose (if tested for reducing substances).

**PATIENT AND CARER ADVICE**

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 9, 14, 21
  - **Nitrofurantoin (Non-proprietary)**
    - Nitrofurantoin 50 mg Nitrofurantoin 50mg tablets | 28 tablet | £35.00 DT price = £10.62 | 100 tablet | £111.89
    - Nitrofurantoin 100 mg Nitrofurantoin 100mg tablets | 28 tablet | £4.16 DT price = £4.16 | 100 tablet | £90.00
  - **Genfura (Genesis Pharmaceuticals Ltd)**
    - Nitrofurantoin 50 mg Genfura 50mg tablets | 28 tablet | £16.80 DT price = £10.62
    - Nitrofurantoin 100 mg Genfura 100mg tablets | 28 tablet | £4.16 DT price = £4.16 | 100 tablet | £58.29

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS** 9, 14, 21
  - **Nitrofurantoin (Non-proprietary)**
    - Nitrofurantoin 50 mg Nitrofurantoin 50mg capsules | 30 capsule | £15.42 DT price = £15.42
    - Nitrofurantoin 100 mg Nitrofurantoin 100mg capsules | 30 capsule | £10.42 DT price = £10.42

**Modified-release capsule**
- **CAUTIONARY AND ADVISORY LABELS** 9, 14, 21, 25
  - **Macrodil (AMCO)**
    - Nitrofurantoin 100 mg Macrodil 100mg modified-release capsules | 14 capsule | £9.50 DT price = £9.50

**Oral suspension**
- **CAUTIONARY AND ADVISORY LABELS** 9, 14, 21
  - **Nitrofurantoin (Non-proprietary)**
    - Nitrofurantoin 5 mg per 1 ml Nitrofurantoin 25mg/5ml oral suspension sugar free sugar-free | 300 ml | £44.95 DT price = £44.95

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### 3 Fungal infection

**Antifungals, systemic use**

**Common fungal infections**
- The systemic treatment of common fungal infections is outlined below; specialist treatment is required in most forms of systemic or disseminated fungal infections. Local treatment is suitable for a number of fungal infections (genital, bladder, eye, ear, oropharynx, and skin).

**Aspergillosis**
- Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the heart, brain, and skin. Voriconazole p. 552 is the treatment of choice for aspergillosis; liposomal amphotericin p. 547 is an alternative first-line treatment when voriconazole cannot be used. Caspofungin p. 546,
Itraconazole p. 550, or posaconazole p. 552 can be used in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin. Itraconazole is also used for the treatment of chronic pulmonary aspergillosis or as an adjunct in the treatment of allergic bronchopulmonary aspergillosis [unlicensed indication].

**Candidiasis**

Many superficial candidal infections including infections of the skin are treated locally; widespread or intractable infection requires systemic antifungal treatment. Vaginal candidiasis may be treated with locally acting antifungals or with fluconazole p. 548 given by mouth; for resistant organisms in adults, itraconazole can be given by mouth. *Oropharyngeal candidiasis* generally responds to topical therapy; fluconazole is given by mouth for unresponsive infections; it is effective and is reliably absorbed. Itraconazole may be used for infections that do not respond to fluconazole. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

For *invasive or disseminated candidiasis*, an echinocandin can be used. Fluconazole is an alternative for *Candida albicans* infection in clinically stable patients who have not received anazole antifungal recently. Amphotericin is an alternative when an echinocandin or fluconazole cannot be used, however, amphotericin should be considered for the initial treatment of CNS candidiasis. Voriconazole can be used for infections caused by fluconazole-resistant *Candida spp.* when oral therapy is required, or in patients intolerant of amphotericin or an echinocandin. In refractory cases, fluconazole p. 554 can be used with intravenous amphotericin.

**Cryptococcosis**

Cryptococcosis is uncommon but infection in the immunocompromised, especially in HIV-positive patients, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is amphotericin by intravenous infusion and fluconosine by intravenous infusion for 2 weeks, followed by fluconazole by mouth for 8 weeks or until cultures are negative. In cryptococcosis, fluconazole is sometimes given alone as an alternative in HIV-positive patients with mild, localised infections or in those who cannot tolerate amphotericin. Following successful treatment, fluconazole can be used for prophyaxis against relapse until immunity recovers.

**Histoplasmosis**

Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected persons. Itraconazole can be used for the treatment of immunocompetent patients with indolent non-meningeal infection, including chronic pulmonary histoplasmosis. Amphotericin by intravenous infusion is used for the initial treatment of fulminant or severe infections, followed by a course of itraconazole by mouth. Following successful treatment, itraconazole can be used for prophyaxis against relapse until immunity recovers.

**Skin and nail infections**

Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy. Systemic therapy is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis). Oral imidazole or triazole antifungals (particularly itraconazole) and terbinafine p. 1089 are used more frequently than griseofulvin p. 554 because they have a broader spectrum of activity and require a shorter duration of treatment.

*Tinea capitis* is treated systemically; additional topical application of an antifungal may reduce transmission. Griseofulvin is used for tinea capitis in adults and children; it is effective against infections caused by *Trichophyton tonsurans* and *Microsporum spp.* Terbinafine is used for tinea capitis caused by *T. tonsurans* [unlicensed indication]. The role of terbinafine in the management of *Microsporum* infections is uncertain.

*Pityriasis versicolor* may be treated with itraconazole by mouth if topical therapy is ineffective; fluconazole by mouth is an alternative. Oral terbinafine is not effective for pityriasis versicolor.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. Terbinafine and itraconazole have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail; terbinafine is considered to be the drug of choice. Itraconazole can be administered as intermittent ‘pulse’ therapy. Topical antifungals also have a role in the treatment of onychomycosis.

**Immunocompromised patients**

Immunocompromised patients are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral triazole antifungals are the drugs of choice for prophylaxis. Fluconazole is more reliably absorbed than itraconazole, but fluconazole is not effective against *Aspergillus spp.* Itraconazole is preferred in patients at risk of invasive aspergillosis. Posaconazole can be used for prophylaxis in patients who are undergoing haematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome, if they are intolerant of fluconazole or itraconazole. Micafungin p. 547 can be used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation when fluconazole, itraconazole or posaconazole cannot be used. Amphotericin by intravenous infusion or caspofungin is used for the empirical treatment of serious fungal infections; caspofungin is not effective against fungal infections of the CNS.

**Triazole antifungals**

Triazole antifungal drugs have a role in the prevention and systemic treatment of fungal infections. Fluconazole is very well absorbed after oral administration. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis. Fluconazole is excreted largely unchanged in the urine and can be used to treat candiduria. Itraconazole is active against a wide range of dermatophytes. Itraconazole capsules require an acid environment in the stomach for optimal absorption. Itraconazole has been associated with liver damage and should be avoided or used with caution in patients with liver disease; fluconazole is less frequently associated with hepatotoxicity.

Posaconazole is licensed for the treatment of invasive fungal infections unresponsive to conventional treatment. Voriconazole is a broad-spectrum antifungal drug which is licensed for use in life-threatening infections.

**Imidazole antifungals**

The imidazole antifungals include clotrimazole p. 758, econazole nitrate p. 759, ketoconazole p. 624, and tioconazole p. 1088. They are used for the local treatment of vaginal candidiasis and for dermatophyte infections. Miconazole p. 760 can be used locally for oral infections; it is also effective in intestinal infections. Systemic absorption may follow use of miconazole oral gel and may result in significant drug interactions.
Polyene antifungals

The polyene antifungals include amphotericin p. 547 and nystatin p. 1073; neither drug is absorbed when given by mouth. Nystatin is used for oral, oropharyngeal, and perioral infections by local application in the mouth. Nystatin is also used for *Candida albicans* infection of the skin.

Amphotericin by intravenous infusion is used for the treatment of systemic fungal infections and is active against most fungi and yeasts. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally amphotericin is toxic and side-effects are common. Lipid formulations of amphotericin (*Abelcet*® and *AmBisome*) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contra-indicated because of toxicity, especially nephrotoxicity or when response to conventional amphotericin is inadequate; lipid formulations are more expensive.

Echinocandin antifungals

The echinocandin antifungals include anidulafungin below, caspofungin below and micafungin p. 547. They are only active against *Aspergillus* spp. and *Candida* spp.; however, anidulafungin and micafungin are not used for the treatment of aspergillosis. Echinocandins are not effective against fungal infections of the CNS.

Other antifungals

Flucytosine p. 554 is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly in HIV-positive patients; weekly blood counts are necessary during prolonged therapy. Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment. Flucytosine has a role in the treatment of systemic candidiasis and cryptococcal meningitis.

Griseofulvin p. 554 is effective for widespread or intractable dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. It is the drug of choice for trichophytion infections in children. Duration of therapy is dependent on the site of the infection and may extend to a number of months.

Terbinafine p. 1089 is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.

ANTIFUNGALS > ECHINOCANDIN ANTIFUNGALS

### Anidulafungin

**INDICATIONS AND DOSE**

**Invasive candidiasis**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 200 mg once daily for 1 day, then 100 mg once daily

**SIDE-EFFECTS**

- **Common or very common** Coagulopathy - convulsion - diarrhoea - flushing - headache - hypokalaemia - nausea - pruritis - raised serum creatinine - rash - vomiting
- **Uncommon** Abdominal pain - cholestasis - hyperglycaemia - hyperpotension - injection-site pain - urticaria
- **Frequency not known** Bronchospasm - dyspnoea - haemorrhage - hypovolaemia - pruritus - rash - sweating

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid unless potential benefit outweighs risk—present in milk in animal studies.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (*Ecalta*®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 100 mg with 30 mL water for injections and allow up to 5 minutes for reconstitution; dilute dose in infusion fluid to a concentration of 770 micrograms/mL; give at a rate not exceeding 1.1 mg/minute. Follow product information if using stock supplied with ethanol solvent.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- *Ecalta* (Pfizer Ltd) Anidulafungin 100 mg Ecalta 100mg powder for concentrate for solution for infusion vials | 1 vial (PFD) £298.99 (Hospital only)

### Caspofungin

**INDICATIONS AND DOSE**

**Invasive aspergillosis** | **Invasive candidiasis** | **Empirical treatment of systemic fungal infections in patients with neutropenia**

- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 81 kg): 70 mg once daily for 1 day, then 50 mg once daily
  - Adult (body-weight 81 kg and above): 70 mg once daily

**INTERACTIONS** > Appendix 1 (caspofungin).

**SIDE-EFFECTS**

- **Common or very common** Arthralgia - diarrhoea - dyspnoea - headache - hypokalaemia - injection-site reactions - nausea - pruritis - rash - sweating - vomiting
- **Frequency not known** Adult respiratory distress syndrome - anaphylaxis

**PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies.

**BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT** 70 mg on first day then 35 mg once daily in moderate impairment. No information available for severe impairment.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (*Cancidas*®), give intermittently in Sodium chloride 0.9%. Allow vial to reach room temperature; initially reconstitute each vial with 10.5 mL water for injections, mixing gently to dissolve then dilute requisite dose in 250 mL infusion fluid (35- or 50-mg doses may be diluted in 100 mL infusion fluid if necessary); give over 60 minutes; incompatible with glucose solutions.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- *Cancidas* (Merck Sharp & Dohme Ltd) Caspofungin (as Caspofungin acetate) 50 mg Cancidas 50mg powder for solution for infusion vials | 1 vial (PFD) £327.67
  - Caspofungin (as Caspofungin acetate) 70 mg Cancidas 70mg powder for solution for infusion vials | 1 vial (PFD) £416.78
Micafungin

**INDICATIONS AND DOSE**

**Invasive candidiasis**
- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 40 kg): 2 mg/kg once daily for at least 14 days; increased if necessary to 4 mg/kg once daily, increase dose if response inadequate
  - Adult (body-weight 40 kg and above): 100 mg once daily for at least 14 days; increased if necessary to 200 mg once daily, increase dose if response inadequate

**Oesophageal candidiasis**
- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 40 kg): 3 mg/kg once daily
  - Adult (body-weight 40 kg and above): 150 mg once daily

**Prophylaxis of candidiasis in patients undergoing bone-marrow transplantation or who are expected to become neutropenic for over 10 days**
- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 40 kg): 1 mg/kg once daily continue for at least 7 days after neutrophil count is in desirable range
  - Adult (body-weight 40 kg and above): 50 mg once daily continue for at least 7 days after neutrophil count is in desirable range

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - anaemia - diarrhoea - fever - headache - hypocalcaemia - hypokalaemia - hypomagnesaemia - leucopenia - nausea - phlebitis - rash - vomitinig
- **Rare** Haemolytic anaemia
- **Frequency not known** Disseminated intravascular coagulation - hepatotoxicity (potentially life-threatening) - renal failure - Stevens-Johnson syndrome - toxic epidermal necrolysis

**PREGNANCY** Manufacturer advises use avoid unless essential—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT** Use with caution; renal function may deteriorate.

**MONITORING REQUIREMENTS**
- Monitor renal function.
- Monitor liver function—discontinue if significant and persistent abnormalities in liver function tests develop.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Mycamine®), give interminently in Glucose 5% or Sodium chloride 0.9%. Reconstitute each vial with 5 mL infusion fluid; gently rotate vial, without shaking, to dissolve; dilute requisite dose with infusion fluid to 100 mL (final concentration of 0.5–2 mg/mL); protect infusion from light; give over 60 minutes.

**INTERACTIONS**
- Appendix 1 (micafungin). Caution with concomitant use of other hepatotoxic drugs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- **Mycamine** (Astellas Pharma Ltd)
  - Micafungin (as Micafungin sodium) 50 mg Mycamine 50mg powder for solution for infusion vials | 1 vial £4.08
  - Micafungin (as Micafungin sodium) 100 mg Mycamine 100mg powder for solution for infusion vials | 1 vial £3.41

**ANTIFUNGALS > POLYENE ANTIFUNGALS**

Amphotericin (Amphotericin B)

**INDICATIONS AND DOSE**

**ABELCET®**
- Severe invasive candidiasis | Severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients
  - **BY INTRAVENOUS INFUSION**
    - Adult: Test dose 1 mg, to be given over 15 minutes, then 5 mg/kg once daily for at least 14 days

**AMBISOME®**
- Severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin | Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials
  - **BY INTRAVENOUS INFUSION**
    - Adult: Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg once daily; maximum 5 mg/kg per day

**Aspergillosis**
- **BY INTRAVENOUS INFUSION**
  - Adult: Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg once daily; maximum 5 mg/kg per day

**Visceral leishmaniasis (unresponsive to the antimonial alone)**
- **BY INTRAVENOUS INFUSION**
  - Adult: 1–3 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg, alternatively 3 mg/kg for 5 consecutive days, followed by 3 mg/kg after 6 days for 1 dose

**FUNGIZONE®**
- **Severe systemic fungal infections**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Test dose 1 mg, to be given over 20–30 minutes, then 250 micrograms/kg daily, gradually increased over 2–4 days, increased if tolerated to 1 mg/kg daily, max. (severe infection) 1.5 mg/kg daily or on alternate days. Prolonged treatment usually necessary; if interrupted for longer than 7 days recommence at 250 micrograms/kg daily and increase gradually

**UNLICENSED USE**
- **AMBISOME®** Use at the maximum dose of 5 mg/kg once daily is an unlicensed dose.

**CAUTIONS**
- Avoid rapid infusion (risk of arrhythmia) - when given parenterally, toxicity common (close supervision necessary and close observation required for at least 30 minutes after test dose)

**CAUTIONS, FURTHER INFORMATION**
- Anaphylaxis. Anaphylaxis can occur with any intravenous amphotericin product and a test dose is advisable before the first infusion; the patient should be carefully observed for at least 30 minutes after the test dose. Prophylactic
antipyrtes or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin is essential).

- **INTERACTIONS** Appendix 1 (amphotericin). Caution—corticosteroids (avoid except to control reactions).

- **SIDE-EFFECTS**
  - **Common** or **very common** Abdominal pain, abnormal liver function (discontinue treatment), anemia, arrhythmias, blood disorders, blood pressure changes, cardiovascular effects, chest pain, diarrhea, disturbances in renal function, dyspnoea, electrolyte disturbances, febrile reactions, headache, hypokalemia, hypomagnesemia, nausea, rash, renal tubular acidosis, thrombocytopenia, vomiting.
  - **Uncommon** Anaphylactoid reactions, bronchospasm, convulsions, diplopia, encephalopathy, hearing loss, neurological disorders, peripheral neuropathy, tremor.
  - **Frequency not known** Anorexia, arthralgia, myalgia, Stevens-Johnson syndrome, toxic epidermal necrolysis.

- **PREGNANCY** Not known to be harmful but manufacturers advise avoid unless potential benefit outweighs risk.

- **BREAST FEEDING** No information available.

- **RENAL IMPAIRMENT** Use only if no alternative; nephrotoxicity may be reduced with use of lipid formulation.

- **MONITORING REQUIREMENTS** Hepatic and renal function tests, blood counts, and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required.

- **DIRECTIONS FOR ADMINISTRATION**

  - **ABELCET®** Amphotericin (lipid complex)
    - For intravenous infusion, give intermittently in Glucose 5%. Allow suspension to reach room temperature, shake gently to ensure no yellow settlement, withdraw requisite dose from vial and introduce into infusion fluid (through the needle provided (fresh needle for each syringe)) and dilute to a concentration of 1 mg/mL (2 mg/mL can be used in fluid restriction and in children); preferably give via an infusion pump at a rate of 2.5 mg/kg/hour (initial test dose of 1 mg over 15 minutes); an in-line filter (pore size no less than 15 micron) may be used; do not use sodium chloride or other electrolyte solutions, flush existing intravenous line with glucose 5% or use separate line.

  - **AMBISOME®** Amphotericin (liposomal)
    - For intravenous infusion (Ambisome®), give intermittently in Glucose 5% or 10%. Reconstitute each vial with 12 mL water for injections and shake vigorously to produce a preparation containing 4 mg/mL; withdraw requisite dose from vial and introduce into infusion fluid through the 5 micron filter provided to produce a final concentration of 0.2–2 mg/mL; infuse over 30–60 minutes, or if non-anaphylactic infusion-related reactions occur infuse over 2 hours (initial test dose of 1 mg over 10 minutes); an in-line filter (pore size no less than 1 micron) may be used; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or 10%, or use separate line.

  - **FUNGIZONE®** Amphotericin (as sodium deoxycholate complex)
    - For intravenous infusion (Fungizone®), give intermittently in Glucose 5%. Reconstitute each vial with 10 mL water of injections and shake immediately to produce a 5 mg/mL colloidal solution; dilute further in infusion fluid to a concentration of 100 micrograms/mL; pH of the glucose must not be below 4.2 (check each container—consult product literature for details of the buffer); infuse over 2–4 hours, or longer if not tolerated (initial test dose of 1 mg over 20–30 minutes); begin infusion immediately after dilution; protect from light; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or use separate line; an in-line filter (pore size no less than 1 micron) may be used.

- **PRESCRIBING AND DISPENSING INFORMATION** Different preparations of intravenous amphotericin vary in their pharmacodynamics, pharmacokinetics, dosage, and administration; these preparations should **not** be considered interchangeable. To avoid confusion, prescribers should specify the brand to be dispensed.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**
    - **EXCIPIENTS:** May contain Sucrose
    - **ELECTROLYTES:** May contain Sodium

    - **Ambisome®** (Gilead Sciences International Ltd)
      - Amphotericin B liposomal 50 mg: AmBisome 50mg powder for solution for infusion (vials) 10 vials £821.87

    - **Fungizone®** (Bristol-Myers Squibb Pharmaceuticals Ltd)
      - Amphotericin B 50 mg: Fungizone Intravenous 50mg powder for solution for infusion (vials) 1 vial £3.99

  - **Suspension for infusion**
    - **ELECTROLYTES:** May contain Sodium
    - **ABELCET®** (Teva UK Ltd)
      - Abelcet® (as Amphotericin B phospholipid complex) 5 mg per 1 ml: Abelcet 100mg/20ml concentrate for suspension for infusion (vials) 10 vials £75.04 (Hospital only)

- **ANTIFUNGALS** > **TRIAZOLE ANTIFUNGALS**

**Fluconazole**

- **INDICATIONS AND DOSE**
  - **Candidal balanitis**
    - **BY MOUTH**
    - Child 16–17 years: 150 mg for 1 dose
    - Adult: 150 mg for 1 dose

  - **Vaginal candidiasis**
    - **BY MOUTH**
    - Child 16–17 years: 150 mg for 1 dose
    - Adult: 150 mg for 1 dose

  - **Vulvovaginal candidiasis (recurrent)**
    - **BY MOUTH**
    - Adult: Initially 150 mg every 72 hours for 3 doses, then 150 mg once weekly for 6 months

  - **Mucosal candidiasis (except genital)**
    - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
    - Child 1 month–11 years: 3–6 mg/kg, dose to be given on first day, then 3 mg/kg daily (max. per dose 100 mg) for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)
    - Child 12–17 years: 50 mg daily for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); increased to 100 mg daily, increased dose only for unusually difficult infections
    - **BY MOUTH**
    - Adult: 50 mg daily given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
bronchopulmonary infections; increased to 100 mg daily, increased dose only for unusually difficult infections

**Tinea pedis, corporis, cruris, pityriasis versicolor** | **Dermal candidiasis**

- **By mouth**
  - Adult: 50 mg daily for 2–4 weeks (for up to 6 weeks in tinea pedis); max. duration of treatment 6 weeks
  - Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis)
    - **By mouth, or by intravenous infusion**
      - Child: 6–12 mg/kg daily (max. per dose 800 mg), treatment continued according to response (at least 8 weeks for cryptococcal meningitis)
      - Adult: 400 mg, dose to be given on first day, then 200–400 mg daily (max. per dose 800 mg once daily), treatment continued according to response (at least 8 weeks for cryptococcal meningitis), maximum dose for use in severe infections

**Prevention of fungal infections in immunocompromised patients**

- **By mouth, or by intravenous infusion**
  - Child: 3–12 mg/kg daily (max. per dose 400 mg), commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose given according to extent and duration of neutropenia
  - Adult: 50–400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose adjusted according to risk

**Prevention of fungal infections in immunocompromised patients (for patients with high risk of systemic infections e.g. following bone-marrow transplantation)**

- **By mouth, or by intravenous infusion**
  - Adult: 400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range

**Prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy**

- **By mouth, or by intravenous infusion**
  - Adult: 200 mg daily

### CONTRA-INDICATIONS
Acute porphyrias p. 930

### CAUTIONS
Susceptibility to QT interval prolongation

### INTERACTIONS
- Appendix 1 (antifungals, triazole); in general, fluconazole interactions in Appendix 1 relate to multiple-dose treatment. Caution with concomitant use of hepatotoxic drugs.

### SIDE-EFFECTS
- **Common or very common** Abdominal discomfort, diarrhoea, flatulence, headache, nausea, rash
- **Uncommon** Alopecia, anaphylaxis, angioedema (in children), dizziness, dyspepsia, hepatic disorders, hyperlipidaemia, hypersensitivity reactions (in adults), pruritus, seizures, Stevens-Johnson syndrome, taste disturbance, toxic epidermal necrolysis, vomiting
- **Frequency not known** Hypokalaemia, leucopenia, thrombocytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**
If rash occurs, discontinue treatment (or monitor closely if infection invasive or systemic); severe cutaneous reactions are more likely in patients with AIDS.

### PREGNANCY
Manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses.

### BREAST FEEDING
Present in milk but amount probably too small to be harmful.

### HEPATIC IMPAIRMENT
Toxicity with related drugs.

### RENAL IMPAIRMENT
- In adults: Usual initial dose then halve subsequent doses if eGFR less than 50 mL/minute/1.73 m².
- In children: Usual initial dose then halve subsequent doses if estimated glomerular filtration rate less than 50 mL/minute/1.73 m².

### MONITORING REQUIREMENTS
Monitor liver function with high doses or extended courses—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis).

### DIRECTIONS FOR ADMINISTRATION
- With intravenous use in children: *For intravenous infusion*, give over 10–30 minutes; do not exceed an infusion rate of 5–10 mL/minute.

### PRESCRIBING AND DISPENSING INFORMATION
Flavours of oral liquid formulations may include orange.

### PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary
Fluconazole Capsules 50 mg may be prescribed.
Fluconazole Oral Suspension 50 mg/5 mL may be prescribed.

### EXCEPTIONS TO LEGAL CATEGORY
Fluconazole capsules can be sold to the public for vaginal candidiasis and associated candidal balanitis in those aged 16–60 years, in a container or packaging containing not more than 150 mg and labelled to show a max. dose of 150 mg.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 9 (50 mg and 200 mg strengths only)
  - Fluconazole (Non-proprietary)
    - Fluconazole 50 mg Fluconazole 50 mg capsules | 7 capsule £0.00 DT price = £0.90
    - Fluconazole 150 mg Fluconazole 150 mg capsules | 1 capsule £0.93 | 1 capsule £0.50 DT price = £0.93
    - Fluconazole 200 mg Fluconazole 200 mg capsules | 7 capsule £0.07 DT price = £6.02
  - Canesten (fluconazole) (Bayer Plc)
    - Fluconazole 150 mg Canesten 150 mg capsules | 1 capsule £0.83
    - Fluconazole 50 mg Canesten 50 mg capsules | 7 capsule £0.16 DT price = £0.90
    - Fluconazole 150 mg Diflucan 150 mg capsules | 1 capsule £0.83
    - Fluconazole 200 mg Diflucan 200 mg capsules | 7 capsule £0.06 DT price = £6.02

**Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS** 9
  - Fluconazole (Non-proprietary)
    - Fluconazole 10 mg per 1 ml Fluconazole 50 mg/5 ml oral suspension | 35 ml £0.51 DT price = £20.51
    - Diflucan (Pfizer Ltd)
      - Fluconazole 10 mg per 1 ml Diflucan 50 mg/5 ml oral suspension | 35 ml £0.16 DT price = £20.51
      - Fluconazole 40 mg per 1 ml Diflucan 200 mg/5 ml oral suspension | 35 ml £0.66 DT price = £66.42
  - **Solution for infusion**
    - **ELECTROLYTES:** May contain Sodium
      - Fluconazole (Non-proprietary)
        - Fluconazole 2 mg per 1 ml Fluconazole 200 mg/50 mL solution for infusion bottles | 5 bottle £12.60
        - Fluconazole 200 mg/100 mL solution for infusion vials | 1 vial £29.28
        - Fluconazole 50 mg/25 mL solution for infusion vials | 1 vial £7.31–7.32
        - Fluconazole 200 mg/100 mL solution for infusion vials | 5 bottle £274.50
        - Diflucan (Pfizer Ltd)
          - Fluconazole 2 mg per 1 ml Diflucan 200 mg/100 mL solution for infusion vials | 1 vial £29.28.
**Isavuconazole**

**DRUG ACTION** Isavuconazole is a triazole antifungal that blocks the synthesis of ergosterol, a key component of the fungal cell membrane.

**INDICATIONS AND DOSE**

- **Invasive aspergillosis | Mucormycosis in patients for whom amphotericin B is inappropriate**
  - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - **Adult:** Loading dose 200 mg every 8 hours for 48 hours (6 administrations in total), then maintenance 200 mg once daily, maintenance dose to be started at least 12 hours after the last loading dose; long-term treatment should be reviewed after 6-months

**CONTRA-INDICATIONS** Short QT syndrome

**CAUTIONS** Elderly—limited information

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain · chest pain · decreased appetite · delirium · diarrhea · dyspnoea · electrolyte disturbances · headache · nausea · pruritus · rash · renal failure · somnolence · thrombophlebitis · vomiting
- **Uncommon** Abdominal distension · alopecia · arrythmias · asthenia · back pain · blood disorders · bronchospasm · constipation · convulsion · depression · dermatitis · dizziness · dyspepsia · encephalopathy · epistaxis · haemoptysis · hepatomegaly · hypersensitivity · hypotension · insomnia · malaise · paraesthesia · peripheral neuropathy · petechiae · syncope · tachynoea · vertigo
- **Frequency not known** Infusion-related reactions · Stevens-Johnson syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** Infusion-related reactions have been reported, including hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache—manufacturer advises discontinue treatment if these reactions occur.

**PREGNANCY** Manufacturer advises avoid unless severe or life-threatening infection—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises use with caution and monitor for toxicity in severe impairment—no information available.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion, reconstitute each 200 mg with 5 mL Water for Injection; dilute dose to concentration of 0.8 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give via a 0.2–1.2 micron filter over at least 1 hour.

**HANDLING AND STORAGE**
- With intravenous use Manufacturer advises store in a refrigerator (2–8°C)—consult product literature for storage after reconstitution or dilution.

**PATIENT AND CARER ADVICE**
- **Driving and skilled tasks** Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of confusion, syncope and dizziness.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS 25, 3**
  - **Cresemba** (Basilea Pharmaceutica International Ltd)
  - Isavuconazole (as Isavuconazonium sulfate) 100 mg Cresemba 100 mg capsules | 14 capsule (Pack) £59.28 (Hospital only)

**Powder for solution for infusion**

- **CAUTIONARY AND ADVISORY LABELS 3**
  - **Cresemba** (Basilea Pharmaceutica International Ltd)
  - Isavuconazole (as Isavuconazonium sulfate) 200 mg Cresemba 200 mg powder for concentrate for solution for infusion vials | 1 vial (Pack) £297.84 (Hospital only)

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**Itraconazole**

**INDICATIONS AND DOSE**

- **Vulvovaginal candidiasis**
  - **BY MOUTH**
  - **Adult:** 200 mg twice daily for 1 day

- **Vulvovaginal candidiasis (recurrent)**
  - **BY MOUTH**
  - **Adult:** 50–100 mg daily for 6 months

- **Oral or oesophageal candidiasis that has not responded to fluconazole**
  - **BY MOUTH USING ORAL SOLUTION**
  - **Adult:** 100–200 mg twice daily for 2 weeks (continue for another 2 weeks if no response; the higher dose should not be used for longer than 2 weeks if no signs of improvement)

- **Oral or oesophageal candidiasis in HIV-positive or other immunocompromised patients**
  - **BY MOUTH USING ORAL SOLUTION**
  - **Adult:** 200 mg daily in 1–2 divided doses for 1 week (continue for another week if no response)

- **Systemic candidiasis where other antifungal drugs inappropriate or ineffective**
  - **BY MOUTH**
  - **Adult:** 100–200 mg once daily
  - **BY INTRAVENOUS INFUSION**
  - **Adult:** 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

- **Systemic candidiasis (invasive or disseminated) where other antifungal drugs inappropriate or ineffective**
  - **BY MOUTH**
  - **Adult:** 200 mg twice daily

- **Pityriasis versicolor**
  - **BY MOUTH**
  - **Adult:** 200 mg once daily for 7 days

- **Tinea pedis | Tinea manuum**
  - **BY MOUTH**
  - **Adult:** 100 mg once daily for 30 days, alternatively 200 mg twice daily for 7 days

- **Tinea corporis | Tinea cruris**
  - **BY MOUTH**
  - **Adult:** 100 mg once daily for 15 days, alternatively 200 mg once daily for 7 days

- **Onychomycosis**
  - **BY MOUTH**
  - **Adult:** 200 mg once daily for 3 months, alternatively 200 mg twice daily for 7 days, subsequent courses repeated after 21-day intervals; fingernails 2 courses, toenails 3 courses

- **Aspergillosis**
  - **BY MOUTH**
  - **Adult:** 200 mg twice daily
Systemic aspergillosis where other antifungal drugs inappropriate or ineffective

- **BY INTRAVENOUS INFUSION**
- Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Histoplasmosis**

- **BY MOUTH**
- Adult: 200 mg 3 times a day for 3 days, then 200 mg 1–2 times a day
- **BY INTRAVENOUS INFUSION**
- Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**CONTRA-INDICATIONS**

Systemic cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective

- **BY MOUTH**
- Adult: 200 mg once daily, dose increased in invasive or disseminated disease and in cryptococcal meningitis, increased to 200 mg twice daily
- **BY INTRAVENOUS INFUSION**
- Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate**

- **BY MOUTH**
- Adult: 200 mg once daily, then increased to 200 mg twice daily, dose increased only if low plasma-itraconazole concentration

**Prophylaxis of deep fungal infections (when standard therapy inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic**

- **BY MOUTH USING ORAL SOLUTION**
- Adult: 5 mg/kg daily in 2 divided doses, to be started before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers, safety and efficacy not established in elderly patients

**UNLICENSED USE** Itraconazole doses in BNF may differ from those in product literature.

### IMPORTANT SAFETY INFORMATION

**HEART FAILURE**

Following reports of heart failure, caution is advised when prescribing itraconazole to patients at high risk of heart failure. Those at risk include:

- Patients receiving high doses and longer treatment courses;
- Older adults and those with cardiac disease;
- Patients with chronic lung disease (including chronic obstructive pulmonary disease) associated with pulmonary hypertension;
- Patients receiving treatment with negative inotropic drugs, e.g. calcium channel blockers.

Itraconazole should be avoided in patients with ventricular dysfunction or a history of heart failure unless the infection is serious.

**CONTRA-INDICATIONS** Acute porphyrias p. 930

**CAUTIONS** Active liver disease · history of hepatotoxicity with other drugs · susceptibility to congestive heart failure

**INTERACTIONS** → Appendix 1 (antifungals, triazole).

**SIDE-EFFECTS**

### GENERAL SIDE-EFFECTS

- **Common or very common** Abdominal pain · diarrhoea · dyspepsia · headache · hepatitis · hypokalaemia · nausea · rash · taste disturbances · vomiting

- **Uncommon** Constipation · dizziness · dyspepsia · flatulence · menstrual disorder · myalgia · oedema · peripheral neuropathy (discontinue treatment)

- **Rare** Alopecia · deafness · erectile dysfunction · heart failure · hypertriglyceridaemia · leucopenia · pancreatitis · photosensitivity · Stevens-Johnson syndrome · tinnitus · toxic epidermal necrolysis · urinary frequency · visual disturbances

- **Frequency not known** Arthralgia · blood pressure changes · confusion · drowsiness · hepatotoxicity · renal impairment · thrombocytopenia · tremor

### SPECIFIC SIDE-EFFECTS

- **With intravenous use** Hyperglycaemia

### SIDE-EFFECTS, FURTHER INFORMATION

- **Hepatotoxicity** Potentially life-threatening hepatotoxicity reported very rarely—discontinue if signs of hepatitis develop.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment and until the next menstrual period following end of treatment.

- **PREGNANCY** Manufacturer advises use only in life-threatening situations (toxicity at high doses in animal studies).

- **BREAST FEEDING** Small amounts present in milk—may accumulate; manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Dose reduction may be necessary. Use only if benefit outweighs risk of hepatotoxicity.

- **RENAL IMPAIRMENT** Risk of congestive heart failure.

- **With oral use** Bioavailability of oral formulations possibly reduced.

- **With intravenous use** Use intravenous infusion with caution if eGFR 30–80 mL/minute/1.73 m²; avoid intravenous infusion if eGFR less than 30 mL/minute/1.73 m².

### MONITORING REQUIREMENTS

- Absorption reduced in AIDS and neutropenia (monitor plasma-itraconazole concentration and increase dose if necessary).

- Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, if history of hepatotoxicity with other drugs, or in hepatic impairment.

### DIRECTIONS FOR ADMINISTRATION

- **With intravenous use** For intravenous infusion (Sporanox®), give intermittently in Sodium Chloride 0.9%; dilute 250 mg in 50 mL infusion fluid and infuse only 60 mL through an in-line filter (0.2 micron) over 60 minutes.

- **With oral use** For oral liquid, do not take with food; swish around mouth and swallow, do not rinse afterwards.

### PRESCRIBING AND DISPENSING INFORMATION

- Flavours of oral liquid formulations may include cherry.

### PATIENT AND CARER ADVICE

- Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine develop.

- Patients or carers should be given advice on how to administer itraconazole oral liquid.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

#### Capsule

**CAPSULE**

**CAUTIONARY AND ADVISORY LABELS** 5, 9, 21, 25

- **Itraconazole (Non-proprietary)**
  - Itraconazole 100 mg [itraconazole 100mg capsules] 15 capsule [PO] £13.77 DT price = £3.44 | 60 capsule [PO] £56.21
  - S**poranox** (Janssen-Cilag Ltd)
    - Itraconazole 100 mg Sporanox-Pulse 100mg capsules 28 capsule [PO] £25.72
Posaconazole

**INDICATIONS AND DOSE**

Invasive aspergillosis in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin | Fusariosis either unresponsive to, or in patients intolerant of, amphotericin | Chromoblastomycosis and mycetoma either unresponsive to, or in patients intolerant of, itraconazole | Coccidiodomycosis either unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole

- **By mouth using oral suspension**
  - Adult: 400 mg twice daily, to be taken with food, alternatively 200 mg 4 times a day, dose if food not tolerated
- **By mouth using tablets**
  - Adult: 300 mg twice daily on first day, then 300 mg once daily

Oropharyngeal candidiasis (severe infection or in immunocompromised patients only)

- **By mouth using oral suspension**
  - Adult: 200 mg 3 times a day start before transplantation or before chemotherapy and continued until neutrophil count recovers, dose to be taken with food
- **By mouth using tablets**
  - Adult: 300 mg twice daily on first day, then 300 mg once daily start before transplantation or before chemotherapy and continued until neutrophil count recovers

Prophylaxis of invasive fungal infections in patients undergoing bone-marrow transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome who are expected to become neutropenic, and who are intolerant of fluconazole or itraconazole

- **By mouth using oral suspension**
  - Adult: 200 mg 3 times a day start before transplantation or before chemotherapy and continued until neutrophil count recovers, dose to be taken with food
- **By mouth using tablets**
  - Adult: 300 mg twice daily on first day, then 300 mg once daily start before transplantation or before chemotherapy and continued until neutrophil count recovers

**DOSE EQUIVALENCE AND CONVERSION**

- Posaconazole oral suspension is not interchangeable with tablets on a milligram-for-milligram basis.

**PHARMACOKINETICS**

Posaconazole oral suspension should be taken with food (preferably a high fat meal) or nutritional supplement to ensure adequate exposure for systemic effects. Where possible, tablets should be used in preference to suspension because tablets have a higher bioavailability.

- **UNLICENSED USE** Tablets not licensed for oropharyngeal candidiasis.
- **CONTRA-INDICATIONS** Acute porphyrias p. 930
- **CAUTIONS** Body-weight over 120 kg—risk of treatment failure possibly increased; body-weight under 60 kg—risk of side effects increased; bradycardia; cardiomyopathy; history of QT interval prolongation—symptomatic arrhythmias

**INTERACTIONS** Appendix 1 (antifungals, triazole). Caution with concomitant use with other drugs known to cause QT-interval prolongation.

**SIDE-EFFECTS**

- Common or very common Abdominal pain | anaemia | anorexia | blood disorders | constipation | diarrhoea | dizziness | drowsiness | dry mouth | dyspepsia | electrolyte disturbances | fatigue | fever | flatulence | gastro-intestinal disturbances | headache | nausea | neutropenia | paraesthesia | pruritus | rash | thrombocytopenia | vomiting
- Rare Adrenal insufficiency | breast pain | cardiac failure | depression | encephalopathy | hearing impairment | ileus | myocardial infarction | pneumonitis | psychosis | Stevens-Johnson syndrome | stroke | syncope | thrombosis

**CONCEPTION AND CONTRACEPTION** Manufacturer recommends effective contraception during treatment.

**PREGNANCY** Manufacturer advises avoid—present in milk in animal studies.

**BREAST FEEDING** Manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Monitor liver function in hepatic impairment.

**MONITORING REQUIREMENTS**

- Monitor electrolytes (including potassium, magnesium, and calcium) before and during therapy.
- Monitor liver function before and during therapy.

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of oral liquid formulations may include cherry.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant tablet**

- **Noxafil** (Merck Sharp & Dohme Ltd)
  - Posaconazole 100 mg
  - **POS** £396.96
  - **96 tablet POS** £2,387.85

**Oral suspension**

- **POS** £491.20 (Hospital only)

Voriconazole

**INDICATIONS AND DOSE**

Invasive aspergillosis | Serious infections caused by Scedosporium spp., Fusarium spp., or invasive fluconazole-resistant Candida spp. (including C. krusei)

- **By mouth**
  - Adult: body-weight up to 40 kg: Initially 200 mg every 12 hours for 2 doses, then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours
  - Adult: body-weight 40 kg and above: Initially 400 mg every 12 hours for 2 doses, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours
- **By intravenous infusion**
  - Adult: Initially 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours; reduced if not tolerated to 3 mg/kg every 12 hours; for max. 6 months

**CONTRA-INDICATIONS** Acute porphyrias p. 930
HEPATIC IMPAIRMENT

BREAST FEEDING

CONCEPTION AND CONTRACEPTION

Hepatotoxicity With intravenous use

Common or very common Abdominal pain · acute renal failure · agitation · alopecia · altered perception · anaemia · anxiety · asthenia · blood disorders · blurred vision · chelitis · chest pain · confusion · depression · diarrhoea · dizziness · haematuria · hallucinations · headache · hypoglycaemia · hypokalaemia · hypotension · influenza-like symptoms · jaundice · leucopenia · nausea · oedema · pancytopenia · paraesthesia · photophobia · photosensitivity · pruritus · rash · respiratory distress syndrome · sinusitis · thrombocytopenia · tremor · visual disturbances · vomiting

Uncommon Adrenocortical insufficiency · arthralgias · arthritis · ataxia · blepharitis · cholecystitis · constipation · duodenitis · dyspepsia · flushing · fulminant hepatic failure · gingivitis · glossitis · hepatitis · hypersensitivity reactions · hypoaesthesia · hyponatraemia · nystagmus · optic neuritis · pancreatitis · psoriasis · QT interval prolongation · raised serum cholesterol · scleritis · Stevens-Johnson syndrome · syncope

Rare Convulsions · discoid lupus erythematosus · extrapyramidal effects · hearing disturbances · hyperthyroidism · hypertonia · hypothyroidism · insomnia · optic atrophy · pseudomembranous colitis · pseudoporphyria · retinal haemorrhage · taste disturbances (more common with oral suspension) · tinnitus · toxic epidermal necrolysis

Frequency not known On long term treatment, squamous cell carcinoma of skin (particularly in presence of phototoxicity) · periostitis (particularly in transplant patients)

SPECIFIC SIDE-EFFECTS

Common or very common

With intravenous use Injection-site reactions

SIDE-EFFECTS, FURTHER INFORMATION

Hepatotoxicity Hepatitis, cholestasis, and fulminant hepatic failure usually occur in the first 10 days; risk of hepatotoxicity increased in patients with haematological malignancy. Consider treatment discontinuation if severe abnormalities in liver function tests.

Photo toxicity Phototoxicity occurs commonly. If phototoxicity occurs, consider treatment discontinuation; if treatment is continued, monitor for pre-malignant skin lesions and squamous cell carcinoma, and discontinue treatment if they occur.

CONCEPTION AND CONTRACEPTION Effective contraception required during treatment.

PREGNANCY Toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT In mild to moderate hepatic cirrhosis use usual initial dose then halve maintenance dose. No information available for severe hepatic cirrhosis—manufacturer advises use only if potential benefit outweighs risk.

RENAL IMPAIRMENT Intravenous vehicle may accumulate if eGFR less than 50 mL/minute/1.73 m²—use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required).

CAUTIONS Avoid exposure to sunlight · bradycardia · cardiomyopathy · electrolyte disturbances · history of QT interval prolongation · patients at risk of pancreatitis · symptomatic arrhythmias

INTERACTIONS → Appendix 1 (antifungals, triazole). Caution with concomitant use with other drugs that prolong QT interval.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

MONITORING REQUIREMENTS

Monitor renal function.

Monitor liver function before starting treatment, then at least weekly for 1 month, and then monthly during treatment.

DIRECTIONS FOR ADMINISTRATION For intravenous infusion, reconstitute each 200 mg with 19 mL Water for Injections or Sodium Chloride 0.9% to produce a 10 mg/mL solution; dilute dose to concentration of 0.5–5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give intermittently at a rate not exceeding 3 mg/kg/hour.

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include orange.

PATIENT AND CARER ADVICE Patients and their carers should be advised to keep the alert card with them at all times.

Patients and their carers should be told how to recognise symptoms of liver disorder, and advised to seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Patients and their carers should be advised that patients should avoid intense or prolonged exposure to direct sunlight, and to avoid the use of sunbeds. In sunlight, patients should cover sun-exposed areas of skin and use a screens with a high sun protection factor. Patients should seek medical attention if they experience sunburn or a severe skin reaction following exposure to light or sun.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 9, 11, 23

Voriconazole (Non-proprietary)

Voriconazole 50 mg Voriconazole 50mg tablets | 28 tablet [POM] £45.43–£275.68

Voriconazole 200 mg Voriconazole 200mg tablets | 28 tablet [POM] £157.49–£1,102.74

VFEND (Pfizer Ltd)

Voriconazole 50 mg VFEND 50mg tablets | 28 tablet [POM] £275.68

Voriconazole 200 mg VFEND 200mg tablets | 28 tablet [POM] £1,102.74

Oral suspension

CAUTIONARY AND ADVISORY LABELS 9, 11, 23

VFEND (Pfizer Ltd)

Voriconazole 40 mg per 1 ml VFEND 40mg/ml oral suspension | 75 ml [POM] £551.37

Powder for solution for infusion

EXCIPIENTS: May contain Sulphobutyler beta cyclodextrin sodium ELECTROLYTES: May contain Sodium

Voriconazole (Non-proprietary)

Voriconazole 200 mg Voriconazole 200mg powder for solution for infusion vials | 1 vial [POM] £77.14 (Hospital only)

VFEND (Pfizer Ltd)

Voriconazole 200 mg VFEND 200mg powder for solution for infusion vials | 1 vial [POM] £77.14 (Hospital only)

Powder and solvent for solution for infusion

EXCIPIENTS: May contain Sulphobutyler beta cyclodextrin sodium ELECTROLYTES: May contain Sodium

VFEND (Pfizer Ltd)

Voriconazole 200 mg VFEND 200mg powder and solvent for solution for infusion vials | 1 vial [POM] £77.14 (Hospital only)
Flucytosine

### INDICATIONS AND DOSE

- **Systemic yeast and fungal infections | Adjunct to amphotericin B in severe systemic candidiasis and in other severe or long-standing infections**
  - By intravenous infusion
  - Adult: Usual dose 200 mg/kg daily in 4 divided doses usually for not more than 7 days, alternatively 100–150 mg/kg daily in 4 divided doses, lower dose may be sufficient for extremely sensitive organisms

- **Cryptococcal meningitis (adjunct to amphotericin)**
  - By intravenous infusion
  - Adult: 100 mg/kg daily in 4 divided doses for 2 weeks

### UNLICENSED USE

- Use in cryptococcal meningitis for 2 weeks is an unlicensed duration.
- **CAUTIONS** Blood disorders - elderly

### INTERACTIONS

- **Appendix 1 (flucytosine).**

### SIDE-EFFECTS

- **Common or very common** Diarrhoea, nausea, rash, vomiting
- **Uncommon** Alterations in liver function tests - cardiotoxicity - confusion - convulsions - hallucinations - headache - sedation - toxic epidermal necrolysis - vertigo
- **Frequency not known** Aplastic anaemia, blood disorders - hepatic necrosis - hepatitis - leucopenia - thrombocytopenia
- **PREGNANCY** Teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid.
- **RENAL IMPAIRMENT** Use 50 mg/kg every 12 hours if creatinine clearance 20–40 mL/minute; use 50 mg/kg every 24 hours if creatinine clearance 10–20 mL/minute; use initial dose of 50 mg/kg if creatinine clearance less than 10 mL/minute and then adjust dose according to plasma-flucytosine concentration. In renal impairment liver- and kidney-function tests and blood counts required weekly.
- **MONITORING REQUIREMENTS**
  - For plasma concentration monitoring, blood should be taken shortly before starting the next infusion; plasma concentration for optimum response 25–50 mg/litre (200–400 micromol/litre)—should not be allowed to exceed 80 mg/litre (620 micromol/litre).
  - Liver- and kidney-function tests and blood counts required (weekly in blood disorders).
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion, give over 20–40 minutes.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Solution for infusion

- **Electrolytes:** May contain Sodium
  - Ancotil (Meda Pharmaceuticals Ltd)
    - Flucytosine 10 mg per 1 ml
    - 25g/250ml solution for infusion bottles | 5 bottle
  - Cost: £151.67 (Hospital only)

Griseofulvin

### INDICATIONS AND DOSE

- **Dermatophyte infections of the skin, scalp, hair and nails where topical therapy has failed or is inappropriate**
  - **BY MOUTH**
  - Adult: 500 mg daily, increased if necessary to 1 g daily, for severe infections; reduce dose when response occurs, daily dose may be taken once daily or in divided doses

### UNLICENSED USE

- Griseofulvin doses in BNF may differ from those in product literature.

### CONTRA-INDICATIONS

- Acute porphyrias p. 930 - systemic lupus erythematosus (risk of exacerbation)

### INTERACTIONS

- **Appendix 1 (griseofulvin).**

### SIDE-EFFECTS

- **Rare** Erythema multiforme - toxic epidermal necrolysis - Very rare - Headache
- **Frequency not known** Abdominal pain - agitation - confusion - depression - diarrhoea - dizziness - dyspepsia - fatigue - glossitis - hepatotoxicity - impaired coordination - impaired hearing - leucopenia - menstrual disturbances - nausea - peripheral neuropathy - photosensitivity - rash - renal failure - sleep disturbances - systemic lupus erythematosus - taste disturbances - vomiting
- **CONCEPTION AND CONTRACEPTION** Effective contraception required during and for at least 1 month after administration to women (important: effectiveness of oral contraceptives may be reduced, additional contraceptive precautions e.g. barrier method, required). Men should avoid fathering a child during and for at least 6 months after administration.
- **PREGNANCY** Avoid (fetotoxicity and teratogenicity in animals).
- **BREAST FEEDING** Avoid—no information available.
- **HEPATIC FEEDING** Avoid in severe liver disease.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - May impair performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

#### Tablet

- **CAUTIONARY AND ADVISORY LABELS 9, 21**
  - Griseofulvin (Non-proprietary)
    - 125 mg
    - 250 mg tablets
    - 500 mg tablets
  - Cost: £96.67 DT price = £99.00

### 3.1 Pneumocystis pneumonia

#### Pneumocystis pneumonia

### Overview

Pneumocystis pneumonia caused by *Pneumocystis jirovecii* (Pneumocystis carinii) occurs in immunosuppressed patients; it is a common cause of pneumonia in AIDS. Pneumocystis pneumonia should generally be treated by those experienced in its management. Blood gas measurement is used to assess disease severity.

### Treatment

**Mild to moderate disease**

- **Co-trimoxazole** p. 518 in high dosage is the drug of choice for the treatment of mild to moderate pneumocystis pneumonia.

- **Atovaquone** p. 555 is licensed for the treatment of mild to moderate pneumocystis infection in patients who cannot tolerate co-trimoxazole. A combination of dapsone p. 532 with trimethoprim p. 529 is given by mouth for the
Antiprotozoals

Treatment of mild to moderate disease [unlicensed indication].

A combination of clindamycin p. 493 and primaquine p. 571 by mouth is used in the treatment of mild to moderate disease [unlicensed indication]; this combination is associated with considerable toxicity.

Severe disease

Co-trimoxazole in high dosage, given by mouth or by intravenous infusion, is the drug of choice for the treatment of severe pneumocystis pneumonia. Pentamidine isetionate below given by intravenous infusion is an alternative for patients who cannot tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a potentially toxic drug that can cause severe hypotension during or immediately after infusion.

Corticosteroid treatment can be lifesaving in those with severe pneumocystis pneumonia.

Adjunctive therapy

In moderate to severe infections associated with HIV infection, prednisolone p. 622 is given by mouth for 5 days (alternatively, hydrocortisone p. 620 may be given parenterally); the dose is then reduced to complete 21 days of treatment. Corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete.

Prophylaxis

Prophylaxis against pneumocystis pneumonia should be given to all patients with a history of the infection. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised patients. Prophylaxis should continue until immunity recovers sufficiently. It should not be discontinued if the patient has oral candidiasis, continues to lose weight, or is receiving cytotoxic therapy or long-term immunosuppressant therapy.

Co-trimoxazole by mouth is the drug of choice for prophylaxis against pneumocystis pneumonia. It is given daily or on alternate days (3 times a week); the dose may be reduced to improve tolerance.

Inhaled pentamidine is better tolerated than parenteral pentamidine isetionate. Intermittent inhalation of pentamidine isetionate is used for prophylaxis against pneumocystis pneumonia in patients unable to tolerate co-trimoxazole. It is effective but patients may be prone to extrapulmonary infection. Alternatively, dapsone can be used. Atovaquone has also been used for prophylaxis [unlicensed indication].

ANTIPROTOZOALS

Atovaquone

- **INDICATIONS AND DOSE**
  
  Treatment of mild to moderate *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia in patients intolerant of co-trimoxazole
  
  - **BY MOUTH**
    
    Adult: 750 mg twice daily for 21 days, dose to be taken with food, particularly high fat food
  
  Prophylaxis against pneumocystis pneumonia
  
  - **BY MOUTH**
    
    Adult: 750 mg twice daily

- **UNLICENSED USE** Not licensed for prophylaxis against pneumocystis pneumonia.

- **CAUTIONS** Other causes of pulmonary disease should be sought and treated: elderly, initial diarrhoea and difficulty in taking with food may reduce absorption (and require alternative therapy)

- **INTERACTIONS** Appendix 1 (atovaquone).

- **SIDE-EFFECTS** Anaemia, diarrhoea, fever, headache, hypotension, nausea, neutropenia, pruritus, rash, Stevens-Johnson syndrome, vomiting

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

- **BREAST FEEDING** Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution. Monitor more closely in hepatic impairment.

- **RENAL IMPAIRMENT** Manufacturer advises caution. Monitor more closely in renal impairment.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include tutti-frutti.

Pentamidine isetionate

- **INDICATIONS AND DOSE**
  
  Treatment of *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia (specialist use only)

  - **BY INTRAVENOUS INFUSION**
    
    Adult: 4 mg/kg once daily for at least 14 days
  
  Prophylaxis of *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia (specialist use only)

  - **BY INHALATION OF NEBULISED SOLUTION**
    
    Adult: 300 mg every 4 weeks, alternatively 150 mg every 2 weeks, using suitable equipment—consult product literature
  
  Visceral leishmaniasis (specialist use only)

  - **BY DEEP INTRAMUSCULAR INJECTION**
    
    Adult: 3–4 mg/kg once daily on alternate days, maximum total of 10 injections, course may be repeated if necessary
  
  Cutaneous leishmaniasis (specialist use only)

  - **BY DEEP INTRAMUSCULAR INJECTION**
    
    Adult: 3–4 mg/kg 1–2 times a week until condition resolves
  
  Trypanosomiasis (specialist use only)

  - **BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION**
    
    Adult: 4 mg/kg once daily or on alternate days for a total of 7–10 injections

- **UNLICENSED USE** Not licensed for primary prevention of *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia by inhalation of nebulised solution.

- **CAUTIONS** Anaemia, bradycardia, coronary heart disease, history of ventricular arrhythmias, hyperglycaemia, hypertension, hypoglycaemia, hypokalaemia, hypomagnesaemia, hypotension, leucopenia, risk of severe hypotension following administration, thrombocytopenia

- **INTERACTIONS** Appendix 1 (pentamidine isetionate). Caution with concomitant use of other drugs that prolong the QT interval.

- **SIDE-EFFECTS**

  **GENERAL SIDE-EFFECTS**

  Abnormal liver-function tests, acute renal failure, anaemia, arthralgias (can be severe and sometimes fatal), azotaemia, dizziness, flushing, hyperglycaemia, hyperkalaemia, hypocalcaemia, hypoglycaemia (can be...
severe and sometimes fatal) · hypotension (can be severe and sometimes fatal) · leucopenia · nausea · pancreatitis (can be severe and sometimes fatal) · rash · Stevens–Johnson syndrome · syncope · taste disturbances · thrombocytopenia · vomiting

**SPECIFIC SIDE-EFFECTS**

- When used by inhalation Bronchoconstriction (may be prevented by prior use of bronchodilators) · cough · shortness of breath
- With intramuscular use or intravenous use Injection site reactions (muscle necrosis, discomfort, pain, induration, abscess formation)
- **PREGNANCY** Manufacturer advises avoid unless essential.
- **BREAST FEEDING** Manufacturer advises avoid unless essential—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution.
- **RENAL IMPAIRMENT** Reduce intravenous dose for severe renal impairment.
- **BREAST FEEDING** Manufacturer advises avoid unless essential.
- **PREGNANCY** 

**MONITORING REQUIREMENTS**

- Monitor blood pressure before starting treatment, during administration, and at regular intervals, until treatment concluded.
- Carry out laboratory monitoring according to product literature.

**DIRECTIONS FOR ADMINISTRATION** Patient should be lying down when receiving drug parenterally. Direct intravenous injection should be avoided whenever possible and never given rapidly; intramuscular injections should be deep and preferably given into the buttck. For **intravenous infusion**, reconstitute 300 mg with 3–5 mL. Water for Injections (displacement value may be significant), then dilute required dose with 50–250 mL. Glucose 5% or Sodium Chloride 0.9%; give over at least 60 minutes.

Powder for injection (dissolved in water for injection) may be used for nebulisation.

**HANDLING AND STORAGE** Pentamidine isetionate is toxic and personnel should be adequately protected during handling and administration—consult product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Pentacarinat** (Sanofi)
  - Pentamidine isetionate 300 mg Pentacarinat 300mg powder for solution for injection vials | 5 vial [ texting ] £158.86

### 4 Helminth infection

#### Helminth infections

**Specialist centres**

Advice on prophylaxis and treatment of helminth infections is available from the following specialist centres:

- **Birmingham** (0121) 424 0357
- **Scotland** Contact local Infectious Diseases Unit
- **Liverpool** (0151) 705 3100
- **London** 0845 155 5000 (treatment)

**Drugs for threadworms**

Anthelmintics are effective in threadworm (pinworms, *Enterobius vermicularis*) infections, but their use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment.

Adult threadworms do not live for longer than 6 weeks and for development of fresh worms, ova must be swallowed and exposed to the action of digestive juices in the upper intestinal tract. Direct multiplication of worms does not take place in the large bowel. Adult female worms lay ova on the perianal skin which causes pruritus; scratching the area then leads to ova being transmitted on fingers to the mouth, often via food eaten with unwashed hands. Washing hands and scrubbing nails before each meal and after each visit to the toilet is essential. A bath taken immediately after rising will remove ova laid during the night.

Mebendazole p. 558 is the drug of choice for treating threadworm infection in patients of all ages over 6 months. It is given as a single dose; as reinfection is very common, a second dose may be given after 2 weeks.

**Ascaridides (common roundworm infections)**

Mebendazole is effective against *Ascaris lumbricoides* and is generally considered to be the drug of choice.

Levamisole p. 558 [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is an alternative when mebendazole cannot be used. It is very well tolerated.

**Drugs for tapeworm infections**

**Taenicides**

- **Niclosamide** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is the most widely used drug for tapeworm infections and side-effects are limited to occasional gastro-intestinal upset, lightheadedness, and pruritus; it is not effective against larval worms. Fears of developing cysticercosis in *Taenia solium* infections have proved unfounded. All the same, an antiemetic can be given before treatment and a laxative can be given 2 hours after niclosamide.

Praziquantel p. 558 [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is as effective as niclosamide.

**Hydatid disease**

Cysts caused by *Echinococcus granulosus* grow slowly and asymptomatic patients do not always require treatment. Surgical treatment remains the method of choice in many situations. Albenzazole p. 557 [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Alveolar echinococcosis due to *E. multilocularis* is usually fatal if untreated. Surgical removal with albendazole cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment.

**Drugs for hookworms**

Hookworms (anaclostomiasis, necatoriasis) live in the upper small intestine and draw blood from the point of their attachment to their host. An iron-deficiency anaemia may occur and, if present, effective treatment of the infection requires not only expulsion of the worms but treatment of the anaemia.

Mebendazole has a useful broad-spectrum activity, and is effective against hookworms. Albenzazole [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is an alternative. Levamisole is also is also effective in children.

**Schistosomicides (bilharziasis)**

Adult *Schistosoma haematobium* worms live in the genito-urinary veins and adult *S. mansoni* in those of the colon and
mesentery. *S. japonicum* is more widely distributed in veins of the alimentary tract and portal system. Praziquantel [unlicensed] is available from Merck Serono (Cysticide®) and is effective against all human schistosomes. No serious adverse effects have been reported. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.

**Filaricides**

Diethylcarbamazine [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is effective against microfilariae and adults of *Loa loa*, *Wuchereria bancrofti*, and *Brugia malayi*. To minimise reactions, treatment in adults and children over 1 month, is commenced with a dose of diethylcarbamazine citrate on the first day and increased gradually over 3 days. Length of treatment varies according to infection type, and usually gives a radical cure for these infections. Close medical supervision is necessary particularly in the early phase of treatment.

In heavy infections there may be a febrile reaction, and in heavy *Loa loa* infection there is a small risk of encephalopathy. In such cases specialist advice should be sought, and treatment must be given under careful in-patient supervision and stopped at the first sign of cerebral involvement.

Ivermectin below [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is very effective in *onchocerciasis* and it is now the drug of choice; reactions are usually slight. Diethylcarbamazine or suramin should no longer be used for *onchocerciasis* because of their toxicity.

**Drugs for cutaneous larva migrans (creeping eruption)**

Dog and cat hookworm larvae may enter human skin where they produce slowly extending itching tracks usually on the foot. Single tracks can be treated with topical tiabendazole (thiabendazole) by mouth [all unlicensed] (available from manufacturers or specialist importing companies).

**Drugs for strongyloidiasis**

Adult *Strongyloides stercoralis* live in the gut and produce larvae which penetrate the gut wall and invade the tissues, setting up a cycle of auto-infection. Ivermectin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is the treatment of choice for chronic *Strongyloides* infection in adults and children over 5 years. Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is an alternative given to adults and children over 2 years.

### Anthelmintics

#### Albendazole

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Chronic <em>Strongyloides</em> infection</th>
</tr>
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<tbody>
<tr>
<td>▶ BY MOUTH</td>
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<tr>
<td>Adult: 400 mg twice daily for 3 days, dose may be repeated after 3 weeks if necessary</td>
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<tr>
<td><strong>Hydatid disease, in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases</strong></td>
</tr>
<tr>
<td>▶ BY MOUTH</td>
</tr>
<tr>
<td>Adult: (consult product literature)</td>
</tr>
</tbody>
</table>

#### Hookworm infections

- BY MOUTH
- Adult: 400 mg for 1 dose

- UNLICENSED USE Albendazole is an unlicensed drug.

- INTERACTIONS → Appendix 1 (albendazole).

#### MEDICAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, chewable tablet, oral suspension.

#### Tablet

**CAUTIONARY AND ADVISORY LABELS 9**

- Albendazole (Non-proprietary)
  - Albendazole 400 mg Eskazole 400mg tablets | 60 tablet [no price available]
  - Albendazole 400 mg Zentel 400mg chewable tablets | 6 tablet [no price available]
  - Albendazole 400 mg Zentel 400mg chewable tablets | 1 tablet [no price available]  3 tablet [no price available]

#### Diethylcarbamazine

**INDICATIONS AND DOSE**

- *Wuchereria bancrofti* infections | *Brugia malayi* infections

- BY MOUTH
- Adult: Initially 1 mg/kg daily on the first day, then increased to 6 mg/kg daily in divided doses, dose to be increased gradually over 3 days

- *Loa loa* infections

- BY MOUTH
  - Adult: Initially 1 mg/kg daily on the first day, then increased to 6 mg/kg daily in divided doses, dose to be increased gradually over 3 days; maximum 9 mg/kg per day

- UNLICENSED USE Diethylcarbamazine is an unlicensed drug.

- INTERACTIONS → Appendix 1 (diethylcarbamazine).

#### MEDICAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

#### Ivermectin

**INDICATIONS AND DOSE**

- **Chronic *Strongyloides* infection**
  - BY MOUTH
  - Adult: 200 micrograms/kg daily for 2 days

- **Onchocerciasis**
  - BY MOUTH
  - Adult: 150 micrograms/kg for 1 dose, retreatment at intervals of 6 to 12 months may be required depending on symptoms

- Scabies, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone
  - BY MOUTH
  - Adult: 200 micrograms/kg for 1 dose, further doses of 200 micrograms/kg may be required

- UNLICENSED USE Ivermectin is an unlicensed drug.

- INTERACTIONS → Appendix 1 (ivermectin).

- SIDE-EFFECTS Aggravation of itching - aggravation of rash
**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Tablet**
- Ivermectin (Non-proprietary)
  - Ivermectin 3 mg | Stromectol 3mg tablets | 4 tablet POM no price available | 20 tablet POM no price available

**Levamisole**

**INDICATIONS AND DOSE**
**Roundworm infections**
- BY MOUTH
  - Adult: 120–150 mg for 1 dose

**UNLICENSED USE**
- Not licensed.

**CONTRA-INDICATIONS**
- Blood disorders

**CAUTIONS**
- Epilepsy
- Sjögren’s syndrome

**INTERACTIONS**
- Appendix 1 (levamisole).

**SIDE-EFFECTS**
- Arthralgia (on prolonged treatment) • blood disorders (on prolonged treatment) • convulsions (on prolonged treatment) • diarrhoea • dizziness • headache • influenza-like syndrome (on prolonged treatment) • insomnia (on prolonged treatment) • myalgia (on prolonged treatment) • nausea • rash (on prolonged treatment) • taste disturbances (on prolonged treatment) • vasculitis (on prolonged treatment) • vomiting

**PREGNANCY**
- Embryotoxic in animal studies, avoid if possible.

**BREAST FEEDING**
- No information available.

**HEPATIC IMPAIRMENT**
- Use with caution—dose adjustment may be necessary.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Tablet**
- Cautionary and Advisory Labels 4
  - Ergamisol (Imported (Belgium))
    - Levamisole (as Levamisole hydrochloride) 50 mg | Ergamisol 50mg tablets | 20 tablet POM no price available

**Mebendazole**

**INDICATIONS AND DOSE**
**Threadworm infections**
- BY MOUTH
  - Child 6 months–17 years: 100 mg for 1 dose, if reinfection occurs, second dose may be needed after 2 weeks
  - Adult: 100 mg for 1 dose, if reinfection occurs, second dose may be needed after 2 weeks

**Whipworm infections**
- BY MOUTH
  - Child 1–17 years: 100 mg twice daily for 3 days
  - Adult: 100 mg twice daily for 3 days

**Roundworm infections**
- BY MOUTH
  - Child 1 year: 100 mg twice daily for 3 days
  - Child 2–17 years: 100 mg twice daily for 3 days, alternatively 500 mg for 1 dose
  - Adult: 100 mg twice daily for 3 days, alternatively 500 mg for 1 dose

**UNLICENSED USE**
- Not licensed for use as a single dose of 500 mg in roundworm infections. Not licensed for use in children under 2 years.

**INTERACTIONS**
- Appendix 1 (mebendazole).

**SIDE-EFFECTS**
- Common or very common: Abdominal pain
- Uncommon: Diarrhoea • flatulence
- Rare: Alopecia • convulsions • dizziness • hepatitis • neutropenia • rash • Stevens–Johnson syndrome • toxic epidermal necrolysis • urticaria

**PREGNANCY**
- Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**
- Amount present in milk too small to be harmful but manufacturer advises avoid.

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral liquid formulations may include banana.

**PATIENT AND CARER ADVICE**
- Medicines for Children leaflet: Mebendazole for worm infections www.medicinesforchildren.org.uk/mebendazole-for-worm-infections

**EXCEPTIONS TO LEGAL CATEGORY**
- Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Chewable tablet**
- Ovex (McNeil Products Ltd)
  - Mebendazole 100 mg | Ovex 100mg chewable tablets sugar-free | 1 tablet P | £2.03 sugar-free | 4 tablet P | £4.74
- Vermox (Janssen-Cilag Ltd)
  - Mebendazole 100 mg | Vermox 100mg chewable tablets sugar-free | 6 tablet P | £1.34 DT price = £1.34

**Oral suspension**
- Ovex (McNeil Products Ltd)
  - Mebendazole 20 mg per 1 ml | Ovex 100mg/5ml oral suspension | 30 ml P | £6.03 DT price = £1.55
- Vermox (Janssen-Cilag Ltd)
  - Mebendazole 20 mg per 1 ml | Vermox 100mg/5ml oral suspension | 30 ml P | £5.55 DT price = £1.55

**Praziquantel**

**INDICATIONS AND DOSE**
**Tapeworm infections (Taenia solium)**
- BY MOUTH
  - Adult: 5–10 mg/kg for 1 dose, to be taken after a light breakfast

**Tapeworm infections (Hymenolepis nana)**
- BY MOUTH
  - Adult: 25 mg/kg for 1 dose, to be taken after a light breakfast

**Schistosoma haematobium worm infections**
- BY MOUTH
  - Adult: 20 mg/kg, followed by 20 mg/kg after 4–6 hours

**Schistosoma japonicum worm infections**
- BY MOUTH
  - Adult: 20 mg/kg 3 times a day for 1 day

**UNLICENSED USE**
- Praziquantel is an unlicensed drug.

**INTERACTIONS**
- Appendix 1 (praziquantel).
Leishmaniasis

5 Protozoal infection

Antiprotozoal drugs

Amoebicides

Metronidazole p. 499 is the drug of choice for acute invasive amoebic dysentery since it is very effective against vegetative forms of Entamoeba histolytica in ulcers. Tinidazole p. 501 is also effective. Metronidazole and tinidazole are also active against amoebae which may have migrated to the liver.

Treatment with metronidazole (or tinidazole) is followed by a 10-day course of diloxanide furoate p. 467. Diloxanide furoate is the drug of choice for asymptomatic patients with E. histolytica cysts in the faeces; metronidazole and tinidazole are relatively ineffective. Diloxanide furoate is relatively free from toxic effects and the usual course is of 10 days, given alone for chronic infections or following metronidazole or tinidazole treatment.

For amoebic abscesses of the liver metronidazole is effective; tinidazole is an alternative. Aspiration of the abscess is indicated where it is suspected that it may rupture and there is no improvement after 72 hours of metronidazole; the aspiration may need to be repeated. Aspiration aids penetration of metronidazole and, for abscesses with more than 100 mL of pus, if carried out in conjunction with drug therapy, may reduce the period of disability.

Diloxanide furoate is not effective against hepatic amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut.

Trichomonacides

Metronidazole is the treatment of choice for Trichomonas vaginalis infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, tinidazole may be tried.

Antigiardial drugs

Metronidazole is the treatment of choice for Giardia lamblia infections. Alternative treatments are tinidazole or mebendazole hydrochloride p. 467.

Leishmaniacides

Cutaneous leishmaniasis frequently heals spontaneously but if skin lesions are extensive or unsightly, treatment is indicated, as it is in visceral leishmaniasis (kala-azar). Leishmaniasis should be treated under specialist supervision.

Sodium stibogluconate below, an organic pentavalent antimony compound, is used for visceral leishmaniasis. The dosage varies with different geographical regions and expert advice should be obtained. Some early non-inflamed lesions of cutaneous leishmaniasis can be treated with intralesional injections of sodium stibogluconate under specialist supervision.

Amphotericin p. 547 is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone; side-effects may be reduced by using liposomal amphotericin (AmBisome®). Abelcet®, a lipid formulation of amphotericin is also likely to be effective but less information is available.

Pentamidine isetionate p. 555 has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects. Other treatments include paromomycin [unlicensed] (available from ’special-order’ manufacturers or specialist importing companies).

Trypanocides

The prophylaxis and treatment of trypanosomiasis is difficult and differs according to the strain of organism. Expert advice should therefore be obtained.

Drugs for toxoplasmosis

Most infections caused by Toxoplasma gondii are self-limiting, and treatment is not necessary. Exceptions are patients with eye involvement (toxoplasmal chorioretinitis), and those who are immunosuppressed. Toxoplasmic encephalitis is a common complication of AIDS. The treatment of choice is a combination of pyrimethamine p. 572 and sulfadiazine p. 520, given for several weeks (expert advice essential). Pyrimethamine is a folate antagonist, and adverse reactions to this combination are relatively common (folinic acid supplements and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine with clindamycin p. 493 or clari-thromycin p. 496 or azithromycin p. 495. Long-term secondary prophylaxis is required after treatment of toxoplasmosis in immunocompromised patients; prophylaxis should continue until immunity recovers.

If toxoplasmosis is acquired in pregnancy, transplacental infection may lead to severe disease in the fetus; specialist advice should be sought on management. Spiramycin [unlicensed] (available from ’special-order’ manufacturers or specialist importing companies) may reduce the risk of transmission of maternal infection to the fetus.

5.1 Leishmaniasis

Other drugs used for Leishmaniasis Amphotericin, p. 547 • Pentamidine isetionate, p. 555

ANTIPROTOZOAIS

Sodium stibogluconate

INDICATIONS AND DOSE

Visceral leishmaniasis (specialist use only)

• BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

• Adult: 20 mg/kg daily for 28 days

Cutaneous leishmaniasis (specialist use only)

• BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

• Adult: 20 mg/kg daily for 20 days

CAUTIONS, FURTHER INFORMATION

• Heart disease (withdraw if conduction disturbances occur) • mucocutaneous disease • predisposition to QT interval prolongation • treat intercurrent infection (e.g. pneumonia)

Mucocutaneous disease Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around the lesions (may be life-threatening
Infection

Medicinal forms

DIRECTIONS FOR ADMINISTRATION

MONITORING REQUIREMENTS

RENAL IMPAIRMENT

HEPATIC IMPAIRMENT

PREGNANCY

SIDE-EFFECTS

If pharyngeal or tracheal involvement)—may require corticosteroid.

INTERACTIONS → Appendix 1 (sodium stibogluconate).

Caution with concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS

Rare Bleeding from gums · bleeding from nose · fever · flushing · jaundice · rash · substernal pain · sweating · vertigo

Frequency not known Abdominal pain · anaphylaxis · anorexia · arthralgia · coughing · diarrhoea · ECG changes · headache · lethargy · myalgia · nausea · pain on intramuscular injection · pain on intravenous administration · pancreatitis · thrombosis on intravenous administration · vomiting

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING Amount probably too small to be harmful.

HEPATIC IMPAIRMENT Use with caution.

RENAL IMPAIRMENT Avoid in significant impairment.

Monitoring requirements Monitor ECG before and during treatment.

DIRECTIONS FOR ADMINISTRATION Intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain occur. Injection should be filtered immediately before administration using a filter of 5 microns or less.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Pentostam (GlaxoSmithKline UK Ltd)
  * Antimony pentavalent (as Sodium stibogluconate) 100 mg per 1 ml. Pentostam 10g/100ml solution for injection vials [1 vial £0.03] £56.43

5.2 Malaria

Antimalarials

Artemether with lumefantrine

Artemether with lumefantrine p. 567 is licensed for the treatment of acute non-complicated falciparum malaria.

Chloroquine

Chloroquine p. 569 is used for the prophylaxis of malaria in areas of the world where the risk of chloroquine-resistant falciparum malaria is still low. It is also used with proguanil hydrochloride p. 571 when chloroquine-resistant falciparum malaria is present but this regimen may not give optimal protection (see recommended regimens for prophylaxis against malaria in Malaria, prophylaxis below).

Chloroquine is no longer recommended for the treatment of falciparum malaria owing to widespread resistance, nor is it recommended if the infective species is not known or if the infection is mixed; in these cases treatment should be with quinine p. 573, Malarone®, or Riamet®. It is still recommended for the treatment of non-falciparum malaria.

Mefloquine

Mefloquine p. 570 is used for the prophylaxis of malaria in areas of the world where there is a high risk of chloroquine-resistant falciparum malaria (for details, see recommended regimens for prophylaxis against malaria in Malaria, prophylaxis below).

Mefloquine is now rarely used for the treatment of falciparum malaria because of increased resistance. It is rarely used for the treatment of non-falciparum malaria because better tolerated alternatives are available.

Mefloquine should not be used for treatment if it has been used for prophylaxis.

Piperazine with artemether

Artemether with lumefantrine p. 567 is not recommended for the first-line treatment of acute uncomplicated falciparum malaria because there is limited experience of its use in travellers who usually reside in areas where malaria is not endemic. Piperazine has a long half-life.

Primaquine

Primaquine p. 571 is used to eliminate the liver stages of P. vivax or P. ovale following chloroquine treatment.

Proguanil

Proguanil hydrochloride is used (usually with chloroquine, but occasionally alone) for the prophylaxis of malaria, (for details, see Recommended regimens for prophylaxis against malaria p. 561).

Proguanil hydrochloride used alone is not suitable for the treatment of malaria; however, Malarone® (a combination of atovaquone with proguanil hydrochloride p. 568) is licensed for the treatment of acute uncomplicated falciparum malaria. Malarone® is also used for the prophylaxis of falciparum malaria in areas of widespread mefloquine or chloroquine resistance. Malarone® is also used as an alternative to mefloquine or doxycycline p. 521. Malarone® is particularly suitable for short trips to highly chloroquine-resistant areas because it needs to be taken only for 7 days after leaving an endemic area.

Pyrimethamine

Pyrimethamine p. 572 should not be used alone, but is used with sulfadoxine.

Pyrimethamine with sulfadoxine p. 572 is not recommended for the prophylaxis of malaria, but can be used in the treatment of falciparum malaria with (or following) quinine.

Quinine

Quinine is not suitable for the prophylaxis of malaria.

Quinine is used for the treatment of falciparum malaria or if the infective species is not known or if the infection is mixed (for details see Malaria, treatment p. 566).

Tetracyclines

Doxycycline is used in adults and children over 12 years for the prophylaxis of malaria in areas of widespread mefloquine or chloroquine resistance. Doxycycline is also used as an alternative to mefloquine or Malarone® (for details, see Recommended regimens for prophylaxis against malaria p. 561).

Malaria, prophylaxis

Prophylaxis

The recommendations on prophylaxis reflect guidelines agreed by UK malaria specialists; the advice is aimed at residents of the UK who travel to endemic areas. The choice of drug for a particular individual should take into account:

- risk of exposure to malaria
- extent of drug resistance
- efficacy of the recommended drugs
- side-effects of the drugs
- patient-related factors (e.g. age, pregnancy, renal or hepatic impairment, compliance with prophylactic regimen)
# Key to recommended regimens for prophylaxis against malaria

<table>
<thead>
<tr>
<th>Codes for regimens</th>
<th>Details of regimens for prophylaxis against malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine only</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine with proguanil</td>
</tr>
<tr>
<td>4</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline or mefloquine</td>
</tr>
<tr>
<td>5</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline</td>
</tr>
</tbody>
</table>

## Specific recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>Risk below 2000 m from May–November</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low risk below 2000 m from December–April</td>
<td>1</td>
</tr>
<tr>
<td>Algeria</td>
<td>Very low risk in Illizi department only</td>
<td>1</td>
</tr>
<tr>
<td>Andaman and Nicobar Islands (India)</td>
<td>Risk present</td>
<td>1</td>
</tr>
<tr>
<td>Angola</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Argentina</td>
<td>Low risk in low altitude areas of Salta provinces bordering Bolivia and in Chaco, Corrientes, and Misiones provinces close to border with Paraguay and Brazil</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in Iguacu Falls and areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Armenia</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>Low to no risk</td>
<td>1</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>High risk in Chittagong Hill Tract districts (but not Chittagong city)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in Chittagong city and other areas, except Chittagong Hill Tract districts</td>
<td>1</td>
</tr>
<tr>
<td>Belize</td>
<td>Low risk in rural areas</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in Belize district (including Belize city and islands)</td>
<td>1</td>
</tr>
<tr>
<td>Benin</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Risk in southern belt districts, along border with India: Chukha, Geyleg-phug, Samchi, Samdrup Jonkhar, and Shemgang</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Bolivia</td>
<td>High risk in Amazon basin</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in rural areas below 2500 m (other than above)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk above 2500 m</td>
<td>1</td>
</tr>
<tr>
<td>Botswana</td>
<td>High risk from November–June in northern half, including Okavango Delta area</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk from July–October in northern half; low to no risk all year in southern half</td>
<td>1</td>
</tr>
<tr>
<td>Brazil</td>
<td>Risk in Amazon basin, including city of Manaus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above, and no risk in Iguacu Falls</td>
<td>1</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>Very low risk</td>
<td>1</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Burundi</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Cambodia</td>
<td>High risk, with widespread chloroquine and mefloquine resistance, in western provinces bordering Thailand</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>High risk in areas other than those above and below</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Angkor Wat and Lake Tonle Sap, including Siem Reap; no risk in Phnom Penh</td>
<td>1</td>
</tr>
<tr>
<td>Cameroon</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Cape Verde</td>
<td>Very low risk on island of Santiago (Sao Tiago) and Boa Vista</td>
<td>1</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Chad</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>China</td>
<td>High risk in Yunnan and Hainan provinces</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above and below</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Hong Kong</td>
<td>1</td>
</tr>
<tr>
<td>Colombia</td>
<td>High risk in rural areas below 1600 m</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low to no risk above 1600 m and in Cartagena</td>
<td>1</td>
</tr>
<tr>
<td>Country</td>
<td>Comments on risk of malaria and regional or seasonal variation</td>
<td>Codes for regimens</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Comoros</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Congo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Risk in Limon province (but not city of Limon)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Cote d’Ivoire (Ivory Coast)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Djibouti</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>Risk in all areas except cities of Santiago and Santo Domingo</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cities of Santiago and Santo Domingo</td>
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<tr>
<td>East Timor (Timor-Leste)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Risk in areas below 1500 m including coastal provinces and Amazon basin (no risk in Galapagos islands or city of Guayaquil)</td>
<td>4</td>
</tr>
<tr>
<td>Egypt</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>El Salvador</td>
<td>Low risk in rural areas of Santa Ana, Ahuachapán, and La Unión provinces in western part of country; low to no risk in other areas</td>
<td>1</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>High risk</td>
<td>4</td>
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<tr>
<td>Eritrea</td>
<td>High risk below 2200 m</td>
<td>4</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>High risk below 2000 m</td>
<td>4</td>
</tr>
<tr>
<td>French Guiana</td>
<td>High risk (particularly in border areas) except city of Cayenne or Devil’s Island (Ile du Diable)</td>
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<tr>
<td></td>
<td>No risk in city of Cayenne or Devil’s Island (Ile du Diable)</td>
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</tr>
<tr>
<td>Gabon</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Gambia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Georgia</td>
<td>Very low risk in rural south east from June–October</td>
<td>1</td>
</tr>
<tr>
<td>Ghana</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guatemala</td>
<td>Low risk below 1500 m</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in Guatemala City, Antigua, or Lake Atitlan</td>
<td>-</td>
</tr>
<tr>
<td>Guinea</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guyana</td>
<td>High risk in all interior regions</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Georgetown and coastal region</td>
<td>1</td>
</tr>
<tr>
<td>Haiti</td>
<td>Risk present</td>
<td>2</td>
</tr>
<tr>
<td>Honduras</td>
<td>Risk below 1000 m and in Roatán and other Bay Islands (no risk in San Pedro Sula or Tegucigalpa)</td>
<td>2</td>
</tr>
<tr>
<td>India</td>
<td>High risk in states of Assam and Orissa, districts of East Godavari, Srikkakulam, Viskakhapatnam, and Vizianagarzam in the state of Andhra Pradesh, and districts of Balaghat, Dindori, Mandla, and Seoni in the state of Madhya Pradesh</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in areas other than those above or below (including Goa, Andaman and Nicobar islands)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Lakshadweep islands</td>
<td>-</td>
</tr>
<tr>
<td>Indonesia</td>
<td>High risk in Lombok and Irian Jaya (Papua)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in areas other than those above or below</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Bali, and cities on islands of Java and Sumatra</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Jakarta</td>
<td>-</td>
</tr>
<tr>
<td>Indonesia (Borneo)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Iran</td>
<td>Risk from March–November in rural south eastern provinces and in north, along Azerbaijan border in Ardabil, and near Turkmenistan border in North Khorasan</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Iraq</td>
<td>Very low risk from May–November in rural northern area below 1500 m</td>
<td>1</td>
</tr>
<tr>
<td>Kenya</td>
<td>High risk below 2500 m (except city of Nairobi)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in the highlands above 2500 m and in city of Nairobi</td>
<td>1</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>Very low risk from June–October in southwest areas bordering Tajikistan and Uzbekistan</td>
<td>1</td>
</tr>
</tbody>
</table>
### Key to recommended regimens for prophylaxis against malaria

<table>
<thead>
<tr>
<th>Codes for regimens</th>
<th>Details of regimens for prophylaxis against malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine only</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine with proguanil</td>
</tr>
<tr>
<td>4</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline or mefloquine</td>
</tr>
<tr>
<td>5</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline</td>
</tr>
</tbody>
</table>

### Specific recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laos</td>
<td>High risk along the border with Myanmar in the provinces of Bokeo and Louang Namtha, and along the border with Thailand in the province of Champasak and Saravan High risk in areas other than those above or below Low to no risk in city of Vientiane</td>
<td>5</td>
</tr>
<tr>
<td>Liberia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Libya</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Madagascar</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Malawi</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Risk in inland forested areas of peninsular Malaysia Very low risk in rest of peninsular Malaysia, including Cameron Highlands and city of Kuala Lumpur</td>
<td>4</td>
</tr>
<tr>
<td>Malaysia (Borneo)</td>
<td>High risk in inland areas of eastern Sabah and in inland, forested areas of Sarawak Very low risk in areas other than those above, including coastal areas of Sabah and Sarawak</td>
<td>1</td>
</tr>
<tr>
<td>Mali</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Mauritania</td>
<td>High risk all year in southern provinces, and from July–October in the northern provinces Low risk from November–June in the northern provinces</td>
<td>4</td>
</tr>
<tr>
<td>Mauritius</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Mayotte</td>
<td>Risk present</td>
<td>4</td>
</tr>
<tr>
<td>Mexico</td>
<td>Low risk in Oaxaca and Chiapas Very low risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Mozambique</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Myanmar</td>
<td>High risk (but not in cities of Mandalay and Yangon) No risk in cities of Mandalay and Yangon</td>
<td>5</td>
</tr>
<tr>
<td>Namibia</td>
<td>High risk all year in regions of Caprivi Strip, Kavango, and Kunene river, and from November–June in northern third of country Low to no risk in areas other than those above; low risk from July–October in northern third of country</td>
<td>4</td>
</tr>
<tr>
<td>Nepal</td>
<td>Risk below 1500 m, particularly in Terai district No risk in city of Kathmandu and on typical Himalayan treks</td>
<td>3</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>Low risk (except Managua) Very low risk in Managua</td>
<td>2</td>
</tr>
<tr>
<td>Niger</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>North Korea</td>
<td>Very low risk in some southern areas</td>
<td>1</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Risk below 2000 m Low to no risk above 2000 m</td>
<td>3</td>
</tr>
<tr>
<td>Panama</td>
<td>Risk east of Canal Zone Low risk west of Canal Zone No risk in Panama City or Canal Zone itself</td>
<td>3</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>High risk below 1800 m Low to no risk above 1800 m</td>
<td>4</td>
</tr>
<tr>
<td>Country</td>
<td>Comments on risk of malaria and regional or seasonal variation</td>
<td>Codes for regimens</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Paraguay</td>
<td>Low risk in departments of Alto Paraná and Caaguazú</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Peru</td>
<td>High risk in Amazon basin along border with Brazil, particularly in Loreto province</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in rural areas below 2000 m (other than those above and below) including in Amazon basin along border with Bolivia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Lima and coastal region south of Chiclayo</td>
<td>1</td>
</tr>
<tr>
<td>Philippines</td>
<td>Risk in rural areas below 600 m and on islands of Luzon, Mindanao, Mindoro, and Palawan</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No risk in cities or on islands of Boracay, Bohol, Catanduanes, Cebu, or Leyte</td>
<td>1</td>
</tr>
<tr>
<td>Rwanda</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>São Tomé and Principe</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Risk in south-western provinces along border with Yemen, including below 2000 m in Asir province</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No risk in cities of Jeddah, Makkah (Mecca), Medina, Riyadh, or Ta’if, or above 2000 m in Asir province</td>
<td>1</td>
</tr>
<tr>
<td>Senegal</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Somalia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>South Africa</td>
<td>Moderate risk from September–May in low altitude areas of Mpumalanga and Limpopo, which border Mozambique and Zimbabwe (including Kruger National Park)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk in north-east KwaZulu-Natal</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Low risk in areas bordering those above</td>
<td>1</td>
</tr>
<tr>
<td>South Korea</td>
<td>Very low risk in northern areas, in Gangwon-do and Gyeonggi-do provinces, and Incheon city (towards Demilitarized Zone)</td>
<td>1</td>
</tr>
<tr>
<td>South Sudan</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Low risk north of Vavuniya</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above and below</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Colombo or Kandy</td>
<td>-</td>
</tr>
<tr>
<td>Sudan</td>
<td>High risk in central and southern areas; risk also present in rest of country (except Khartoum)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Khartoum</td>
<td>1</td>
</tr>
<tr>
<td>Suriname</td>
<td>High risk (except coastal districts or city of Paramaribo)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in coastal districts; no risk in city of Paramaribo</td>
<td>1</td>
</tr>
<tr>
<td>Swaziland</td>
<td>High risk in northern and eastern regions bordering Mozambique and South Africa, including all of Lubombo district and Big Bend, Mhlume, Simunye, and Tshaneni regions</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in the areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Syria</td>
<td>Very low risk in small, remote foci of El Hasakah</td>
<td>1</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>Risk below 2000 m from June–October</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low risk below 2000 m from November–May</td>
<td>1</td>
</tr>
<tr>
<td>Tanzania</td>
<td>High risk below 1800 m; risk also in Zanzibar</td>
<td>4</td>
</tr>
<tr>
<td>Thailand</td>
<td>High risk, with chloroquine and mefloquine resistance, in rural forested borders with Cambodia, Laos, and Myanmar</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above, including Kanchanaburi (Kwai Bridge); no risk in cities of Bangkok, Chiang Mai, Chiang Rai, Koh Phangan, Koh Samui, and Pattaya</td>
<td>1</td>
</tr>
<tr>
<td>Togo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Turkey</td>
<td>Low risk from May–October along the border plain with Syria, around Adana and east of Adana</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Very low risk from November–April along the border plain with Syria, around Adana and east of Adana; very low risk all year in rest of country</td>
<td>1</td>
</tr>
<tr>
<td>Uganda</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>Very low risk in extreme south-east</td>
<td>1</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>Risk present</td>
<td>4</td>
</tr>
</tbody>
</table>
Protection against bites
Prophylaxis is not absolute, and breakthrough infection can occur with any of the drugs recommended. Personal protection against being bitten is very important. Mosquito nets impregnated with permethrin provide the most effective barrier protection against insects; mats and vapourised insecticides are also useful. Diethyltoluamide (DEET) 20–50% in lotions, sprays, or roll-on formulations is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during pregnancy and breast-feeding. The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. When sunscreen is also required, DEET should be applied after the sunscreen. DEET reduces the SPF of sunscreen, so a sunscreen of SPF 30–50 should be applied. Long sleeves and trousers worn after dusk also provide protection against bites.

Length of prophylaxis
In order to determine tolerance and to establish habit, prophylaxis should generally be started one week (2–3 weeks in the case of mefloquine p. 570) before travel into an endemic area; Malarone® or doxycycline p. 521 prophylaxis should be started 1–2 days before travel. Prophylaxis should be continued for 4 weeks after leaving (except for Malarone® prophylaxis which should be stopped 1 week after leaving). For extensive journeys across different regions, the traveller must be protected in all areas of risk.

In those requiring long-term prophylaxis, chloroquine p. 569 and proguanil hydrochloride p. 571 may be used for periods of over 5 years. Mefloquine is licensed for up to 1 year (although, if it is tolerated in the short term, there is no evidence of harm when it is used for up to 3 years). Doxycycline can be used for up to 2 years. Malarone® can be used for up to 1 year. Prophylaxis with mefloquine, doxycycline, or Malarone® may be considered for longer durations if it is justified by the risk of exposure to malaria.

Specialist advice should be sought for long-term prophylaxis.

Return from malarial region
It is important to be aware that any illness that occurs within 1 year and especially within 3 months of return might be malaria even if all recommended precautions against malaria were taken. Travellers should be warned of this and told that if they develop any illness, particularly within 3 months of their return they should go immediately to a doctor and specifically mention their exposure to malaria.

Epilepsy
Both chloroquine and mefloquine are unsuitable for malaria prophylaxis in individuals with a history of epilepsy. In areas without chloroquine resistance, proguanil alone is recommended; in areas with chloroquine resistance, doxycycline or Malarone® may be considered.

Asplenia
Asplenic individuals (or those with severe splenic dysfunction) are at particular risk of severe malaria. If travel to malarious areas is unavoidable, rigorous precautions are required against contracting the disease.

Renal impairment
Avoidance (or dosage reduction) of proguanil hydrochloride is recommended since it is excreted by the kidneys. Malarone® should not be used for prophylaxis in patients with estimated glomerular filtration rate less than 30 mL/minute/1.73m². Chloroquine is only partially excreted by the kidneys and reduction of the dose for prophylaxis is not required except in severe impairment. Mefloquine is considered to be appropriate to use in renal impairment and does not require dosage reduction. Doxycycline is also considered to be appropriate.
Pregnancy
Travel to malarious areas should be avoided during pregnancy; if travel is unavoidable, effective prophylaxis must be used. Chloroquine and proguanil hydrochloride can be given in the usual doses during pregnancy, but these drugs are not appropriate for most areas because their effectiveness has declined, particularly in Sub-Saharan Africa; in the case of proguanil hydrochloride, folic acid p. 898 (dosed as a pregnancy ‘at high-risk’ of neural tube defects) should be given for at least the first trimester. The centres listed (see Malaria, treatment below) should be consulted for advice on prophylaxis in chloroquine-resistant areas. Although the manufacturer advises that mefloquine should not be used during pregnancy, particularly in the first trimester, unless the potential benefit outweighs the risk, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas. Doxycycline is contra-indicated during pregnancy; however, it can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks’ gestation [unlicensed]. Malarone® should be avoided during pregnancy, however, it can be considered during the second and third trimesters if there is no suitable alternative.

Breast-feeding
Prophylaxis is required in breast-fed infants; although antimalarials are present in milk, the amounts are too variable to give reliable protection.

Anticoagulants
Travellers taking warfarin sodium p. 131 should begin chemoprophylaxis 2–3 weeks before departure. The INR should be stable before departure. It should be measured before starting chemoprophylaxis, 7 days after starting, and after completing the course. For prolonged stays, the INR should be checked at regular intervals.

Standby treatment
Travellers visiting remote, malarious areas for prolonged periods should carry standby treatment if they are likely to be more than 24 hours away from medical care. Self-medication should be avoided if medical help is accessible.

In order to avoid excessive self-medication, the traveller should be provided with written instructions that urgent medical attention should be sought if fever (38°C or more) develops 7 days (or more) after arriving in a malarious area and that self-treatment is indicated if medical help is not available within 24 hours of fever onset.

In view of the continuing emergence of resistant strains and of the different regimens required for different areas, expert advice should be sought on the best treatment course for an individual traveller. A drug used for chemoprophylaxis should not be considered for standby treatment for the same traveller.

Specific recommendations
Where a journey requires two regimens, the regimen for the higher risk area should be used for the whole journey. Those travelling to remote or little-visited areas may require expert advice. See Recommended regimens for prophylaxis against malaria.

Important
Settled immigrants (or long-term visitors) to the UK may be unaware that any immunity they may have acquired while living in malarious areas is lost rapidly after migration to the UK, or that any non-malarious areas where they lived previously may now be malarious.

Malaria, treatment

Advice for healthcare professionals
A number of specialist centres are able to provide advice on specific problems.

PHE (Public Health England) Malaria Reference Laboratory (020) 7637 0248 (fax) (prophylaxis only) www.malaria-reference.co.uk

National Travel Health Network and Centre 0845 602 6712
Travel Medicine Team, Health Protection Scotland (registered users of Travax only) www.travax.nhs.uk
(for registered users of the NHS Travax website only) (0141) 300 1100 (weekdays 2–4 p.m. only)
Birmingham (0121) 424 2358
Liverpool (0151) 705 3100
London 0845 155 5000 (treatment)
Oxford (01865) 225 430

Advice for travellers
Hospital for Tropical Diseases Travel Healthline (020) 7950 7799 www.fitfortravel.nhs.uk
WHO advice on international travel and health www.who.int/ith
National Travel Health Network and Centre (NaTHNaC) www.nathnac.net

Treatment of malaria
Recommendations on the treatment of malaria reflect guidelines agreed by UK malaria specialists.

If the infective species is not known, or if the infection is mixed, initial treatment should be as for falciparum malaria with quinine p. 573, Malarone® (atovaquone with proguanil hydrochloride p. 568), or Riamet® (artemether with lumefantrine p. 587). Falciparum malaria can progress rapidly in unprotected individuals and antimalarial treatment should be considered in those with features of severe malaria and possible exposure, even if the initial blood tests for the organism are negative.

Falciparum malaria (treatment)
Falciparum malaria (malignant malaria) is caused by Plasmodium falciparum. In most parts of the world P. falciparum is now resistant to chloroquine p. 569 which should not therefore be given for treatment.

Quinine, Malarone®, (atovaquone with proguanil hydrochloride), or Riamet® (artemether with lumefantrine) can be given by mouth if the patient can swallow and retain tablets and there are no serious manifestations (e.g. impaired consciousness); quinine should be given by intravenous infusion if the patient is seriously ill or unable to take tablets. Mefloquine p. 570 is now rarely used for treatment because of concerns about resistance.

Oral quinine is given by mouth for 5–7 days, together with or followed by either doxycycline p. 521 for 7 days or clindamycin p. 493 for 7 days [unlicensed].

If the parasite is likely to be sensitive, pyrimethamine with sulfadoxine p. 572 as a single dose [unlicensed] may be given (instead of either clindamycin or doxycycline) together with, or after, a course of quinine.

Alternatively, Malarone®, or Riamet® may be given instead of quinine. It is not necessary to give clindamycin, doxycycline, or pyrimethamine with sulfadoxine after Malarone® or Riamet® treatment.

If the patient is seriously ill or unable to take tablets, or if more than 2% of red blood cell are parasitized, quinine should be given by intravenous infusion [unlicensed] (until patient can swallow tablets to complete the 7-day course together with or followed by either doxycycline or clindamycin).
Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for 'named-patient' use.

**Pregnancy**

Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The adult treatment doses or oral and intravenous quinine (including the loading dose) can safely be given to pregnant women. Clinamycin should be given after quinine [unlicensed indication]. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development); pyrimethamine with sulfafoxine, Malarone®, and Riamet® are also best avoided until more information is available. Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for 'named patient' use.

**Non-falciparum malaria (treatment)**

Non-falciparum malaria is usually caused by *Plasmodium vivax* and less commonly by *P. ovale* and *P. malariae*. *P. knowlesi* is also present in the Asia-Pacific region.

Chloroquine is the drug of choice for the treatment of non-falciparum malaria (but chloroquine-resistant *P. vivax* has been reported in the Indonesian archipelago, the Malay Peninsula, including Myanmar, and eastward to Southern Vietnam).

For the treatment of chloroquine-resistant non-falciparum malaria, Malarone® [unlicensed indication], quinine, or Riamet® [unlicensed indication] can be used; as with chloroquine, primaquine p. 571 should be given for radical cure.

Chloroquine alone is adequate for *P. malariae* and *P. knowlesi* infections but in the case of *P. vivax* and *P. ovale*, a radical cure (to destroy parasites in the liver and thus prevent relapses) is required. This is achieved with primaquine [unlicensed] given after chloroquine, with the dose dependent on the infecting organism. For a radical cure, primaquine [unlicensed] is then given for 14 days, with the dose also dependent on the infecting organism.

**Parenteral**

If the patient is unable to take oral therapy, quinine can be given by intravenous infusion [unlicensed], changed to oral chloroquine as soon as the patient’s condition permits.

**Pregnancy**

The adult treatment doses of chloroquine can be given for non-falciparum malaria. In the case of *P. vivax* or *P. ovale*, however, the radical cure with primaquine should be postponed until the pregnancy is over; instead chloroquine should be continued, given weekly during the pregnancy.

**Antiprotozoals > Antimalarials**

Artemether with lumefantrine

- **INDICATIONS AND DOSE**
  - **Treatment of acute uncomplicated falciparum malaria**
  - **Treatment of chloroquine-resistant non-falciparum malaria**
    - **BY MOUTH**
      - Adult (body-weight 35 kg and above): Initially 4 tablets, followed by 4 tablets for 5 doses each given at 8, 24, 36, 48 and 60 hours (total 24 tablets over 60 hours)
  - **UNLICENSED USE** Use in treatment of non-falciparum malaria is an unlicensed indication.
  - **CONTRA-INDICATIONS** Family history of congenital QT interval prolongation - family history of sudden death - history of arrhythmias - history of clinically relevant bradycardia - history of congestive heart failure accompanied by reduced left ventricular ejection fraction

**CAUTIONS** Avoid in acute porphyrias p. 930 - electrolyte disturbances

**INTERACTIONS** → Appendix 1 (artemether with lumefantrine). Caution if concomitant use with other drugs known to cause QT-interval prolongation.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - anorexia - arthralgia - asthenia - cough - diarrhoea - dizziness - headache - myalgia - nausea - palpitation - paraesthesia - prolonged QT interval - pruritus - rash - sleep disturbances - vomiting
- **Uncommon** Ataxia - clonus - hypoaesthesia

**PREGNANCY** Toxicity in animal studies with artemether. Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid breast-feeding for at least 1 week after last dose. Present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in severe impairment.

**RENAL IMPAIRMENT**

Manufacturer advises caution in severe impairment. In severe renal impairment monitor ECG and plasma potassium concentration.

**MONITORING REQUIREMENTS**

Monitor patients unable to take food (greater risk of recrudescence).

**DIRECTIONS FOR ADMINISTRATION**

Tablets may be crushed just before administration.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks.

Dizziness may affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 21
  - **Riamet** (Novartis Pharmaceuticals UK Ltd)
    - Artemether 20 mg, Lumefantrine 120 mg Riamet tablets | 24 tablet | £22.50

Artemether with piperaquine phosphate

(Piperaquine tetraphosphate with dihydroartemisinin)

- **INDICATIONS AND DOSE**
  - **Treatment of uncomplicated falciparum malaria**
    - **BY MOUTH**
      - Child 6 months-17 years (body-weight 7-12 kg): 0.5 tablet once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
      - Child 6 months-17 years (body-weight 12-23 kg): 1 tablet once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
      - Child 6 months-17 years (body-weight 24-35 kg): 2 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
      - Child 6 months-17 years (body-weight 36-74 kg): 3 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
      - Child 6 months-17 years (body-weight 75-99 kg): 4 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
      - Child 6 months-17 years (body-weight ≥100 kg): 5 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
**Protozoal infection**

- **Adult (body-weight 36-74 kg):** 3 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
- **Adult (body-weight 75-99 kg):** 4 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

**CONTRA-INDICATIONS** Acute myocardial infarction - bradycardia - congenital long QT syndrome - electrolyte disturbances - family history of sudden death - heart failure with reduced left ventricular ejection fraction - history of symptomatic arrhythmias - left ventricular hypertrophy - risk factors for QT interval prolongation - severe hypertension

**INTERACTIONS** → Appendix 1 (артенимол with piperaquine).

Piperaquine has a long half-life; there is a potential for drug interactions to occur for up to 3 months after treatment has been stopped. Concomitant use with other drugs known to prolong the QT interval contra-indicated.

**SIDE-EFFECTS**


**PREGNANCY** Teratogenic in animal studies — manufacturer advises use only if no other antimalarials cannot be used.

**BREAST FEEDING** Manufacturer advises avoid — present in milk in animal studies.

**HEPATIC IMPAIRMENT** No information available in moderate to severe impairment. Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe hepatic impairment.

**RENAL IMPAIRMENT** No information available in moderate to severe impairment. Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe renal impairment.

**MONITORING REQUIREMENTS**

- Consider obtaining ECG in all patients before third dose and 4–6 hours after third dose. If QTc interval more than 500 milliseconds, discontinue treatment and monitor ECG for a further 24–48 hours.
- Obtain ECG as soon as possible after starting treatment then continue monitoring in those taking medicines that increase plasma-piperaquine concentration, in females children who are vomiting, or in the elderly.

**DIRECTIONS FOR ADMINISTRATION** Tablets to be taken at least 3 hours before and at least 3 hours after food. Tablets may be crushed and mixed with water immediately before administration.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer tablets containing piperaquine phosphate with artenimol.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Eurartesim** (Sigma-Tau Pharma Ltd)
  - Artenimol 40 mg, Piperaquine phosphate 320 mg
  - Eurartesim 320mg/40mg tablets | 12 tablet **£40.00**

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**Atovaquone with proguanil hydrochloride**

**INDICATIONS AND DOSE**

**MALARONE®**

Prophylaxis of falciparum malaria, particularly where resistance to other antimalarial drugs suspected

- **BY MOUTH**
  - Adult (body-weight 41 kg and above): 1 tablet daily, to be started 1–2 days before entering endemic area and continued for 1 week after leaving

Treatment of acute uncomplicated falciparum malaria | Treatment of non-falciparum malaria

- **BY MOUTH**
  - Adult: 4 tablets once daily for 3 days

**UNLICENSED USE** Not licensed for treatment of non-falciparum malaria.

**CAUTIONS** Diarrhoea or vomiting (reduced absorption of atovaquone) - efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure)

**INTERACTIONS** → Appendix 1 (proguanil, atovaquone).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - abnormal dreams - anorexia - cough - depression - diarrhoea - dizziness - fever - headache - insomnia - nausea - pruritus - rash - vomiting

- **Uncommon** Anxiety - blood disorders - hair loss - hypotension - palpitation - stomatitis

- **Frequency not known** Cholestasis - hallucinations - hepatitis - mouth ulcers - photosensitivity - seizures - Stevens-Johnson syndrome - tachycardia - vasculitis

**PREGNANCY** Manufacturer advises avoid unless essential.

**BREAST FEEDING** Use only if no suitable alternative available.

**RENAL IMPAIRMENT** Avoid for malaria prophylaxis (and if possible for malaria treatment) if eGFR less than 30 mL/minute/1.73m².

**PATIENT AND CARER ADVICE** Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

**NATIONAL FUNDING/ACCESS DECISIONS**

NHS restrictions Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
  - **Malaron** (GlaxoSmithKline UK Ltd)
    - Proguanil hydrochloride 25 mg, Atovaquone 62.5 mg
    - Malaron Paediatric tablets | 12 tablet **£6.26**
    - Proguanil hydrochloride 100 mg, Atovaquone 250 mg
    - Malaron tablets | 12 tablet **£25.21**

- ****
In adults

Doses expressed as chloroquine base. Chloroquine base

Adult:

BY MOUTH

Adult:

Prophylaxis of malaria

INITIALLY BY MOUTH USING SYRUP

Child 14-5 weeks (body-weight up to 4.5 kg): 25 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 6 weeks-5 months (body-weight 4.5-7 kg): 50 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 6-11 months (body-weight 8-10 kg): 75 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 1-2 years (body-weight 11-14 kg): 100 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 3-4 years (body-weight 15-16.4 kg): 125 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 5-7 years (body-weight 16.5-24 kg): 150 mg once weekly, alternatively (by mouth using tablets) 155 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 8-13 years (body-weight 25-44 kg): 225 mg once weekly, alternatively (by mouth using tablets) 232.5 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

INITIALLY BY MOUTH USING TABLETS

Child 14-17 years (body-weight 45 kg and above): 310 mg once weekly, alternatively (by mouth using syrup) 300 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Adult (body-weight 45 kg and above): 310 mg once weekly, alternatively (by mouth using syrup) 300 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Treatment of non-falciparum malaria

BY MOUTH

Child: Initially 10 mg/kg (max. per dose 620 mg), then 5 mg/kg after 6–8 hours (max. per dose 310 mg), then 5 mg/kg daily (max. per dose 310 mg) for 2 days

Adult: Initially 620 mg, then 310 mg after 6–8 hours, then 310 mg daily for 2 days, approximate total cumulative dose of 25 mg of base

P. vivax or P. ovale infection during pregnancy while radical cure is postponed

BY MOUTH

Adult: 310 mg once weekly

DOSE EQUIVALENCE AND CONVERSION

Doses expressed as chloroquine base. Chloroquine base 150 mg = chloroquine sulfate 200 mg = chloroquine phosphate 250 mg (approx).

DOSES AT EXTREMES OF BODY-WEIGHT

In adults In active rheumatoid arthritis and systemic and discoid lupus erythematosus, to avoid excessive dosage in obese patients, the daily maximum dose should be calculated on the basis of ideal body weight.
Infection

EXCEPTIONS TO LEGAL CATEGORY

l HEPATIC IMPAIRMENT Use with caution in moderate to severe impairment.

l RENAL IMPAIRMENT Only partially excreted by the kidneys and reduction of the dose is not required for prophylaxis of malaria except in severe impairment. For rheumatoid arthritis and lupus erythematosus, reduce dose. Manufacturers advise caution.

l MONITORING REQUIREMENTS
  ▶ in adults Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory.
  ▶ in children Ophthalmic examination with long-term therapy.

l PATIENT AND CARER ADVICE Warn travellers going to malarious areas about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

l NATIONAL FUNDING/ACCESS DECISIONS

NHS restrictions Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials are prescribed.

l EXCEPTIONS TO LEGAL CATEGORY Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria.

l MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Table
CAUTIONARY AND ADVISORY LABELS 5

Avloclor (Alliance Pharmaceuticals Ltd)
Chloroquine phosphate 250 mg Avloclor 250mg tablets | 20 tablet [PO] £7.95 DT price = £7.95

Oral solution
CAUTIONARY AND ADVISORY LABELS 5

Malarivon (Wallace Manufacturing Chemists Ltd)
Chloroquine phosphate 16 mg per 1 ml Malarivon 80mg/5ml syrup | 75 ml [PO] £30.00

Chloroquine with proguanil

The properties listed below are those particular to the combination only. For the properties of the components please consider, chloroquine p. 569, proguanil hydrochloride p. 571.

l INDICATIONS AND DOSE

Prophylaxis of malaria
  ▶ BY MOUTH
  ▶ Adult: (consult product literature)

l EXCEPTIONS TO LEGAL CATEGORY Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria.

l MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablets

Paludrine/Avloclor (Alliance Pharmaceuticals Ltd)
Paludrine/Avloclor tablets anti-malarial travel pack | 112 tablet [P] £13.50

Mefloquine

l INDICATIONS AND DOSE

Treatment of malaria
  ▶ BY MOUTH
  ▶ Adult: (consult product literature)

Prophylaxis of malaria
  ▶ BY MOUTH
  ▶ Child (body-weight 5–15 kg): 62.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving
  ▶ Child (body-weight 16–24 kg): 125 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving
  ▶ Child (body-weight 25–44 kg): 187.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving
  ▶ Child (body-weight 45 kg and above): 250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving
  ▶ Adult (body-weight 45 kg and above): 250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving

l UNLICENSED USE Mefloquine doses in BNF Publications may differ from those in product literature.
  ▶ in children Not licensed for use in children under 5 kg body-weight and under 3 months.

l CONTRA-INDICATIONS Avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions • avoid for standby treatment if history of convulsions • history of blackwater fever

l CAUTIONS Cardiac conduction disorders • epilepsy (avoid for prophylaxis) • not recommended in infants under 3 months (5 kg) • traumatic brain injury

l CAUTIONS, FURTHER INFORMATION

Neuropsychiatric reactions Mefloquine is associated with potentially serious neuropsychiatric reactions. Abnormal dreams, insomnia, anxiety, and depression occur commonly. Psychosis, suicidal ideation, and suicide have also been reported. Psychiatric symptoms such as nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event. Adverse reactions may occur and persist up to several months after discontinuation because mefloquine has a long half-life. For a prescribing checklist, and further information on side-effects, particularly neuropsychiatric side-effects, which may be associated with the use of mefloquine for malaria prophylaxis, see the Guide for Healthcare Professionals provided by the manufacturer.

l INTERACTIONS → Appendix 1 (mefloquine).

l SIDE-EFFECTS

▶ Common or very common Abdominal pain • diarrhoea • dizziness • headache • nausea • neuropsychiatric reactions • pruritus • visual disturbances • vomiting

▶ Very rare Optic neuropathy

▶ Frequency not known Alopecia • amnesia • anorexia • arrhythmias • arthralgia • ataxia • blood disorders • bradycardia • cataract • chest pain • confusion • drowsiness • dyspepsia • dyspnoea • encephalopathy • fever • flushing • hepatic failure • hyperhidrosis • hypertension • hypotension • leucocytosis • leucopenia • malaise • motor neuropathies • muscle weakness • myalgia • oedema • palpitation • panic attacks • pneumonitis • rash • seizures • sensory neuropathies • speech disturbances • Stevens–Johnson syndrome • syncope • tachycardia • thrombocytopenia • tremor • vestibular disorders

l ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with hypersensitivity to quinine.
Proguanil hydrochloride

**INDICATIONS AND DOSE**

**Prophylaxis of malaria**

- **BY MOUTH**
  - Adult: 30 mg daily for 14 days
  - Adult: 15 mg daily for 14 days

**Adjunct in the treatment of non-falciparum malaria caused by *P.falciparum* infection**

- **BY MOUTH**
  - Adult: 45 mg once weekly for 8 weeks

**Treatment of mild to moderate pneumocystis infection (in combination with clindamycin)**

- **BY MOUTH**
  - Adult: 30 mg daily, this combination is associated with considerable toxicity

**UNLICENSED USE**

Proguanil doses in BNF Publications may differ from those in product literature.

**INTERACTIONS**

- **Common or very common** Constipation; diarrhoea; mild gastrointestinal intolerance
  - **Very rare** Cholestasis; hair loss; skin reactions; vasculitis
  - **Frequency not known** Mouth ulcers; stomatitis

**PREGNANCY**

Benefit of prophylaxis in malaria outweighs risk. Adequate folate supplements should be given to mother.

**BREAST FEEDING**

Amount in milk probably too small to be harmful when used for malaria prophylaxis.
Protozoal infection

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Pyrimethamine

**INDICATIONS AND DOSE**

Toxoplasmosis in pregnancy (in combination with sulfadiazine and folic acid)

- **BY MOUTH**
  - Adult: 50 mg once daily until delivery

Malaria

- **BY MOUTH**
  - Adult: No dose stated because not recommended alone

**CAUTIONS**

- Avoid large loading doses - predisposition to folate deficiency

**INTERACTIONS**

- Appendix 1 (pyrimethamine).

**SIDE-EFFECTS**

- Anaemia (with high doses) - blood disorders (with high doses) - diarrohea - dizziness - headache - leucopenia (with high doses) - nausea - rash - thrombocytopenia (with high doses) - vomiting

- Abnormal skin pigmentation - fever

- Buccal ulceration - colic - convulsions

**PREGNANCY**

- Theoretical teratogenic risk in first trimester (folate antagonist).

**BREAST FEEDING**

- Significant amount in milk - avoid administration of other folate antagonists to infant. Avoid breast-feeding during toxoplasmosis treatment.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution.

**RENAL IMPAIRMENT**

- Manufacturer advises caution.

**MONITORING REQUIREMENTS**

- Blood counts required with prolonged treatment.

**LESS SUITABLE FOR PRESCRIBING**

- Pyrimethamine should not be used alone for malaria, but is used with sulfadoxine.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- Daraprim (GlaxoSmithKline UK Ltd)
- Pyrimethamine 25 mg Daraprim 25mg tablets 30 tablet £13.00

**Pyrimethamine with sulfadoxine**

**INDICATIONS AND DOSE**

Adjuvant to quinine in treatment of Plasmodium falciparum malaria

- **BY MOUTH**
  - Child 1 month–4 years (body-weight 5 kg and above): 12.5/250 mg for 1 dose
  - Child 5–6 years: 25/500 mg for 1 dose
  - Child 7–9 years: 37.5/750 mg for 1 dose
  - Child 10–13 years: 50/1000 mg for 1 dose
  - Child 14–17 years: 75/1500 mg for 1 dose
  - Adult: 75/1500 mg for 1 dose

**Malaria prophylaxis**

- **BY MOUTH**
  - Adult: Not recommended by UK malaria experts

**DOSE EQUIVALENCE AND CONVERSION**

- Dose quantities are expressed in the form x/y where x and y are the strengths in milligrams of pyrimethamine and sulfadoxine respectively.

**UNLICENSED USE**

- Not licensed for use in children of body-weight under 5 kg.

**CONTRA-INDICATIONS**

- Acute porphyrias p. 930

**CAUTIONS**

- Avoid in blood disorders (unless under specialist supervision) - avoid in infants under 6 weeks - elderly - G6PD deficiency - history of seizures - avoid large loading doses - not recommended for prophylaxis (severe side-effects on long-term use) - predisposition to folate deficiency - predisposition to hyperkalaemia (in adults)

**INTERACTIONS**

- Appendix 1 (pyrimethamine, sulfonamides).

**SIDE-EFFECTS**

- Diarrohea - headache - hyperkalaemia - nausea - rash

- Vomiting


**Frequency not known**

- Allergic alveolitis - eosinophilic alveolitis - pulmonary infiltrates

**SIDE-EFFECTS, FURTHER INFORMATION**

- Discontinue immediately if blood disorders or rash occur. Discontinue if cough or shortness of breath occur.

**ALLERGY AND CROSS-SENSITIVITY**

- Contra-indicated in patients with sulfonamide allergy.
**PREGNANCY** Possible teratogenic risk in *first trimester* (pyrimethamine a folate antagonist); in *third trimester*—risk of neonatal haemolysis and methaemoglobinemia. Fear of increased risk of kernicterus in neonates appears to be unfounded.

**BREAST FEEDING** Small risk of kernicterus in jaundiced infants; risk of haemolysis in G6PD-deficient infants (due to sulfadoxine).

**MONITORING REQUIREMENTS** Monitor blood counts on prolonged treatment.

**PRESCRIBING AND DISPENSING INFORMATION** Also known as Fansidar®.

**PATIENT AND CARER ADVICE** Patients should be advised to maintain adequate fluid intake.

**UNLICENSED USE** Injection not licensed.

**CONTRA-INDICATIONS** Haemoglobinuria, myasthenia gravis, optic neuritis, tinnitus.

**CAUTIONS** Atrial fibrillation (monitor ECG during parenteral treatment) – cardiac disease (monitor ECG during parenteral treatment) – conduction defects (monitor ECG during parenteral treatment) – elderly (monitor ECG during parenteral treatment) (in adults) – G6PD deficiency – heart block (monitor ECG during parenteral treatment)

**SIDE-EFFECTS** Agitation, tinnitus, abdominal pain, acute renal failure, angioedema, blood disorders, cardiovascular effects, cinchonism, confusion, diarrhoea, dyspnoea, flushed skin, headache, hearing impairment, hot flush, hypersensitivity reactions, hypoglycaemia (especially after parenteral administration), intravascular coagulation, muscle weakness, nausea, photosensitivity, rashes, temporary blindness, thrombocytopenia, vertigo, visual disturbances, vomiting.

**OVERDOSE** Quinine is very toxic in overdosage; life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

For details on the management of poisoning, see Emergency treatment of poisoning p. 1204.

**PREGNANCY** High doses are teratogenic in *first trimester*, but in malaria benefit of treatment outweighs risk.

**BREAST FEEDING** Present in milk but not known to be harmful.

**HEPATIC IMPAIRMENT** with intravenous use – For treatment of malaria in severe impairment, reduce parenteral maintenance dose to 5–7 mg/kg of quinine salt.

**RENAL IMPAIRMENT** with intravenous use – For treatment of malaria in severe impairment, reduce parenteral maintenance dose to 5–7 mg/kg of quinine salt.

**MONITORING REQUIREMENTS** with intravenous use – Monitor blood glucose and electrolyte concentration during parenteral treatment.

In adults Patients taking quinine for nocturnal leg cramps should be monitored closely during the early stages for adverse effects as well as for benefit.

**DIRECTIONS FOR ADMINISTRATION** with intravenous use in children – For intravenous infusion, dilute to a concentration of 2 mg/mL (max. 30 mg/mL in fluid restriction) with Glucose 5% or Sodium Chloride 0.9% and give over 4 hours.

With intravenous use in adults – For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride 0.9%. To be given over 4 hours.

**PRESCRIBING AND DISPENSING INFORMATION** Intravenous injection of quinine is so hazardous that it has been superseded by infusion.

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**Quinine**

**INDICATIONS AND DOSE**

**Nocturnal leg cramps**

- **BY MOUTH**
  - Adult: 200–300 mg once daily, to be taken at bedtime

**Non-falciparum malaria**

- **BY INTRAVENOUS INFUSION**
  - Adult: 10 mg/kg every 4 hours (max. per dose 700 mg), infused over 4 hours, given if patient is unable to take oral therapy. Changed to oral chloroquine as soon as the patient's condition permits

**Falciparum malaria**

- **BY MOUTH**
  - Child: 10 mg/kg every 8 hours (max. per dose 600 mg) for 7 days, together with or followed by either doxycycline (in children over 12 years), or clindamycin
  - Adult: 600 mg every 8 hours for 5–7 days, the quinine should be given together with or followed by either doxycycline or clindamycin

- **BY INTRAVENOUS INFUSION**
  - Adult: Loading dose 20 mg/kg (max. per dose 1.4 g), infused over 4 hours, the loading dose of 20 mg/kg should not be used if the patient has received quinine or mefloquine during the previous 12 hours, then maintenance 10 mg/kg every 8 hours (max. per dose 700 mg) until patient can swallow tablets to complete the 7-day course, maintenance dose to be given 8 hours after the start of the loading dose and infused over 4 hours, the quinine should be given together with or followed by either doxycycline or clindamycin

**Falciparum malaria (in intensive care unit)**

- **BY INTRAVENOUS INFUSION**
  - Adult: Loading dose 7 mg/kg, infused over 30 minutes, followed immediately by 10 mg/kg, infused over 4 hours, then maintenance 10 mg/kg every 8 hours (max. per dose 700 mg) until patient can swallow tablets to complete the 7-day course, maintenance dose to be given 8 hours after the start of the loading dose and infused over 4 hours, the quinine should be given together with or followed by either doxycycline or clindamycin

**DOSE EQUIVALENCE AND CONVERSION**

- When using quinine for malaria, doses are valid for quinine hydrochloride, dihydrochloride, and sulfate; they are not valid for quinine bisulfate which contains a correspondingly smaller amount of quinine.
- Quinine (anhydrous base) 100 mg = quinine bisulfate 169 mg; quinine dihydrochloride 122 mg; quinine hydrochloride 122 mg; and quinine sulfate 121 mg.
6 Viral infection

6.1 Hepatitis

Hepatitis

Overview
Treatment for viral hepatitis should be initiated by a specialist. The management of uncomplicated acute viral hepatitis is largely asymptomatic. Early treatment of acute hepatitis C with interferon alfa p. 850 can reduce the risk of chronic infection. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. Active or passive immunisation against hepatitis A and B infections can be given.

Chronic hepatitis B
Peginterferon alfa p. 576 is an option for the initial treatment of chronic hepatitis B and may be preferable to interferon alfa. The use of peginterferon alfa and interferon alfa is limited by a response rate of 30–40% and relapse is frequent. Treatment should be discontinued if no improvement occurs after 4 months. The manufacturers of peginterferon alfa-2a and interferon alfa contra-indicate use in decompensated liver disease, but low doses can be used with great caution in these patients. Although interferon alfa is contra-indicated in patients receiving immunosuppressant treatment (or who have received it recently), cautious use of peginterferon alfa-2a may be justified in some cases.

Entecavir p. 575, or tenofovir disoproxil p. 599 are options for the initial treatment of chronic hepatitis B. If the response is inadequate after 6–9 months of treatment, a change in treatment should be considered. Other drugs that are licensed for the treatment of chronic hepatitis B include adefovir dipivoxil p. 576, lamivudine p. 598, or telbivudine p. 575.

Entecavir alone, tenofovir disoproxil alone, or a combination of lamivudine with either adefovir dipivoxil or tenofovir disoproxil can be used in patients with decompensated liver disease.

If drug-resistant hepatitis B virus emerges during treatment, another antiviral drug to which the virus is sensitive should be added. Hepatitis B viruses with reduced susceptibility to lamivudine have emerged following extended therapy. Adefovir dipivoxil or tenofovir disoproxil can be given with lamivudine in lamivudine-resistant chronic hepatitis B; telbivudine or entecavir should not be used because cross-resistance can occur.

If there is no toxicity or less in efficacy, treatment with adefovir dipivoxil, entecavir, lamivudine, telbivudine, or tenofovir disoproxil is usually continued until 6 months after adequate seroconversion has occurred. Treatment is usually continued long-term in patients with decompensated liver disease.

Tenofovir disoproxil, or a combination of tenofovir disoproxil with either emtricitabine p. 598 or lamivudine may be used with other antiretrovirals, as part of ‘highly active antiretroviral therapy’ in patients who require treatment for both HIV and chronic hepatitis B. If patients infected with both HIV and chronic hepatitis B only require treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV, such as peginterferon alfa or adefovir dipivoxil. Treatment may be continued long-term, even if adequate seroconversion occurs. Management of these patients should be coordinated between HIV and hepatology specialists.

Chronic hepatitis C
Before starting treatment, the genotype of the infecting hepatitis C virus should be determined and the viral load measured as this may affect the choice and duration of treatment. A combination of ribavirin p. 578 and peginterferon alfa is used for the treatment of chronic hepatitis C. The combination of ribavirin and interferon alfa is less effective than the combination of peginterferon alfa and ribavirin. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Ribavirin monotherapy is ineffective.

Boceprevir p. 581 and telaprevir p. 583 are protease inhibitors that inhibit the replication of hepatitis C virus genotype 1, but they are less effective against other genotypes of the virus. Monotherapy is not recommended because there is a high likelihood of resistance developing.

Either boceprevir or telaprevir is licensed for use in combination with ribavirin and peginterferon alfa for the treatment of chronic hepatitis C infection of genotype 1 in patients with compensated liver disease; these combinations are more effective than dual therapy with ribavirin and peginterferon alfa. However, triple therapy is associated with a higher incidence and greater severity of anaemia than dual therapy. Neutropenia seems to be more common during treatment with regimens containing boceprevir than with those containing telaprevir. Rash is a particular concern with telaprevir, and to a lesser extent with boceprevir.

Daclatasvir p. 577 is licensed for use in combination with sofosbuvir p. 580 for the treatment of chronic hepatitis C infection of genotypes 1 or 4, with or without compensated cirrhosis; the addition of ribavirin should be considered for patients with advanced liver disease or with other negative prognostic factors, such as prior treatment experience. It is also licensed in combination with sofosbuvir and ribavirin for the treatment of chronic hepatitis C infection of genotype 3 in patients who are treatment experienced, with or without compensated cirrhosis, and in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C infection of genotype 4. Daclatasvir must not be given as monotherapy.

Ombitasvir with paritaprevir and ritonavir p. 578 (Viekirax ®), is licensed for use in combination with dasabuvir p. 583, with or without ribavirin, for the treatment of chronic hepatitis C infection of genotype 1 in patients with or without compensated cirrhosis; it is also licensed for use in combination with ribavirin for the treatment of chronic hepatitis C infection of genotype 4 with or without compensated cirrhosis.

Sofosbuvir is a pro-drug of a nucleoside inhibitor that is effective against hepatitis C virus polymerase NS5B. It is licensed for use in combination with ribavirin, with or without peginterferon alfa, for the treatment of chronic hepatitis C infection of genotypes 1, 2, 3, 4, 5, or 6 in patients with compensated liver disease. Sofosbuvir monotherapy is not recommended because it is less effective than combination therapy.

Ledipasvir is licensed for use in combination with sofosbuvir (soshofuvir with ledipasvir p. 581), with or...
6.2a Chronic hepatitis B

Other drugs used for Chronic hepatitis B [Interferon alfa, p. 850 • Lamivudine, p. 598 • Tenofovir disoproxil, p. 599]

ANTIVIRALS  NUCLEOSIDE ANALOGUES

Entecavir

- **INDICATIONS AND DOSE**
  Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) not previously treated with nucleoside analogues
    - **BY MOUTH**
    - **Adult:** 500 micrograms once daily
  Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) and lamivudine–resistance
    - **BY MOUTH**
    - **Adult:** 1 mg once daily, consider other treatment if inadequate response after 6 months
  Chronic hepatitis B in patients with decompensated liver disease
    - **BY MOUTH**
    - **Adult:** 1 mg once daily

- **CAUTIONS**
  HIV infection—risk of HIV resistance in patients not receiving 'highly active antiretroviral therapy' • lamivudine–resistant chronic hepatitis B—risk of entecavir resistance

- **CAUTIONS, FURTHER INFORMATION**
  Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

- **SIDE-EFFECTS**
  Common or very common
    - Diarrhoea, dizziness, dyspepsia, fatigue, headache, nausea, raised serum amylase, raised serum lipase, sleep disturbances, vomiting
  Uncommon
    - Alopecia, rash, thrombocytopenia

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

- **PREGNANCY** Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **RENAI IMPAIRMENT** Reduce dose if eGFR less than 50 mL/minute/1.73 m². Consult product literature.

- **MONITORING REQUIREMENTS**
  Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).

- **DIRECTIONS FOR ADMINISTRATION**
  To be taken at least 2 hours before or 2 hours after food.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Flavours of oral liquid formulations may include orange.

- **PATIENT AND CARER ADVICE**
  Patients or carers should be counselled on the administration of entecavir tablets and oral solution.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  NICE technology appraisals (TAs)
  Entecavir for chronic hepatitis B (August 2008) NICE TA153
  Entecavir is an option for the treatment of chronic hepatitis B.
  www.nice.org.uk/TA153

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

Tablet
  - **Baraclude** (Bristol-Myers Squibb Pharmaceuticals Ltd)
    - Entecavir (as Entecavir monohydrate) 1 mg Baraclude 1mg tablets
      - 30 tablet (POM) £36.30
    - Entecavir (as Entecavir monohydrate) 500 microgram Baraclude 0.5mg tablets
      - 30 tablet (POM) £36.30

Oral solution
  - **Baraclude** (Bristol-Myers Squibb Pharmaceuticals Ltd)
    - Entecavir (as Entecavir monohydrate) 50 microgram per 1 ml Baraclude 0.05mg/ml oral solution sugar-free
      - 210 ml (POM) £423.80

Telbivudine

- **INDICATIONS AND DOSE**
  Chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis, when other treatment is not appropriate
    - **BY MOUTH**
    - **Adult:** 600 mg once daily

- **CAUTIONS**
  Lamivudine–resistant chronic hepatitis B—risk of telbivudine resistance

- **CAUTIONS, FURTHER INFORMATION**
  Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

- **INTERACTIONS**
  Appendix 1 (telbivudine).

- **SIDE-EFFECTS**
  Common or very common
    - Abdominal pain, cough, diarrhoea, dizziness, fatigue, headache, nausea, raised serum amylase, raised serum lipase, rash
  Uncommon
    - Arthralgia, myalgia, myopathy (discontinue treatment) • peripheral neuropathy • taste disturbance
  Rare
    - Lactic acidosis, rhabdomyolysis

- **PREGNANCY**
  Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING**
  Manufacturer advises avoid—present in milk in animal studies.

- **RENAI IMPAIRMENT**
  600 mg every 48 hours if eGFR 30–49 mL/minute/1.73 m²; 600 mg every 72 hours if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  Monitor liver function tests every 3 months and viral markers of hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).

- **PATIENT AND CARER ADVICE**
  Muscle effects and peripheral neuropathy. Patients should be advised to promptly report unexplained muscle pain,
tenderness, or weakness, or numbness, tingling or burning sensations.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Telbivudine for chronic hepatitis B (August 2008)** NICE TAI54
  Telbivudine is not recommended for the treatment of chronic hepatitis B. Patients currently receiving telbivudine can continue treatment until they and their clinician consider it appropriate to stop.
  www.nice.org.uk/TAI54

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Tablet

- **Sebivo** (Novartis Pharmaceuticals UK Ltd)
  - Telbivudine 600 mg Sebivo 600mg tablets | 28 tablet £290.33

**ANTIVIRALS ▶ NUCLEOTIDE ANALOGUES**

### Adefovir dipivoxil

**INDICATIONS AND DOSE**

**Chronic hepatitis B infection with either compensated liver disease with evidence of viral replication, and histologically documented active liver inflammation and fibrosis, when other treatment not appropriate or decompensated liver disease in combination with another antiviral for chronic hepatitis B that has no cross-resistance to adefovir**

- **BY MOUTH**
  - Adult: 10 mg once daily

**CAUTIONS**

**Elderly**

Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

**SIDE-EFFECTS**

Abdominal pain, asthenia, diarrhoea, dyspepsia, flatulence, headache, hypophosphataemia, nausea, pancreatitis, pruritus, rash, renal failure, vomiting.

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment.

**PREGNANCY**

Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT**

10 mg every 48 hours if eGFR 30–50 mL/minute/1.73 m²; 10 mg every 72 hours if eGFR 10–30 mL/minute/1.73 m². No information available if eGFR less than 10 mL/minute/1.73 m². Monitor renal function more frequently in patients with renal impairment.

**MONITORING REQUIREMENTS**

- Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).
- Monitor renal function before treatment then every 3 months, more frequently in patients receiving nephrotoxic drugs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Tablet

- **Heptiva** (Gilead Sciences International Ltd)
  - Adefovir dipivoxil 10 mg Heptiva 10mg tablets | 30 tablet £252.22

**IMMUNOSTIMULANTS ▶ INTERFERONS**

### Peginterferon alfa

**DRUG ACTION**

Polyethylene glycol-conjugated (‘pegylated’ derivatives of interferon alfa (peginterferon alfa-2a and peginterferon alfa-2b)) are available; pegylation increases the persistence of the interferon in the blood.

**INDICATIONS AND DOSE**

**PEGASYS®**

- Combined with ribavirin for chronic hepatitis C
- Monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated

**BY SUBCUTANEOUS INJECTION**

- Adult: (consult product literature)

**VIRAFERONPEG®**

- Combined with ribavirin for chronic hepatitis C
- Combined with ribavirin and boceprevir for chronic hepatitis C
- Injection of genotype 1 in patients with compensated liver disease
- Monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated

**BY SUBCUTANEOUS INJECTION**

- Adult: (consult product literature)

**CONTRA-INDICATIONS**

For contra-indications consult product literature.

**CAUTIONS**

For cautions consult product literature.

**INTERACTIONS**

Appendix 1 (interferons).

**SIDE-EFFECTS**

- Common or very common: Anorexia, diarrhoea, influenza-like symptoms, leucopenia, nausea
- Frequency not known: Alopecia, arrhythmias, cardiovascular problems, coma (usually with high doses in the elderly), confusion, depression, hepatotoxicity, hyperglycaemia, hypersensitivity reactions, hypertension, hypertriglyceridaemia (sometimes severe), hypotension, myelosuppression (particularly affecting granulocyte counts), nephrotoxicity, ocular side-effects, palpitation, psoriasisiform rash, seizures (usually with high doses in the elderly), suicidal behaviour, thyroid abnormalities

**SIDE-EFFECTS, FURTHER INFORMATION**

For information on side effects consult product literature.

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment—consult product literature.

**PREGNANCY**

Manufacturers recommend avoid unless potential benefit outweighs risk (toxicity in animal studies).

**BREAST FEEDING**

Manufacturers advise avoid—no information available.

**HEPATIC IMPAIRMENT**

Avoid in severe impairment. Close monitoring required in mild to moderate hepatic impairment.

**RENAL IMPAIRMENT**

Reduce dose in moderate to severe impairment. For information on peginterferon alfa use in renal impairment consult product literature. Close monitoring required in renal impairment.

**MONITORING REQUIREMENTS**

Monitoring of lipid concentration is recommended.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006 and September 2010) NICE TA200
  The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the...
disease has reached a moderate stage (‘watchful waiting’). Peginterferon alfa alone can be used if ribavirin is contra-indicated or not tolerated.

www.nice.org.uk/TA200

- Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200

The combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:
- not previously treated with interferon alfa or peginterferon alfa;
- treated previously with interferon alfa alone or in combination with ribavirin;
- whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;
- co-infected with HIV.

Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk.

Patients receiving interferon alfa may be switched to peginterferon alfa.

www.nice.org.uk/TA200

- Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol

- Pegasys (Roche Products Ltd)

Peginterferon alfa-2a 180 microgram per 1 ml Pegasys 90micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £76.51

Peginterferon alfa-2a 270 microgram per 1 ml Pegasys 135micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £107.76

Pegasys 135micrograms/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection £107.76

Peginterferon alfa-2a 360 microgram per 1 ml Pegasys 180micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £497.60

Peginterferon alfa-2a 50 microgram per 1 ml Pegasys 25micrograms/0.1ml solution for injection pre-filled syringes | 21 pre-filled disposable injection £66.46

Peginterferon alfa-2a 80 microgram per 1 ml Peginterferon Peg 80microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection £106.34

Peginterferon alfa-2b 100 microgram per 1 ml Viraferon Peg 100microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection £132.92

Peginterferon alfa-2b 120 microgram per 1 ml Viraferon Peg 120microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection £159.51

Peginterferon alfa-2b 150 microgram per 1 ml Viraferon Peg 150microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection £199.38

6.2b Chronic hepatitis C

Other drugs used for Chronic hepatitis C Interferon alfa, p. 850 - Peginterferon alfa, p. 576

**Antivirals > Non-Structural Protein 5A Inhibitors**

Daclatasvir

- Drug action Daclatasvir is an inhibitor of the multifunctional protein NS5A, which is an essential component of the hepatitis C virus replication process.

- Indications and dose

  In combination with sofosbuvir for the treatment of chronic hepatitis C infection of genotypes 1 or 4, with or without compensated cirrhosis | In combination with sofosbuvir and ribavirin for the treatment of chronic hepatitis C infection of genotype 3 in patients who are treatment experienced, with or without compensated cirrhosis | In combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C infection of genotype 4

  - By mouth
    - Adult: Usual dose 60 mg once daily (for duration of treatment consult product literature

- Dose adjustments due to interactions

Reduce dose to 30 mg once daily with concomitant use of potent CYP3A4 inhibitors (e.g. atazanavir boosted with ritonavir, boceprevir, clarithromycin, cobicistat, itraconazole, ketoconazole, posaconazole, telaprevir, telithromycin, and voriconazole).

Increase dose to 90 mg once daily with concomitant use of moderate CYP3A4 inducers (e.g. efavirenz).

- Cautions

Decompensated liver disease · hepatitis B virus co-infection · human immunodeficiency virus co-infection · organ transplant patients · retreatment—efficacy not established in patients with prior exposure to a NS5A inhibitor

- Interactions > Appendix 1 (daclatasvir).

- Side-effects

  - Common or very common Abdominal pain · alopecia · anaemia · anxiety · arthralgia · blurred vision · constipation · cough · decreased appetite · depression · diarrhoea · disturbance in attention · dizziness · dry mouth · dry skin · dysphoria · flatulence · gastro-oesophageal reflux · headache · hot flush · insomnia · irritable bowel syndrome · malaise · migraine · myalgia · nasal congestion · nausea · neutropenia · pruritus · pyrexia · rash · reduced visual acuity · vomiting

  - Side-effects, further information

   Side-effects listed are reported when daclatasvir is used in combination with sofosbuvir with or without ribavirin or with ribavirin and peginterferon alfa.

  - Conception and contraception Highly effective contraception required during and for 5 weeks after treatment.

  - Pregnancy

    Manufacturer advises avoid (toxicity in animal studies).

  - Breast feeding

    Manufacturer advises avoid—present in milk in animal studies.

  - Patient and carer advice

    Missed doses

    If a dose is more than 20 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

    Driving and skilled tasks

    May affect performance of skilled tasks (e.g. driving)
Ombitasvir with paritaprevir and ritonavir

The properties listed below are those particular to the combination only. For the properties of the components please consider, ritonavir p. 604.

INDICATIONS AND DOSE

Chronic hepatitis C of genotype 1 (in combination with dasabuvir, with or without ribavirin) Chronic hepatitis C of genotype 4 (in combination with ribavirin)

- BY MOUTH
  - Adult: 2 tablets once daily for duration of treatment consult product literature, to be taken with food

CONTRA-INDICATIONS

HIV co-infection without suppressive antiretroviral therapy

CAUTIONS

Retreatment—efficacy not established

INTERACTIONS

Appendix 1 (ombitasvir, paritaprevir, ritonavir).

SIDE-EFFECTS

Common or very common Anaemia - asthenia - fatigue - insomnia - nausea

Frequency not known Transient hyperbilirubinemia

SIDE-EFFECTS, FURTHER INFORMATION

Side-effects listed are reported when ombitasvir with paritaprevir and ritonavir is used in combination with dasabuvir, with or without ribavirin.

CONCEPTION AND CONTRACEPTION

For women of child-bearing potential, exclude pregnancy before initiation of treatment; effective contraception should be used during treatment.

PREGNANCY

Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises avoid in moderate or severe impairment.

PATIENT AND CARER ADVICE

Missed doses

If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
Chronic hepatitis C genotype 2 or 3 (not previously treated, or patients infected with HIV and hepatitis C (in combination with peginterferon alfa)

- **BY MOUTH**
  - Adult: Usual dose 400 mg twice daily

**REBETOL® CAPSULES**

Chronic hepatitis C (in combination with interferon alfa 2b, or peginterferon alfa 2b with or without boceprevir)

- **BY MOUTH**
  - Adult (body-weight up to 65 kg): 400 mg twice daily
  - Adult (body-weight 65–80 kg): 400 mg, dose to be taken in the morning and 600 mg, dose to be taken in the evening
  - Adult (body-weight 81-104 kg): 600 mg twice daily
  - Adult (body-weight 105 kg and above): 600 mg, dose to be taken in the morning and 800 mg, dose to be taken in the evening

**REBETOL® ORAL SOLUTION**

Chronic hepatitis C (in combination with interferon alfa 2b, or peginterferon alfa 2b with or without boceprevir)

- **BY MOUTH**
  - Adult (body-weight up to 65 kg): 400 mg twice daily
  - Adult (body-weight 65–80 kg): 400 mg daily, dose to be taken in the morning and 600 mg daily, dose to be taken in the evening
  - Adult (body-weight 81-104 kg): 600 mg twice daily
  - Adult (body-weight 105 kg and above): 600 mg daily, dose to be taken in the morning and 800 mg daily, dose to be taken in the evening

- **UNLICENSED USE** Inhalation licensed for use in children (age range not specified by manufacturer). Intravenous preparation not licensed.

- **CONTRA-INDICATIONS**
  - With systemic use Active severe psychiatric condition (in children) - autoimmune disease (in children) - autoimmunie hepatitis (in children) - consult product literature for specific contra-indications when ribavirin p. 578 used in combination with other medicinal products - haemoglobinopathies - history of severe psychiatric condition (in children) - severe cardiac disease (in adults) - severe debilitating medical conditions - severe, uncontrolled cardiac disease in children with chronic hepatitis C - unstable or uncontrolled cardiac disease in previous 6 months (in adults)

- **CAUTIONS**
  - When used by inhalation Maintain standard supportive respiratory and fluid management therapy
  - With systemic use Anaemia (haemoglobin concentration should be monitored during the treatment and corrective action taken) (in adults) - cardiac disease (assessment including ECG recommended before and during treatment — discontinue if deterioration) - consult product literature for specific cautions when ribavirin p. 578 used in combination with other medicinal products - gout (in adults) - haemolysis (haemoglobin concentration should be monitored during the treatment and corrective action taken) (in adults) - patients with a transplant — risk of rejection - risk of growth retardation in children, the reversibility of which is uncertain — if possible, consider starting treatment after pubertal growth spurt - severe dental disorders (in adults) - severe ocular disorders (in adults) - severe periodontal disorders (in adults) - severe psychiatric effects (in adults)

- **INTERACTIONS**
  - Appendix 1 (ribavirin).

- **SIDE-EFFECTS**
  - When used by inhalation Bacterial pneumonia - haemolysis - non-specific anaemia - pneumothorax - worsening respiration

**SIDE-EFFECTS, FURTHER INFORMATION**

- With oral use Side effects listed are reported when oral ribavirin is used in combination with peginterferon alfa or interferon alfa, consult product literature for details.

- **CONCEPTION AND CONTRACEPTION**
  - With systemic use Exclude pregnancy before treatment in females of childbearing age. Effective contraception essential during treatment and for 4 months after treatment in females and for 7 months after treatment in males of childbearing age. Routine monthly pregnancy tests recommended. Condoms must be used if partner of male patient is pregnant (ribavirin excreted in semen).
  - When used by inhalation Women planning pregnancy should avoid exposure to aerosol.

- **PREGNANCY** Avoid; teratogenicity in animal studies.
  - When used by inhalation Pregnant women should avoid exposure to aerosol.

- **BREAST FEEDING** Avoid — no information available.

- **HEPATIC IMPAIRMENT** No dosage adjustment required. Avoid oral ribavirin in severe hepatic dysfunction or decompensated cirrhosis.
RENAL IMPAIRMENT Plasma-ribavirin concentration increased.
- In adults Manufacturer advises avoid oral ribavirin unless essential if eGFR less than 50 mL/minute/1.73 m²—monitor haemoglobin concentration closely.
- In children Manufacturer advises avoid oral ribavirin if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²—monitor haemoglobin concentration closely. Manufacturer advises use intravenous preparation with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
- When used by inhalation Monitor electrolytes closely. Monitor equipment for precipitation.
- With systemic use Determine full blood count, platelets, electrolytes, glucose, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop (consult product literature).
- With systemic use in children Test thyroid function before treatment and then every 3 months. Eye examination also recommended during treatment if pre-existing ophthalmological disorder deteriorates or if new ophthalmological disorder develops. Manufacturer advises avoid oral ribavirin unless plasma-ribavirin concentration closely. Manufacturer advises use monthly if eGFR less than 30mL/minute/1.73m²—monitor haemoglobin concentration.
- In children Manufacturer advises avoid oral ribavirin if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²—monitor haemoglobin concentration closely. Manufacturer advises use intravenous preparation with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include bubble-gum.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006 and September 2010) NICE TA200 The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the disease has reached a moderate stage (‘watchful waiting’). www.nice.org.uk/TA200
- Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200 The combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:
  - not previously treated with interferon alfa or peginterferon alfa;
  - treated previously with interferon alfa alone or in combination with ribavirin;
  - whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;
  - co-infected with HIV. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa. www.nice.org.uk/TA200

LESS SUITABLE FOR PRESCRIBING Ribavirin inhalation is less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS
- Copegus (Roche Products Ltd)
  - Ribavirin 200 mg Copegus 200mg tablets | 42 tablet POM £92.50 | 112 tablet POM £224.65
  - Ribavirin 400 mg Copegus 400mg tablets | 56 tablet POM £369.98

Capsule
CAUTIONARY AND ADVISORY LABELS
- Rebetol (Merck Sharp & Dohme Ltd)
  - Ribavirin 200 mg Rebetol 200mg capsules | 84 capsule POM £160.69 | 140 capsule POM £267.81
  - Rebetol 400 mg per 1 ml Rebetol 40mg/ml oral solution | 100 ml POM £67.08

Solution for injection
- Virazole (Meda Pharmaceuticals Ltd)
  - Ribavirin 100 mg per 1 ml Virazole 1.2g/12ml solution for injection vials | 5 vials POM £360.00

ANTIVIRALS > NUCLEOTIDE ANALOGUES

Sofosbuvir

INDICATIONS AND DOSE
In combination with ribavirin (Copegus®), with or without peginterferon alfa, for chronic hepatitis C infection of genotypes 1, 3, 4, 5, or 6 in patients with compensated liver disease | In combination with ribavirin (Copegus®) for chronic hepatitis C infection of genotype 2 in patients with compensated liver disease | In combination with daclatasvir for chronic hepatitis C infection of genotype 1, 3, or 4
- BY MOUTH
  - Adult: 400 mg once daily, for duration of treatment consult product literature

CAUTIONS, FURTHER INFORMATION
In chronic hepatitis C of genotype 1, 4, 5, or 6, only use sofosbuvir with ribavirin in those with intolerance or contra-indications to peginterferon alfa who require urgent treatment.

INTERACTIONS
- Appendix 1 (sofosbuvir).

SIDE-EFFECTS
Abdominal discomfort, agitation, alopecia, anaemia, anxiety, arthralgia, asthenia, blurred vision, chest pain, constipation, cough, decreased appetite, depression, diarrhoea, disturbance in attention, dizziness, dry mouth, dysphoria, gastro-oesophageal reflux, headache, influenza-like symptoms, insomnia, irritability, memory impairment, migraine, myalgia, nausea, neutropenia, rash, vomiting, weight loss

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects listed are reported when sofosbuvir is used in combination with ribavirin; or with ribavirin and peginterferon alfa.

PREGNANCY
Manufacturer advises avoid.

BREAST FEEDING
Manufacturer advises avoid—metabolites present in milk in animal studies.

RENAL IMPAIRMENT
Safety and efficacy not established if eGFR less than 30 mL/minute/1.73 m²—accumulation may occur.

PRESCRIBING AND DISPENSING INFORMATION
Dispense in original container (contains desiccant).

PATIENT AND CARER ADVICE
Missed doses
If a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Sofosbuvir for treating chronic hepatitis C (February 2015) NICE TA330 Sofosbuvir in combination with peginterferon alfa and ribavirin is an option for treating adults with chronic hepatitis C infection:
Sofosbuvir is a nucleotide analogue inhibitor and ledipasvir is an HCV inhibitor; they reduce viral load by inhibiting hepatitis C virus RNA replication.

**INDICATIONS AND DOSE**

- **Chronic hepatitis C of genotypes 1, 4, 5 or 6 in patients with or without compensated cirrhosis (with or without ribavirin)**
- **Chronic hepatitis C of genotypes 1, 4, 5 or 6 in post-liver transplant patients, with or without compensated cirrhosis (with or without ribavirin)**

**TREATMENT FAILURE**

- By mouth
- Adult: 1 tablet once daily, for duration of treatment consult product literature

**CAUTIONS**

- Retreatment following treatment failure—efficacy not established

**INTERACTIONS**

- Appendix 1 (sofosbuvir, ledipasvir)

**SIDE-EFFECTS**

- Common or very common: Headache, malaise

**BREAST FEEDING**

- Manufacturer advises avoid—present in milk in animal studies.

**PRESCRIBING AND DISPENSING INFORMATION**

Dispense in original container (contains desiccant).

**PATIENT AND CARER ADVICE**

- **Missed doses**
  - If a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
  - Vomiting: If vomiting occurs within 5 hours of administration, an additional dose should be taken.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**
  - Ledipasvir with sofosbuvir for the treatment of chronic hepatitis C (November 2015) NICE TA363
  - Ledipasvir with sofosbuvir is recommended as an option for treating adults with chronic hepatitis C infection:
    - of genotype 1 without cirrhosis (treatment naive patients)—8 weeks' treatment
    - of genotype 1 or 4 with cirrhosis (treatment naive patients)—12 weeks' treatment
    - of genotype 1 or 4 without cirrhosis (or with cirrhosis but only if the person has a low risk of the disease getting worse) that has not responded adequately to previous treatment—12 weeks' treatment

  In addition, ledipasvir with sofosbuvir is only recommended in patients with cirrhosis for the durations mentioned above if the following criteria are met:
  - Child-Pugh class A
  - platelet count of 75 000/mm$^3$ or more
  - no features of portal hypertension
  - no history of an HCV-associated decompensation episode
  - not previously treated with an NSSA inhibitor

  Patients whose treatment with ledipasvir with sofosbuvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their clinician consider it appropriate to stop.

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (June 2014) that sofosbuvir (Sovaldi®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis C infection of genotypes 1 to 6; its use in combination with ribavirin as dual therapy for chronic hepatitis C infection of either genotype 2 (in treatment naive patients) or genotype 3 is restricted to those who cannot use peginterferon alfa because of intolerance or contra-indications.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21, 25

- **Sovaldi®** (Gilead Sciences International Ltd)
- **Sofosbuvir 400 mg**
- **Sofosbuvir 400 mg tablets**
- **12 tablet**
- **POM**
- **£11,660.98**

**Boceprevir**

**INDICATIONS AND DOSE**

- Chronic hepatitis C infection of genotype 1 in patients with compensated liver disease (in combination with ribavirin and peginterferon alfa)
  - By mouth
  - Adult: 800 mg 3 times a day, for duration of treatment consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Appendix 1 (boceprevir). Caution with concomitant use of other drugs known to prolong QT interval.

**CONTRA-INDICATIONS**

- Autoimmune hepatitis
In combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 or 4. In combination with sofosbuvir (with or without ribavirin) for urgent treatment of chronic hepatitis C infection of genotype 1 or 4 when peginterferon alfa cannot be used because of intolerance or contra-indications.

> BY MOUTH
> Adult: 150 mg once daily (for duration of treatment consult product literature)

### Simeprevir

#### INDICATIONS AND DOSE

In combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 or 4. In combination with sofosbuvir (with or without ribavirin) for urgent treatment of chronic hepatitis C infection of genotype 1 or 4 when peginterferon alfa cannot be used because of intolerance or contra-indications.

> BY MOUTH
> Adult: 150 mg once daily (for duration of treatment consult product literature)

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

### Simeprevir

#### INDICATIONS AND DOSE

In combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 or 4. In combination with sofosbuvir (with or without ribavirin) for urgent treatment of chronic hepatitis C infection of genotype 1 or 4 when peginterferon alfa cannot be used because of intolerance or contra-indications.

> BY MOUTH
> Adult: 150 mg once daily (for duration of treatment consult product literature)

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.
Telaprevir

INDICATIONS AND DOSE
In combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 in patients with compensated liver disease

BY MOUTH
Adult: 1.125 g every 12 hours, alternatively 750 mg every 8 hours, for duration of treatment consult product literature

CAUTIONS
Bradycardia, congenital or family history of QT interval prolongation, electrolyte disturbances, family history of sudden death, heart failure with reduced left ventricular ejection fraction, hypoalbuminaemia, low platelets, prolongation of QT interval

CAUTIONS, FURTHER INFORMATION
Low platelets or hypoalbuminaemia. Not recommended in patients with low platelets or hypoalbuminaemia—if initiated in these patients monitor closely for signs of infection, worsening liver impairment, and anaemia (increased risk of severe morbidity and mortality).

INTERACTIONS
Caution in concomitant use with other drugs known to prolong QT interval.

SIDE-EFFECTS
Common or very common: Anaemia, anal fissure, diarrhoea, eczema, haemorrhoids, hyperbilirubinaemia, hyperuricaemia, hypokalaemia, nausea, peripheral oedema, pruritus, rash, syncope, taste disturbances, thrombocytopenia, vomiting
Uncommon: Gout, proctitis, retinopathy, urticaria
Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects listed are reported when telaprevir is used in combination with ribavirin and peginterferon alfa.

Rash
Rash occurs very commonly. If rash mild or moderate, may continue without interruption, but monitor for deterioration. If moderate rash deteriorates, consider permanent discontinuation of telaprevir; if rash does not improve within 7 days of discontinuation, suspend ribavirin. If severe rash or if rash accompanied by blistering or mucosal ulceration, discontinue telaprevir permanently; if rash does not improve within 7 days of discontinuation, consider discontinuation of ribavirin and peginterferon alfa. If serious rash, or if severe rash deteriorates, or if rash accompanied by systemic symptoms, discontinue telaprevir, ribavirin, and peginterferon alfa permanently.

CONCEPTION AND CONTRACEPTION
Effectiveness of hormonal contraceptives reduced during treatment and for 2 months after stopping telaprevir—effective non-hormonal methods of contraception necessary during this time.

PREGNANCY
Manufacturer advises avoid.

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Manufacturer advises avoid in moderate to severe impairment.

MONITORING REQUIREMENTS
Monitor full blood count, platelets, electrolytes, serum creatinine, uric acid, and liver and thyroid function tests before starting treatment and then on weeks 2, 4, 8, and 12 of treatment, then as indicated clinically.

PRESCRIBING AND DISPENSING INFORMATION
Dispense in original container (contains desiccant).

PATIENT AND CARER ADVICE
Missed doses
If a dose is more than 6 hours late with the 12 hourly regimen (or more than 4 hours late with the 8 hourly regimen), the missed dose should not be taken and the next dose should be taken at the normal time.

Patients should be told to seek immediate medical attention if a rash develops or if an existing rash worsens.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
Telaprevir for chronic hepatitis C infection of genotype 1 (April 2012) NICE TA252
Telaprevir in combination with ribavirin and peginterferon alfa is an option for the treatment of chronic hepatitis C infection of genotype 1 in adults with compensated liver disease:

- who have not been treated previously;
- in whom previous treatment (e.g. with peginterferon alfa in combination with ribavirin) has failed.

www.nice.org.uk/TA252

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

No licensed medicines identified.

ANTIVIRALS

Dasabuvir

29-Mar-2016

DRUG ACTION
Dasabuvir is a non-nucleoside inhibitor of hepatitis C virus polymerase NS5B, which is an essential component of the hepatitis C virus replication process.

INDICATIONS AND DOSE
Chronic hepatitis C infection of genotype 1, in combination with other antiviral drugs (ombitasvir with paritaprevir and ritonavir, with or without ribavirin)

BY MOUTH
Adult: 250 mg twice daily for details of duration of treatment, consult product literature, dose to be taken in the morning and evening.

CONTRA-INDICATIONS
HIV co-infection without suppressive antiretroviral therapy

CAUTIONS
Retreatment—efficacy not established

INTERACTIONS
Appendix 1 (dasabuvir).

SIDE-EFFECTS
Common or very common: Anaemia, asthenia, fatigue, insomnia, nausea

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects listed are reported when dasabuvir is used in combination with Viekirax® (ombitasvir with paritaprevir and ritonavir), with or without ribavirin.

PREGNANCY
Manufacturer advises avoid—no information available.

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Manufacturer advises avoid in moderate to severe impairment.
PATIENT AND CARER ADVICE
Missed doses
If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Ombitasvir with paritaprevir and ritonavir with or without dasabuvir for treating chronic hepatitis C (November 2015) NICE TA365
Dasabuvir, in combination with ombitasvir with paritaprevir and ritonavir p. 578, is recommended, within its marketing authorisation, as an option for treating genotype 1 or 4 chronic hepatitis C in adults only if the manufacturer provides it with the discount agreed in the patient access scheme. www.nice.org.uk/guidance/ta365

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 3, 21, 25
- Exviera (AbbVie Ltd) ▼ Dasabuvir (as Dasabuvir sodium monohydrate) 250 mg Exviera 250mg tablets | 56 tablet POM £933.33

6.3 Herpesvirus infections

Herpesvirus infections
Herpes simplex and varicella–zoster infection
The two most important herpesvirus pathogens are herpes simplex virus (herpesvirus hominis) and varicella–zoster virus.
Herpes simplex infections
Herpes infection of the mouth and lips and in the eye is generally associated with herpes simplex virus serotype 1 (HSV-1); other areas of the skin may also be infected, especially in immunodeficiency. Genital infection is most often associated with HSV-2 and also HSV-1. Treatment of herpes simplex infection should start as early as possible and usually within 5 days of the appearance of the infection.
In individuals with good immune function, mild infection of the eye (ocular herpes) and of the lips (herpes labialis or cold sores) is treated with a topical antiviral drug. Primary herpetic gingivostomatitis is managed by changes to diet and with analgesics. Severe infection, neonatal herpes infection or infection in immunocompromised individuals requires treatment with a systemic antiviral drug. Primary or recurrent genital herpes simplex infection is treated with an antiviral drug given by mouth. Persistence of a lesion or recurrence in an immunocompromised patient may signal the development of resistance.
Specialist advice should be sought for systemic treatment of herpes simplex infection in pregnancy.
Varicella–zoster infections
Regardless of immune function and the use of any immunoglobulins, neonates with chickenpox should be treated with a parenteral antiviral to reduce the risk of severe disease. Oral therapy in children is not recommended as absorption is variable. Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required.
Chickenpox is more severe in adolescents and adults than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adults and adolescents. Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g. because of severe cardiovascular or respiratory disease or chronic skin disorder); in such cases, an antiviral is given for 10 days with at least 7 days of parenteral treatment.
Pregnant women who develop severe chickenpox may be at risk of complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.
Those who have been exposed to chickenpox and are at special risk of complications may require prophylaxis with varicella–zoster immunoglobulin (see under Disease Specific Immunoglobulins).
In herpes zoster (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days. Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.
Chronic pain which persists after the rash has healed (postherpetic neuralgia) requires specific management.

Choice
Aciclovir p. 585 is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of herpes simplex infections of the skin and mucous membranes. It is used by mouth for severe herpetic stomatitis. Aciclovir eye ointment is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster.
Famciclovir p. 587, a prodrug of penciclovir, is similar to aciclovir and is licensed for use in herpes zoster and genital herpes.
Valaciclovir p. 587 is an ester of aciclovir, licensed for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed for preventing cytomegalovirus disease following solid organ transplantation. Famciclovir or valaciclovir are suitable alternatives to aciclovir for oral lesions associated with herpes zoster. Valaciclovir once daily may reduce the risk of transmitting genital herpes to heterosexual partners—specialist advice should be sought.
Foscarnet sodium p. 589 is used for mucocutaneous herpes simplex virus infection unresponsive to aciclovir in immunocompromised patients; it is toxic and can cause renal impairment.
Inosine pranobex p. 585 has been used by mouth for herpes simplex infections; its effectiveness remains unproven.

Cytomegalovirus infection
Ganciclovir p. 588 is related to aciclovir but it is more active against cytomegalovirus (CMV); it is also much more toxic than aciclovir and should therefore be prescribed only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the initial treatment of CMV infection. Ganciclovir causes profound myelosuppression when given with zidovudine p. 601; the two should not normally be given together particularly during initial ganciclovir therapy. The likelihood of ganciclovir resistance increases in patients with a high viral load or in those who receive the drug over a long duration. Valaciclovir is licensed for prevention of cytomegalovirus disease following renal transplantation.
Valganciclovir p. 589 is an ester of ganciclovir which is licensed for the initial treatment and maintenance treatment of CMV retinitis in AIDS patients. Valganciclovir is also licensed for preventing CMV disease following solid organ transplantation from a cytomegalovirus-positive donor. Foscarnet sodium is also active against cytomegalovirus; it is toxic and can cause renal impairment. See local treatment of CMV retinitis.
INOSINE COMPLEXES

Inosine pranobex
(Inosine acedoben dimepranol)

**INDICATIONS AND DOSE**

- **Mucocutaneous herpes simplex**
  - **BY MOUTH**
  - Adult: 1 g 4 times a day for 7–14 days
- **Adjunctive treatment of genital warts**
  - **BY MOUTH**
  - Adult: 1 g 3 times a day for 14–28 days
- **Subacute sclerosing panencephalitis**
  - **BY MOUTH**
  - Adult: 50–100 mg/kg daily in 6 divided doses

**CAUTIONS**

- History of gout · history of hyperuricaemia

**SIDE-EFFECTS**

- **Common or very common** Reversible increase in serum uric acid · reversible increase in urinary uric acid
- **Uncommon** Arthralgia · epigastric discomfort · fatigue · headache · itching · nausea · rashes · vertigo · vomiting
- **Rare** Anxiety · constipation · diarrhoea · polyuria · sleep disturbances

**PREGNANCY**

Manufacturer advises caution; metabolised to uric acid.

**LESS SUITABLE FOR PRESCRIBING**

Inosine pranobex is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 9

- **Imunovir** (KoRa Healthcare)
  - Inosine acedoben dimepranol 500 mg
  - Imunovir 500 mg tablets
  - 100 tablet [PO] £33.50

NUCLEOSIDE ANALOGUES

Aciclovir
(Acyclovir)

**INDICATIONS AND DOSE**

- **Herpes simplex, suppression**
  - **BY MOUTH**
  - Child 12–17 years: 400 mg twice daily, alternatively 200 mg 4 times a day; increased to 400 mg 3 times a day, dose may be increased if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation), therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
  - Adult: 400 mg twice daily, alternatively 200 mg 4 times a day; increased to 400 mg 3 times a day, dose may be increased if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation), therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
- **Herpes simplex, prophylaxis in the immunocompromised**
  - **BY MOUTH**
  - Child 1–2 years: 100–200 mg 4 times a day
  - Child 2–7 years: 200–400 mg 4 times a day
  - Adult: 200–400 mg 4 times a day

- **Herpes simplex, treatment (non-genital)**
  - **BY MOUTH**
  - Adult: 200 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
- **Herpes simplex, treatment (non-genital) in immunocompromised or if absorption impaired**
  - **BY MOUTH**
  - Adult: 400 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
- **Herpes simplex, treatment**
  - **BY MOUTH**
  - Child 1–2 years: 200 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
  - Child 2–13 years: 200 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
- **Herpes simplex, treatment, in immunocompromised or if absorption impaired**
  - **BY MOUTH**
  - Child 1–23 months: 100 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
  - Child 2–17 years: 400 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
- **Herpes simplex, treatment of first episode**
  - **BY MOUTH**
  - Adult: 200 mg 5 times a day, alternatively 400 mg 3 times a day both courses usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
- **Herpes simplex, treatment, in immunocompromised or HIV-positive**
  - **BY MOUTH**
  - Adult: 400 mg 5 times a day for 7–10 days (longer if new lesions appear during treatment or if healing incomplete)
- **Severe genital herpes simplex, treatment, initial infection**
  - **Treatment of herpes simplex in the immunocompromised**
  - **BY INTRAVENOUS INFUSION**
  - Adult: Initially 5 mg/kg every 8 hours usually for 5 days, alternatively 10 mg/kg every 8 hours for at least 14 days in encephalitis (at least 21 days if also immunocompromised)—confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment, higher dose to be used only if resistant organisms suspected or in simplex encephalitis
- **Varicella zoster (chickenpox), treatment | Herpes zoster (shingles), treatment**
  - **BY MOUTH**
  - Child 1–23 months: 200 mg 4 times a day for 5 days
  - Child 2–5 years: 400 mg 4 times a day for 5 days
  - Child 6–11 years: 800 mg 4 times a day for 5 days
  - Child 12–17 years: 800 mg 5 times a day for 7 days
  - Adult: 800 mg 5 times a day for 7 days
BY INTRAVENOUS INFUSION
- Adult: 5 mg/kg every 8 hours usually for 5 days

Varicella zoster (chickenpox), treatment in immunocompromised | Herpes zoster (shingles), treatment in immunocompromised
- BY INTRAVENOUS INFUSION
- Adult: 10 mg/kg every 8 hours usually for 5 days

Herpes zoster (shingles), treatment in immunocompromised
- BY MOUTH
- Child 1–23 months: 200 mg 4 times a day continued for 2 days after crusting of lesions
- Child 2–5 years: 400 mg 4 times a day continued for 2 days after crusting of lesions
- Child 6–11 years: 800 mg 4 times a day continued for 2 days after crusting of lesions
- Child 12–17 years: 800 mg 5 times a day continued for 2 days after crusting of lesions
- Adult: 800 mg 5 times a day continued for 2 days after crusting of lesions

Herpes zoster, treatment in encephalitis | Varicella zoster, treatment in encephalitis
- BY INTRAVENOUS INFUSION
- Adult: 10 mg/kg every 8 hours usually for 10–14 days in encephalitis, possibly longer if also immunocompromised or if severe infection

Varicella zoster (chickenpox), attenuation of infection if varicella–zoster immunoglobulin not indicated
- BY MOUTH
- Child: 10 mg/kg 4 times a day for 7 days, to be started 1 week after exposure
- Adult: 10 mg/kg 4 times a day for 7 days, to be started 1 week after exposure

DOSES AT EXTREMES OF BODY-WEIGHT
To avoid excessive dosage in obese patients parenteral dose should be calculated on the basis of ideal weight for height.

UNLICENSED USE Tablets and suspension not licensed for suppression of herpes simplex or for treatment of herpes zoster in children. Aciclovir doses in BNF may differ from those in product literature. Attenuation of chickenpox is an unlicensed indication.

CAUTIONS Elderly (risk of neurological reactions) - maintain adequate hydration (especially with infusion or high doses)

INTERACTIONS → Appendix 1 (aciclovir).

SIDE-EFFECTS
- Common or very common Abdominal pain, diarrhea, fatigue, headache, nausea, photosensitivity, pruritus, rash, urticaria, vomiting
- Very rare Acute renal failure, anaemia, ataxia, confusion, convulsions, dizziness, drowsiness, dysarthria, dyspnoea, hallucinations, hepatitis, jaundice, leucopenia, neurological reactions, thrombocytopenia
- With intravenous use Agitation, fever, psychosis, severe local inflammation (sometimes leading to ulceration), tremors

PREGNANCY Not known to be harmful — manufacturers advise use only when potential benefit outweighs risk.

BREAST FEEDING Significant amount in milk after systemic administration — not known to be harmful but manufacturer advises caution.

RENAL IMPAIRMENT
- With systemic use Risk of neurological reactions increased. Maintain adequate hydration (especially during renal impairment).
- With intravenous use Use normal intravenous dose every 12 hours if eGFR 25–50 mL/minute/1.73 m² (every 24 hours if eGFR 10–25 mL/minute/1.73 m²). Consult product literature for intravenous dose if eGFR less than 10 mL/minute/1.73 m².

With oral use in adults For herpes zoster, use normal oral dose every 8 hours if eGFR 10–25 mL/minute/1.73 m² (every 12 hours if eGFR less than 10 mL/minute/1.73 m²). For herpes simplex, use normal oral dose every 12 hours if eGFR less than 10 mL/minute/1.73 m².

With oral use in children For herpes zoster, use normal oral dose every 8 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m² (every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²).

For herpes simplex, use normal dose every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion Zovirax IV®, Aciclovir IV (Genus), give intermittently in Sodium chloride 0.9% or Sodium chloride and glucose; initially reconstitute to 25 mg/mL in water for injection or sodium chloride 0.9% then dilute to not more than 5 mg/mL with the infusion fluid; to be given over 1 hour; alternatively, may be administered in a concentration of 25 mg/mL using a suitable infusion pump and given over 1 hour; for Aciclovir IV (Hospira) dilute to not more than 5 mg/mL with infusion fluid; give over 1 hour.

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid preparations may include banana, or orange.

PATIENT AND CARER ADVICE Medicines for Children leaflet: Aciclovir (oral) for viral infections www.medicinesforchildren.org.uk/aciclovir-for-viral-infections

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ Formulary
Aciclovir Tablets 200 mg or 800 mg may be prescribed. Aciclovir Oral Suspension 200 mg/5mL may be prescribed.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

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Dispersible tablet

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Oral suspension

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<tr>
<td>Aciclovir 80 mg per 1 ml</td>
<td>Zovirax Double Strength 400mg/5ml oral suspension sugar-free</td>
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Famciclovir

- **INDICATIONS AND DOSE**
  - **Herpes zoster infection, treatment**
    - **BY MOUTH**
      - Adult: 500 mg 3 times a day for 7 days, alternatively 750 mg 1–2 times a day for 7 days
  - **Herpes zoster infection, treatment in immunocompromised patients**
    - **BY MOUTH**
      - Adult: 500 mg 3 times a day for 10 days, continue for 2 days after crusting of lesions
  - **Genital herpes, suppression**
    - **BY MOUTH**
      - Adult: 250 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
  - **Genital herpes, suppression in immunocompromised or HIV-positive patients**
    - **BY MOUTH**
      - Adult: 500 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
  - **Genital herpes infection, treatment of first episode**
    - **BY MOUTH**
      - Adult: 250 mg 3 times a day for 5 days or longer if new lesions appear during treatment or if healing incomplete
  - **Genital herpes infection, treatment of first episode in immunocompromised or HIV-positive patients**
    - **BY MOUTH**
      - Adult: 500 mg twice daily for 10 days
  - **Genital herpes infection, treatment of recurrent infection**
    - **BY MOUTH**
      - Adult: 125 mg twice daily for 5 days, alternatively 1 g twice daily for 1 day
  - **Genital herpes infection, treatment of recurrent infections in immunocompromised or HIV-positive patients**
    - **BY MOUTH**
      - Adult: 500 mg twice daily for 5–10 days

- **Herpes simplex infection (non-genital), treatment in immunocompromised patients**
  - **BY MOUTH**
    - Adult: 500 mg twice daily for 7 days

- **SIDE-EFFECTS**
  - Common or very common: Headache, nausea, vomiting
  - Rare: Confusion
  - Very rare: Dizziness, drowsiness, hallucinations, jaundice, rash, Stevens-Johnson syndrome, thrombocytopenia
  - Frequency not known: Constipation, abdominal pain, diarrhea, fatigue, fever, pruritus, sweating
  - **PREGNANCY** Manufacturers advise avoid unless potential benefit outweighs risk.
  - **BREAST FEEDING** No information available—present in milk in animal studies.
  - **HEPATIC IMPAIRMENT** Usual dose in well compensated liver disease (information not available on decompensated).
  - **RENAL IMPAIRMENT** Reduce dose; consult product literature.
  - **PRESCRIBING AND DISPENSING INFORMATION** Famciclovir is a pro-drug of penciclovir.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

  **Tablet**

  **CAUTIONARY AND ADVISORY LABELS 9**

  - Famciclovir (Non-proprietary)
  - Famciclovir 125 mg Famciclovir 125 mg tablets | 10 tablet [POM] £37.12 DT price = £36.29
  - Famciclovir 250 mg Famciclovir 250 mg tablets | 15 tablet [POM] £115.87 DT price = £115.43 | 56 tablet [POM] £407.60 | £415.67
  - Famiclovir 500 mg Famciclovir 500 mg tablets | 14 tablet [POM] £207.86 DT price = £206.86 | 30 tablet [POM] £345.45 | £345.28
  - Famvir (Novartis Pharmaceuticals UK Ltd)
  - Famciclovir 125 mg Famvir 125 mg tablets | 10 tablet [POM] £53.45 DT price = £53.29
  - Famciclovir 250 mg Famvir 250 mg tablets | 15 tablet [POM] £187.04 DT price = £186.86 | 56 tablet [POM] £598.56
  - Famciclovir 500 mg Famvir 500 mg tablets | 14 tablet [POM] £249.43 DT price = £248.86 | 30 tablet [POM] £614.21

Valaciclovir

- **INDICATIONS AND DOSE**
  - **Herpes zoster infection, treatment**
    - **BY MOUTH**
      - Adult: 1 g 3 times a day for 7 days
  - **Herpes zoster infection, treatment in immunocompromised patients**
    - **BY MOUTH**
      - Adult: 1 g 3 times a day for at least 7 days and continued for 2 days after crusting of lesions
  - **Herpes simplex, treatment of first infective episode**
    - **BY MOUTH**
      - Adult: 500 mg twice daily for 5 days (longer if new lesions appear during treatment or healing is incomplete)
  - **Herpes simplex infections treatment of first episode in immunocompromised or HIV-positive patients**
    - **BY MOUTH**
      - Adult: 1 g twice daily for 10 days
  - **Herpes simplex, treatment of recurrent infections**
    - **BY MOUTH**
      - Adult: 500 mg twice daily for 3–5 days
  - **Treatment of recurrent herpes simplex infections in immunocompromised or HIV-positive patients**
    - **BY MOUTH**
      - Adult: 1 g twice daily for 5–10 days continued 

- **UNLICENSED USE** Famciclovir doses in BNF may differ from those in product literature.
- **INTERACTIONS** ➔ Appendix 1 (famciclovir).
Herpes labialis treatment

- BY MOUTH
  - Child 12–17 years: Initially 2 g, then 2 g after 12 hours
  - Adult: Initially 2 g, then 2 g after 12 hours

Herpes simplex, suppression of infections

- BY MOUTH
  - Adult: 500 mg daily in 1–2 divided doses, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

Herpes simplex, suppression of infections in immunocompromised or HIV-positive patients

- BY MOUTH
  - Adult: 500 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

Genital herpes, reduction of transmission (administered on expert advice)

- BY MOUTH
  - Adult: 500 mg once daily, to be taken by the infected partner

Prevention of cytomegalovirus disease following solid organ transplantation when valganciclovir or ganciclovir cannot be used

- BY MOUTH
  - Adult: 2 g 4 times a day usually for 90 days, preferably starting within 72 hours of transplantation

- CAUTIONS Elderly (risk of neurological reactions) • maintain adequate hydration (especially with high doses)

- INTERACTIONS ➔ Appendix 1 (valaciclovir).

- SIDE-EFFECTS
  - Very rare: Acute renal failure • anaemia • ataxia • confusion • convulsions • dizziness • drowsiness • dysarthria • dysphonia • hallucinations • hepatitis • jaundice • leucopenia • neurological reactions • thrombocytopenia
  - Frequency not known: Abdominal pain • diarrhoea • fatigue • headache • nausea • photosensitivity • pruritus • rash • urticaria • vomiting

SIDE-EFFECTS, FURTHER INFORMATION

- Neurological reactions: Neurological reactions (including dizziness, confusion, hallucinations, convulsions, ataxia, dysarthria, and drowsiness) more frequent with higher doses.

- PREGNANCY Not known to be harmful—manufacturers advise use only when potential benefit outweighs risk.

- BREAST FEEDING Significant amount in milk after systemic administration—not known to be harmful but manufacturer advises caution.

- HEPATIC IMPAIRMENT Manufacturer advises caution with high doses used for herpes labialis and prevention of cytomegalovirus disease—no information available.

- RENAL IMPAIRMENT
  - In adults: For herpes zoster, 1 g every 12 hours if eGFR 30–50 mL/minute/1.73 m² (1 g every 24 hours if eGFR 10–30 mL/minute/1.73 m²; 500 mg every 24 hours if eGFR less than 10 mL/minute/1.73 m²). For treatment of herpes simplex, 500 mg (1 g in immunocompromised or HIV-positive patients) every 24 hours if eGFR less than 30 mL/minute/1.73 m². For treatment of herpes labialis, if eGFR 30–50 mL/minute/1.73 m², initially 1 g, then 1 g 12 hours after initial dose (if eGFR 10–30 mL/minute/1.73 m², initially 500 mg, then 500 mg 12 hours after initial dose; if eGFR less than 10 mL/minute/1.73 m², 500 mg as a single dose). For suppression of herpes simplex, 250 mg (500 mg in immunocompromised or HIV-positive patients) every 24 hours if eGFR less than 30 mL/minute/1.73 m². For reduction of genital herpes transmission, 250 mg every 24 hours if eGFR less than 15 mL/minute/1.73 m². Reduce dose according to eGFR for cytomegalovirus prophylaxis following solid organ transplantation (consult product literature).
  - In children: For treatment of herpes labialis, if estimated glomerular filtration rate 30–50 mL/minute/1.73 m², initially 1 g, then 1 g 12 hours after initial dose (if estimated glomerular filtration rate 10–30 mL/minute/1.73 m², initially 500 mg, then 500 mg 12 hours after initial dose; if estimated glomerular filtration rate less than 10 mL/minute/1.73 m², 500 mg as a single dose).

- PRESCRIBING AND DISPENSING INFORMATION Valaciclovir is a pro-drug of aciclovir.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 9

- Valaciclovir (Non-proprietary)
  - Valaciclovir (as Valaciclovir hydrochloride) 500 mg Valaciclovir 500mg tablets | 10 tablet (PoT) £20.59 DT price = £3.18 | 42 tablet (PoT) £86.30
  - Valtrex (GlaxoSmithKline Ltd)
    - Valaciclovir (as Valaciclovir hydrochloride) 250 mg Valtrex 250mg tablets | 60 tablet (PoT) £123.28 DT price = £123.28
    - Valaciclovir (as Valaciclovir hydrochloride) 500 mg Valtrex 500mg tablets | 10 tablet (PoT) £20.59 DT price = £3.18 | 42 tablet (PoT) £86.30

6.3a Cytomegalovirus infections

ANTIVIRALS ➔ NUCLEOSIDE ANALOGUES

Ganciclovir

- INDICATIONS AND DOSE
  - Prevention of cytomegalovirus disease during immunosuppressive therapy following organ transplantation
    - BY INTRAVENOUS INFUSION
      - Adult: 5 mg/kg every 12 hours for 7–14 days
  - Treatment of life-threatening or sight-threatening cytomegalovirus infections in immunocompromised patients only
    - BY INTRAVENOUS INFUSION
      - Adult: Initially 5 mg/kg every 12 hours for 14–21 days, followed by maintenance 6 mg/kg daily on 5 days of the week, alternatively 5 mg/kg daily until adequate recovery of immunity, maintenance only for patients at risk of relapse of retinitis, if retinitis progresses initial induction treatment may be repeated

- CONTRA-INDICATIONS Abnormally low haemoglobin count (consult product literature) • abnormally low neutrophil count (consult product literature) • abnormally low platelet count (consult product literature)

- CAUTIONS Children (possible risk of long-term carcinogenic or reproductive toxicity) • ensure adequate hydration • history of cytopenia • potential carcinogen • potential teratogen • radiotherapy • vesicant

- INTERACTIONS ➔ Appendix 1 (ganciclovir).
  - Increased risk of myelosuppression with other myelosuppressive drugs—consult product literature.

- SIDE-EFFECTS
  - Common or very common: Abdominal pain • abnormal thinking • anaemia • anorexia • anxiety • arthralgia • chest pain • confusion • constipation • convulsions • cough • depression • dermatitis • diarrhoea • dizziness • dyspepsia • dysphagia • dysphonia • ear pain • eye pain • fatigue •
flatulence • headache • hepatic dysfunction • infection • injection-site reactions • insomnia • leucopenia • macular oedema • myalgia • nausea • night sweats • pancytopenia • peripheral neuropathy • pruritus • pyrexia • renal impairment • retinal detachment • taste disturbance • thrombocytopenia • vitreous floaters • vomiting • weight loss

Uncommon Alopecia • anaphylactic reactions • arrhythmias • disturbances in hearing and vision • haematuria • hypotension • male infertility • mouth ulcers • pancreatitis • psychosis • tremor

Allergy and Cross-sensitivity Contra-indicated in patients hypersensitive to valganciclovir, aciclovir, or valaciclovir.

Conception and Contraception Ensure effective contraception during treatment and barrier contraception for men during and for at least 90 days after treatment.

Pregnancy Avoid—teratogenic risk.

Breast Feeding Avoid—no information available.

Renal Impairment Reduce dose if eGFR less than 70 mL/minute/1.73 m²; consult product literature.

Monitoring Requirements Monitor full blood count closely (severe deterioration may require correction and possibly treatment interruption).

Directions for Administration Infuse into vein with adequate flow preferably using plastic cannula. For intravenous infusion (Cymevene®) give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially in water for injections (500 mg/10 mL then dilute to not more than 10 mg/mL with infusion fluid (usually 100 mL); give over 1 hour.

Handling and Storage Caution in handling. Ganciclovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with soap and water.

Medicinal Forms There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion electrolytes: May contain Sodium

Cymevene (Roche Products Ltd)
Ganciclovir (as Ganciclovir sodium) 500 mg

Powder for solution for infusion vials | 5 vial £148.83

Valganciclovir

Indications and Dose

Cytomegalovirus retinitis, induction and maintenance treatment in patients with AIDS

By mouth

Adult: Initially 900 mg twice daily for 21 days, then 900 mg daily, induction regimen may be repeated if retinitis progresses

Prevention of cytomegalovirus disease following solid organ transplantation from a cytomegalovirus positive donor

By mouth

Adult: 900 mg daily for 100 days (for 100–200 days following kidney transplantation), to be started within 10 days of transplantation

Dose Equivalence and Conversion

Oral valganciclovir 900 mg twice daily is equivalent to intravenous ganciclovir 5 mg/kg twice daily.

Contra-indications

Abnormally low haemoglobin count (consult product literature) • abnormally low neutrophil count (consult product literature) • abnormally low platelet count (consult product literature)

Caution

Children (possible risk of long-term carcinogenic or reproductive toxicity) • history of cytopenia • potential carcinogen • potential teratogen • radiotherapy

Interactions

Appendix 1 (valganciclovir).

Side-effects

Common or very common Abdominal pain • abnormal thinking • anaemia • anxiety • arthralgia • chest pain • confusion • constipation • convulsions • cough • depression • dermatitis • diarrhoea • dizziness • dyspepsia • dysphagia • dyspnoea • ear pain • eye pain • fatigue • flatulence • headache • hepatic dysfunction • infection • insomnia • leucopenia • macular oedema • myalgia • nausea • night sweats • pancytopenia • peripheral neuropathy • pruritus • pyrexia • renal impairment • retinal detachment • taste disturbance • thrombocytopenia • vitreous floaters • vomiting • weight loss

Uncommon Alopecia • anaphylactic reactions • arrhythmias • disturbances in hearing • disturbances in vision • haematuria • hypotension • male infertility • mouth ulcers • pancreatitis • psychosis • tremor

Allergy and Cross-sensitivity Contra-indicated in patients hypersensitive to ganciclovir, aciclovir, or valaciclovir.

Conception and Contraception Ensure effective contraception during treatment and barrier contraception for men during and for at least 90 days after treatment.

Pregnancy Avoid—teratogenic risk.

Breast Feeding Avoid—no information available.

Renal Impairment Reduce dose, consult product literature.

Monitoring Requirements Monitor full blood count closely (severe deterioration may require correction and possibly treatment interruption).

Prescribing and Dispensing Information Valganciclovir is a pro-drug of ganciclovir. Flavours of oral liquid formulations may include tutti-frutti.

Handling and Storage Caution in handling. Valganciclovir is a potential teratogen and carcinogen and caution is advised when handling the powder, reconstituted solution, or broken tablets; if these come into contact with skin or mucosa, wash off immediately with water; avoid inhalation of powder.

Medicinal Forms There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

Cautionary and Advisory Labels 21

Valcyte (Roche Products Ltd)
Valganciclovir (as Ganciclovir hydrochloride) 450 mg

Valcyte 450mg tablets | 60 tablet £1,081.46

Oral solution

Cautionary and Advisory Labels 21

Valcyte (Roche Products Ltd)
Valganciclovir (as Ganciclovir hydrochloride) 50 mg per

1 ml Valcyte 50mg/ml oral solution sugar-free | 100 ml £230.32

AntiViralS

Foscarnet sodium

Indications and Dose

Cytomegalovirus disease

By intravenous infusion

Adult: Initially 60 mg/kg every 8 hours for 2–3 weeks, alternatively initially 90 mg/kg every 12 hours for 2–3 weeks, then maintenance continued
60 mg/kg daily, then increased if tolerated to 90–120 mg/kg daily, if disease progresses on maintenance dose, repeat induction regimen

Mucocutaneous herpes simplex virus infections unresponsive to aciclovir in immunocompromised patients

- By intravenous infusion
- Adult: 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal

**UNLICENSED USE** Licensed for CMV retinitis in AIDS patients only. Foscarnet doses in BNF may differ from those in product literature.

**CAUTIONS** Ensure adequate hydration

**INTERACTIONS** → Appendix 1 (foscarnet).

**SIDE-EFFECTS**

- Common or very common Abdominal pain, acute renal failure, aggression, agitation, anaemia, anorexia, anxiety, changes in blood pressure, changes in ECG, confusion, constipation, convulsions, depression, diarrhoea, dizziness, dyspepsia, dysuria, electrolyte disturbances, genital irritation and ulceration (due to high concentrations excreted in urine), granulocytopenia, headache, hepatic dysfunction, hypocalcaemia, hypokalaemia, hypomagnesaemia, leucopenia, malaise, myalgia, nausea (reduce infusion rate), neurological disorders, oedema, palpitation, pancreatitis, paraesthesia (reduce infusion rate), polyuria, pruritus, rash, renal impairment, thrombocytopenia, thrombophlebitis if given undiluted by peripheral vein, tremor, vomiting

- Uncommon Acidosis

- Frequency not known Diabetes insipidus, myasthenia, myositis, oesophageal ulceration, rhabdomyolysis, ventricular arrhythmias

**CONCEPTION AND CONTRACEPTION** Men should avoid fathering a child during and for 6 months after treatment.

**PREGNANCY** Manufacturer advises avoid.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**RENAL IMPAIRMENT** Reduce dose; consult product literature.

**MONITORING REQUIREMENTS**

- Monitor electrolytes, particularly calcium and magnesium.
- Monitor serum creatinine every second day during induction and every week during maintenance.

**DIRECTIONS FOR ADMINISTRATION** Avoid rapid infusion. For intravenous infusion (Foscavir®), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of 12 mg/mL for infusion into peripheral vein (undiluted solution via central venous line only); infuse over at least 1 hour (infuse doses greater than 60 mg/kg over 2 hours).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Electrolytes:** May contain sodium
- **Foscarnet sodium 24 mg per 1 ml** Foscavir® (Clinigent Healthcare Ltd)
  - Foscavir 6g/250ml solution for infusion bottles | 1 bottle | £119.85 (Hospital only)

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### 6.4 HIV infection

#### HIV infection

**Overview**

There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs slow or halt disease progression. Drugs for HIV infection (antiretrovirals) may be associated with serious side-effects. Although antiretrovirals increase life expectancy considerably and decrease the risk of complications associated with premature ageing, mortality and morbidity remain slightly higher than in uninfected individuals. Treatment should be undertaken only by those experienced in their use.

**Principles of treatment**

Treatment aims to prevent the mortality and morbidity associated with chronic HIV infection whilst minimising drug toxicity. Although it should be started before the immune system is irreversibly damaged, the need for early drug treatment should be balanced against the risk of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and patient tolerance. The development of drug resistance is reduced by using a combination of drugs; such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.

Treatment also reduces the risk of HIV transmission to sexual partners, but the risk is not eliminated completely; this risk and strategies to reduce HIV transmission should be discussed with patients and their sexual partners.

**Initiation of treatment**

The optimum time for initiating antiretroviral treatment depends primarily on the CD4 cell count. The timing and choice of treatment should also take account of clinical symptoms, comorbidities, and the possible effect of antiretroviral drugs on factors such as the risk of cardiovascular events. Treatment includes a combination of drugs known as ‘highly active antiretroviral therapy’.

Treatment of HIV-1 infection is initiated with 2 nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor, or an integrase inhibitor; the regimens of choice contain tenofovir disoproxil p. 599 and emtricitabine p. 598 with either efavirenz p. 593 or ritonavir-boosted atazanavir p. 602, or ritonavir-boosted darunavir p. 602, or ritavgravir p. 593. Alternative regimens contain abacavir p. 596 and lamivudine p. 598 with either lopinavir with ritonavir p. 604, or ritonavir-boosted fosamprenavir p. 603, or nevirapine p. 594, or rilpivirine p. 595. Patients who require treatment for both HIV and chronic hepatitis B should be treated with antivirals active against both diseases.

**Switching therapy**

Deterioration of the condition (including clinical and virological changes) may require a change in therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance.

**Pregnancy**

Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although information on the teratogenic potential of most antiretroviral drugs is limited), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. All treatment options require careful assessment by a specialist. Combination antiretroviral therapy maximises the chance of preventing transmission and represents optimal therapy for the mother. However, it may be associated with a greater risk of preterm delivery. Pregnancies in HIV-positive women and babies born to them should be reported prospectively to the National Study of HIV in Pregnancy and Childhood at www.ucl.ac.uk/nshpc/
and to the Antiretroviral Pregnancy Registry at www.apregistry.com.

Breast-feeding
Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

Post-exposure prophylaxis
Prophylaxis with antiretroviral drugs [unlicensed indication] may be appropriate following exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed (by the Chief Medical Officer’s Expert Advisory Group on AIDS), www.gov.uk/dh and local ones may also be available. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity. Prompt prophylaxis with antiretroviral drugs [unlicensed indication] is also appropriate following potential sexual exposure to HIV; recommendations have been developed by the British Association for Sexual Health and HIV, www.bashh.org.

Drugs for HIV infection
Zidovudine p. 601, a nucleoside reverse transcriptase inhibitor (or ‘nucleoside analogue’), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include abacavir, didanosine p. 597, emtricitabine, lamivudine, stavudine p. 598, and tenofovir disoproxil.

The protease inhibitors include atazanavir, darunavir, fosamprenavir (a pro-drug of amprenavir), indinavir p. 603, lopinavir (available as lopinavir with ritonavir), ritonavir, saquinavir p. 605, and tipranavir p. 605. Indinavir is rarely used in the treatment of HIV-infection because it is associated with nephrolithiasis. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, indinavir, lopinavir (available as lopinavir with ritonavir), saquinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects.

The non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine p. 594, nevirapine, and rilpivirine are used in the treatment of HIV-1 infection, but not against the subtype HIV-2, a subtype that is rare in the UK. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz and etravirine but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz; CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz has also been associated with an increased plasma-cholesterol concentration. Etravirine is used in regimens containing a boosted protease inhibitor for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Enfuvirtide below, which inhibits the fusion of HIV to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide should be combined with other potentially active antiretroviral drugs.

Maraviroc p. 606 is an antagonist of the CCR5 chemokine receptor. It is licensed for patients exclusively infected with CCR5-tropic HIV.

Dolutegravir p. 592, elvitegravir p. 592 and raltegravir are inhibitors of HIV integrase. They are licensed for the treatment of HIV infection in combination with other antiretroviral drugs.

Cobicistat p. 606 is a pharmacokinetic enhancer that boosts the concentrations of other antiretrovirals, but it has no antiretroviral activity itself.

Immune reconstitution syndrome
Improvement in immune function as a result of antiretroviral treatment may provoke a marked inflammatory reaction against residual opportunistic organisms; these reactions may occur within the first few weeks or months of initiating treatment. Autoimmune disorders (such as Graves’ disease) have also been reported many months after initiation of treatment.

Osteonecrosis
Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

HIV infection in children
HIV disease in children has a different natural progression to adults. Children infected with HIV should be managed within a formal paediatric HIV clinical network by specialists with access to guidelines and information on antiretroviral drugs for children.

ANTIVIRALS > HIV-FUSION INHIBITORS

Enfuvirtide
- **DRUG ACTION** Enfuvirtide inhibits the fusion of HIV to the host cell.
- **INDICATIONS AND DOSE** HIV infection in combination with other antiretroviral drugs for resistant infection or for patients intolerant to other antiretroviral regimens
  - By subcutaneous injection
  - Adult: 90 mg twice daily
- **INTERACTIONS** > Appendix 1 (enfuvirtide).
- **SIDE-EFFECTS**
  - Common or very common Acne · anorexia · anxiety · asthenia · conjunctivitis · diabetes mellitus · dry skin · erythema · gastro-oesophageal reflux disease · haematuria · hypertriglyceridaemia · impaired concentration · influenza-like illness · injection-site reactions · irritability · lymphadenopathy · myalgia · nightmares · pancreatitis · peripheral neuropathy · pneumonia · renal calculi · sinusitis · skin papilloma · tremor · vertigo · weight loss
  - Uncommon Hypersensitivity reactions
  - Frequency not known Osteonecrosis
- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Hypersensitivity reactions Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported; discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge.
  - Osteonecrosis For further information see HIV infection p. 590.
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution— no information available; chronic hepatitis B or C (possibly greater risk of hepatic side-effects).
- **DIRECTIONS FOR ADMINISTRATION** For subcutaneous injection, reconstitute with 1.1 mL Water for Injections and allow to stand (for up to 45 minutes) to dissolve; do not shake or invert vial.
- **PATIENT AND CARER ADVICE** Hypersensitivity reactions Patients or carers should be told how to recognise signs of hypersensitivity, and advised to...
Infection

PATIENT AND CARER ADVICE

DIRECTIONS FOR ADMINISTRATION

HEPATIC IMPAIRMENT

PREGNANCY

▶ Osteonecrosis

Hypersensitivity reactions

▶ Uncommon

Common or very common

INTERACTIONS

▶ >> Appendix 1 (dolutegravir).

Caution—avoid concomitant use with etravirine, unless used in combination with atazanavir, darunavir, or lopinavir.

SIDE-EFFECTS

▶ Common or very common Abdominal pain · abnormal dreams · diarrhoea · dizziness · fatigue · flatulence · headache · insomnia · nausea · pruritus · raised creatine kinase · rash · vomiting

▶ Uncommon Hepatitis · hypersensitivity reactions

▶ Frequency not known Osteonecrosis

SIDE-EFFECTS, FURTHER INFORMATION

Hypersensitivity reactions Hypersensitivity reactions (including severe rash, or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, oral lesions, conjunctivitis, angioedema, eosinophilia, or raised liver enzymes) reported uncommonly. Discontinue immediately if any sign or symptoms of hypersensitivity reactions develop.

Osteonecrosis For further information see HIV infection p. 590.

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment—no information available.

DIRECTIONS FOR ADMINISTRATION Avoid antacids 6 hours before or 2 hours after taking dolutegravir.

PATIENT AND CARER ADVICE

Missed doses

If a dose is more than 20 hours late on the once daily regimen (or more than 8 hours late on the twice daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time.

Patients or carers should be given advice on how to administer dolutegravir tablets.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

ELECTROLYTES: May contain Sodium

▶ Fuzeon (Roche Products Ltd)

Enfuvirtide 108 mg Fuzeon 108mg powder and solvent for solution for injection via 60 vial £1,081.57

ANTIVIRALS > HIV-INTEGRASE INHIBITORS

Dolutegravir

DRUG ACTION Dolutegravir is an inhibitor of HIV integrase.

INDICATIONS AND DOSE

HIV infection without resistance to other inhibitors of HIV integrase, in combination with other antiretroviral drugs

▶ BY MOUTH

Adult: 50 mg once daily

HIV infection in patients where resistance to other inhibitors of HIV integrase suspected, in combination with other antiretroviral drugs

▶ BY MOUTH

Adult: 50 mg twice daily, dose to be taken with food

HIV infection in combination with other antiretroviral drugs (with concomitant carbamazepine, efavirenz, etravirine (without boosted protease inhibitors, but see also Interactions), fosphenytoin, phenobarbital, phenytoin, primidone, nevirapine, oxcarbazepine, St John’s wort, rifampicin, or tipranavir)

▶ BY MOUTH

Adult: 50 mg twice daily, avoid concomitant use with these drugs if resistance to other inhibitors of HIV integrase suspected

INTERACTIONS → Appendix 1 (dolutegravir).

ELVITEGRAVIR

DRUG ACTION Elvitegravir is an inhibitor of HIV integrase, which is an enzyme required for viral replication.

INDICATIONS AND DOSE

HIV infection without resistance to other inhibitors of HIV integrase, in combination with low-dose ritonavir and atazanavir or lopinavir

▶ BY MOUTH

Adult: 85 mg once daily, take at the same time as a once daily ritonavir-boosted regimen or with the first dose of a twice daily ritonavir-boosted regimen

HIV infection without resistance to other inhibitors of HIV integrase, in combination with low-dose ritonavir and darunavir or fosamprenavir

▶ BY MOUTH

Adult: 150 mg once daily, take with the first dose of a twice daily ritonavir-boosted regimen

CAUTIONS Elderly—limited information available

INTERACTIONS → Appendix 1 (elvitegravir).

SIDE-EFFECTS

▶ Common or very common Diarrhoea · fatigue · headache · nausea · rash · vomiting

▶ Uncommon Abdominal distension · depression · dizziness · dysgeusia · dyspepsia · flatulence · insomnia · paraesthesia · somnolence · suicidal ideation (in patients with history of depression or psychiatric illness)

▶ Frequency not known Hyperglycaemia · increased blood lipids · osteonecrosis · weight gain

SIDE-EFFECTS, FURTHER INFORMATION

Osteonecrosis For further information see HIV infection p. 590.

PREGNANCY Manufacturer advises use with caution in severe impairment—no information available.

HEPATIC IMPAIRMENT Manufacturer advises use with caution in severe impairment—no information available.

Use with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects).

PATIENT AND CARER ADVICE

Missed doses

Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. If vomiting occurs within 1 hour of taking a dose, a replacement dose should be taken.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

▶ Vitekta (Gilead Sciences International Ltd)

Elvitegravir 85 mg Vitekta 85mg tablets | 30 tablet £523.79

Elvitegravir 150 mg Vitekta 150mg tablets | 30 tablet £523.79
Raltegravir

**DRUG ACTION** Raltegravir is an inhibitor of HIV integrase.

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**

- **BY MOUTH USING TABLETS**
  - Adult: 400 mg twice daily

**DOSE EQUIVALENCE AND CONVERSION**

- The bioavailability of Isentress® chewable tablets is higher than that of the 'standard' 400 mg tablets; the chewable tablets are not interchangeable with the 'standard' tablets on a milligram-for-milligram basis.

**CAUTIONS**

Psychiatric illness (may exacerbate underlying illness including depression) - risk factors for myopathy - risk factors for rhabdomyolysis

**INTERACTIONS** → Appendix 1 (raltegravir).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - abnormal dreams - asthenia - depression - diarrhoea - dizziness - dyspepsia - flatulence - headache - hyperactivity - hypertiglyceridaemia - insomnina - nausea - rash - vomiting


- **Frequency not known** Osteonecrosis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Rash Rash occurs commonly. Discontinue if severe rash or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, mouth ulceration, conjunctivitis, angioedema, hepatitis, or eosinophilia.

- Lipodystrophy syndrome For further information see HIV infection p. 590.

- Osteonecrosis For further information see HIV infection p. 590.

**PREGNANCY** Manufacturer advises avoid — toxicity in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment — no information available. Use with caution in patients with chronic hepatitis B or C (at greater risk of hepatic side-effects).

**PRESCRIBING AND DISPENSING INFORMATION** Dispense raltegravir chewable tablets in original container (contains desiccant).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (April 2010) that raltegravir (Isentress®) is accepted for restricted use within NHS Scotland for the treatment of HIV infection when non-nucleoside reverse transcriptase inhibitors or protease inhibitors cannot be used because of intolerance, drug interactions, or resistance.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

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<td>Isentress (Merck Sharp &amp; Dohme Ltd)</td>
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**RALTEGRAVIR**

**ANTIVIRALS** → NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

**Efavirenz**

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**

- **BY MOUTH USING CAPSULES**
  - Adult: 600 mg once daily

**DOSE EQUIVALENCE AND CONVERSION**

- The bioavailability of Sustiva® oral solution is lower than that of the capsules and tablets; the oral solution is not interchangeable with either capsules or tablets on a milligram-for-milligram basis.

**UNLICENSED USE** Opening capsules and adding contents to food is an unlicensed method of administration.

**CAUTIONS** Acute porphyrias p. 930. Elderly. History of psychiatric disorders. History of seizures

**INTERACTIONS** → Appendix 1 (efavirenz).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - abnormal dreams - anxiety - depression - diarrhoea - dizziness - fatigue - headache - impaired concentration - nausea - pruritus - rash - sleep disturbances - Stevens-Johnson syndrome - vomiting

- **Uncommon** Amnesia - ataxia - blurred vision - convulsions - flushing - gynaecomastia - hepatitis - hypersensitivity - mania - pancreatitis - psychosis - suicidal ideation - tinnitus - tremor - vertigo

- **Rare** Hepatic failure - photosensitivity - suicide

- **Frequency not known** Lipodystrophy syndrome - osteonecrosis - raised serum cholesterol

**SIDE-EFFECTS, FURTHER INFORMATION**

- Rash Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption — usually resolves within 1 month.

- CNS effects Administration at bedtime especially in first 2–4 weeks reduces CNS effects.

- Lipodystrophy syndrome For further information see HIV infection p. 590.

- Osteonecrosis For further information see HIV infection p. 590.

- Immune Reconstitution Syndrome For further information see HIV infection p. 590.

**PREGNANCY** Reports of neural tube defects when used in first trimester.

**HEPATIC IMPAIRMENT** Greater risk of hepatic side-effects in chronic hepatitis B or C. Avoid in moderate to severe impairment. In mild liver disease, monitor for dose related side-effects (e.g. CNS effects) and monitor liver function.

**RENAL IMPAIRMENT** Manufacturer advises caution in severe renal failure — no information available.
Etravirine

- **INDICATIONS AND DOSE**
  HIV infection resistant to other non-nucleoside reverse transcriptase inhibitor and protease inhibitors in combination with other antiretroviral drugs (including a boosted protease inhibitor)
  - **BY MOUTH**
  - Adult: 200 mg twice daily, to be taken after food

- **CONTRA-INDICATIONS**
  Acute porphyrias p. 930

- **INTERACTIONS**
  → Appendix 1 (etravirine).

- **SIDE-EFFECTS**
  - Common or very common
    - Abdominal pain · anaemia · diabetes · flatulence · gastritis · gastro-oesophageal reflux · hyperlipidaemia · hypertension · Lipodystrophy Syndrome · myocardial infarction · nausea · peripheral neuropathy · rash · renal failure
  - Uncommon
    - Angina · blurred vision · bronchospasm · drowsiness · dry mouth · gynaecomastia · haematemesis · hepatitis · malaise · pancreatitis · sweating
  - Rare
    - Stevens-Johnson syndrome
  - Very rare
    - Toxic epidermal necrolysis
  - Frequency not known
    - Haemorrhagic stroke · hypersensitivity reactions · osteonecrosis

SIDE-EFFECTS, FURTHER INFORMATION
Hypersensitivity reactions Rash, usually in the second week, is the most common side-effect and appears more frequently in females. Life-threatening hypersensitivity reactions reported usually during week 3–6 of treatment and characterised by rash, eosinophilia, and systemic symptoms (including fever, general malaise, myalgia, arthralgia, blistering, oral lesions, conjunctivitis, and hepatitis). Discontinue permanently if hypersensitivity reaction or severe rash develop. If rash mild or moderate (without signs of hypersensitivity reaction), may continue without interruption—usually resolves within 2 weeks.

- **Lipodystrophy** For further information see HIV infection p. 590.
- **Osteonecrosis** For further information see HIV infection p. 590.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in moderate impairment; avoid in severe impairment—no information available; greater risk of hepatic side-effects in chronic hepatitis B or C.

- **DIRECTIONS FOR ADMINISTRATION**
  Patients with swallowing difficulties may disperse tablets in a glass of water just before administration.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Dispense in original container (contains desiccant).

- **PATIENT AND CARER ADVICE**
  Hypersensitivity reactions Patients or carers should be told how to recognise hypersensitivity reactions and advised to seek immediate medical attention if hypersensitivity reaction or severe rash develop.

Missed doses
If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Nevirapine

- **INDICATIONS AND DOSE**
  HIV infection in combination with other antiretroviral drugs (initial dose)
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 200 mg once daily for first 14 days, initial dose titration using ‘immediate-release’ preparation should not exceed 28 days; if rash occurs and is not resolved within 28 days, alternative treatment should be sought. If treatment interrupted for more than 7 days, restart using the lower dose of the ‘immediate-release’ preparation for the first 14 days as for new treatment

**HIV infection in combination with other antiretroviral drugs (maintenance dose following initial dose titration if no rash present)**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 200 mg twice daily
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 400 mg once daily

- **CONTRA-INDICATIONS**
  Acute porphyrias p. 930 · post-exposure prophylaxis

- **CAUTIONS**
  Females (at greater risk of hepatic side effects) · high CD4 cell count (at greater risk of hepatic side effects)

- **CAUTIONS, FURTHER INFORMATION**
  Hepatic effects Patients with chronic hepatitis B or C, high CD4 cell count, and women are at increased risk of hepatic side effects—if plasma HIV-1 RNA detectable, manufacturer advises avoid in women with CD4 cell count greater than 250 cells/mm³ or in men with CD4 cell count greater than 400 cells/mm³ unless potential benefit outweighs risk.
Rilpivirine

28-Sep-2016

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy and if plasma HIV-1 RNA concentration less than or equal to 100 000 copies/mL

- **BY MOUTH**
  - Adult: 25 mg once daily

**INTERACTIONS** → Appendix 1 (rilpivirine).

**SIDE-EFFECTS**

- Abdominal pain - diarrhoea - fatigue - fever - granulocytopenia - headache - hepatitis - hypersensitivity reactions (may involve hepatic reactions and rash) - nausea - rash - Stevens-Johnson syndrome - toxic epidermal necrolysis - vomiting

- **Uncommon** Anaemia - arthralgia - myalgia

- **Frequency not known** Osteonecrosis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Hepatic effects Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in first 6 weeks; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction.

- Rash Rash, usually in first 6 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased gradually (after 14 days); Discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves.

- Osteonecrosis For more information see HIV infection p. 590.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid modified-release preparation—no information available; use ‘immediate-release’ preparation with caution in moderate impairment and avoid in severe impairment. Use with caution in patients with chronic hepatitis B or C (at greater risk of hepatic side effects).

**RENAL IMPAIRMENT** Manufacturer advises avoid modified-release preparation—no information available.

**MONITORING REQUIREMENTS**

- Hepatic disease Close monitoring of liver function required during first 18 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then regularly.

- Rash Monitor closely for skin reactions during first 18 weeks.

**PATIENT AND CARER ADVICE**

Hypersensitivity reactions Patients or carers should be told how to recognise hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if severe skin reaction, hypersensitivity reactions, or symptoms of hepatitis develop.

**Missed doses**

If a dose is more than 8 hours late with the ‘immediate-release’ preparation (or more than 12 hours late with the modified-release preparation), the missed dose should not be taken and the next dose should be taken at the usual time.

**MEDICINAL FORMS**

There can be variation in the licensing of these medicines containing the same drug.

**Tablet**

- **Nevirapine (Non-proprietary)**
  - Nevirapine 200 mg Nevirapine 200mg tablets | 14 tablet POM £33.69 | 60 tablet POM £214.45–£170.00
  - Viramune (Boehringer Ingelheim Ltd)
  - Nevirapine 200 mg Viramune 200mg tablets | 14 tablet POM £39.67 | 60 tablet POM £170.00

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 25

- **Nevirapine (Non-proprietary)**
  - Nevirapine 400 mg Nevirapine 400mg modified-release tablets | 30 tablet POM £52.13–£61.50
  - Viramune (Boehringer Ingelheim Ltd)
  - Nevirapine 100 mg Viramune 100mg modified-release tablets | 90 tablet POM £127.50 (Hospital only)
  - Nevirapine 400 mg Viramune 400mg modified-release tablets | 30 tablet POM £170.00 (Hospital only)

**Oral suspension**

- Viramune (Boehringer Ingelheim Ltd)
  - Nevirapine (as Nevirapine hemihydrate) 10 mg per 1 ml Viramune 50mg/5ml oral suspension | 240 ml POM £50.40

**Tenofovir with emtricitabine and rilpivirine**, p. 601
ANTIVIRALS > NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside reverse transcriptase inhibitors

- **SIDE-EFFECTS** Abdominal pain · anaemia · anorexia · arthralgia · blood disorders · cough · diarrhoea · dizziness · dyspnoea · fatigue · fever · flatulence · gastro-intestinal disturbances · headache · insomnia · liver damage · metabolic effects · myalgia · nausea · neutropenia · osteonecrosis · pancreatitis · rash · thrombocytopenia · urticaria · vomiting

SID-EFFECTS, FURTHER INFORMATION

- Osteonecrosis For further information see HIV infection p. 590.

- **PREGNANCY** Mitochondrial dysfunction has been reported in infants exposed to nucleoside reverse transcriptase inhibitors in utero; the main effects include haematological, metabolic, and neurological disorders; all infants whose mothers received nucleoside reverse transcriptase inhibitors during pregnancy should be monitored for relevant signs or symptoms.

- **HEPATIC IMPAIRMENT** Use with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects).

Abacavir

- **INDICATIONS AND DOSE** HIV infection in combination with other antiretroviral drugs
  - **BY MOUTH**
  - Adult: 600 mg daily in 1–2 divided doses

- **CAUTIONS** HIV load greater than 100 000 copies/mL · patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%)

- **INTERACTIONS** → Appendix 1 (abacavir).

- **SIDE-EFFECTS**
  - Very rare Stevens-Johnson syndrome · toxic epidermal necrolysis
  - **Frequency not known** Hypersensitivity reactions

SIDE-EFFECTS, FURTHER INFORMATION

- Hypersensitivity reactions Life-threatening hypersensitivity reactions reported—characterised by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache, and myalgia; less frequently mouth ulceration, oedema, hypotension, sore throat, acute respiratory distress syndrome, anaphylaxis, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and renal failure; rarely myolysis; laboratory abnormalities may include raised liver function tests and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time.
  - Discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity.
  - Rash More common in children.

- **ALLERGY AND CROSS-SENSITIVITY** Caution—increased risk of hypersensitivity reaction in presence of HLA-B*5701 allele.

- **HEPATIC IMPAIRMENT** Monitor closely in mild impairment (combination preparations not recommended as reduced abacavir dose may be required). Avoid in moderate impairment unless essential—close monitoring recommended. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Manufacturer advises avoid in end-stage renal disease.

- **PRE-TREATMENT SCREENING** Test for HLA-B*5701 allele before treatment or if restarting treatment and HLA-B*5701 status not known.

- **MONITORING REQUIREMENTS** Monitor for symptoms of hypersensitivity reaction every 2 weeks for 2 months.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include banana, or strawberry.

- **PATIENT AND CARER ADVICE** Patients should be provided with an alert card and advised to keep it with them at all times.
  - Patients and their carers should be told the importance of regular dosing (interruption therapy may increase the risk of sensitisation), how to recognise signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Zialegen (ViiV Healthcare UK Ltd)
    - **Abacavir (as Abacavir sulfate)** 300 mg Ziaugen tablets | 60 tablet £17.60
  - Oral solution
    - EXCIPIENTS: May contain Propylene glycol
    - Zialegen (ViiV Healthcare UK Ltd)
    - **Abacavir (as Abacavir sulfate)** 20 mg per 1 ml Ziaugen 20mg/ml oral solution sugar-free | 240 ml £47.36

Abacavir with dolutegravir and lamivudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir above, lamivudine p. 598, dolutegravir p. 592.

- **INDICATIONS AND DOSE** HIV infection
  - **BY MOUTH**
  - Adult (body-weight 40 kg and above): 1 tablet once daily

- **RENAL IMPAIRMENT** Avoid Triumeq® if eGFR less than 50 mL/minute/1.73 m² (consult product literature).

- **PATIENT AND CARER ADVICE**
  - Missed doses
    - If a dose is more than 20 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Triumeq (ViiV Healthcare UK Ltd)
    - **Dolutegravir (as Dolutegravir sodium)** 50 mg, Lamivudine 300 mg, Abacavir (as Abacavir sulfate) 600 mg Triumeq 50mg/600mg/300mg tablets | 30 tablet £79.16
Abacavir with lamivudine
The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 596, lamivudine p. 598.

- **INDICATIONS AND DOSE**
  - **HIV infection in combination with other antiretrovirals**
    - **BY MOUTH**
    - Adult (body-weight 40 kg and above): 1 tablet once daily

- **RENAL IMPAIRMENT** Avoid *Kivexa* if eGFR less than 50 mL/minute/1.73 m²; consult product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Abacavir with lamivudine (Non-proprietary)
      - Lamivudine 300 mg, Abacavir (as Abacavir sulfate) 600 mg: Abacavir 600 mg / Lamivudine 300 mg tablets | 30 tablet PO £194.62—£284.44 | 30 tablet PO £224.56 (Hospital only)
    - *Kivexa* (ViiV Healthcare UK Ltd)
      - Lamivudine 300 mg, Abacavir (as Abacavir sulfate) 600 mg: *Kivexa* 600 mg/300 mg tablets | 30 tablet PO £299.41

Abacavir with lamivudine and zidovudine
The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 596, lamivudine p. 598, zidovudine p. 601.

- **INDICATIONS AND DOSE**
  - **HIV infection (use only if patient is stabilised for 6–8 weeks on the individual components in the same proportions)**
    - **BY MOUTH**
    - Adult: 1 tablet twice daily

- **RENAL IMPAIRMENT** Avoid *Trizivir* if eGFR less than 50 mL/minute/1.73 m²; consult product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - *Trizivir* (ViiV Healthcare UK Ltd)
      - Lamivudine 150 mg, Abacavir (as Abacavir sulfate) 300 mg, Zidovudine 300 mg: *Trizivir* tablets | 60 tablet PO £432.70

Didanosine
(ddI; DDI)

- **INDICATIONS AND DOSE**
  - **HIV infection in combination with other antiretroviral drugs**
    - **BY MOUTH**
    - Adult (body-weight up to 60 kg): 250 mg daily in 1–2 divided doses
    - Adult (body-weight 60 kg and above): 400 mg daily in 1–2 divided doses

- **CAUTIONS** History of pancreatitis (preferably avoid, otherwise extreme caution) - hyperuricaemia - lactic acidosis - peripheral neuropathy

CAUTIONS, FURTHER INFORMATION

- Lactic acidosis. Lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with didanosine. Use with caution in patients with hepatomegaly, hepatitis, or other risk factors for liver disease and hepatic steatosis (including obesity and alcohol abuse). Discontinue treatment if symptoms of hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function become apparent.

- **INTERACTIONS** Appendix 1 (didanosine).
  - Antacids in tablet formulation might affect absorption of other drugs—give at least 2 hours apart.

- **SIDE EFFECTS** Acute renal failure - alopecia - anaphylactic reactions - diabetes mellitus - dry eyes - dry mouth - hyperuricaemia (suspect if raised significantly) - hypoglycaemia - lactic acidosis - lipodystrophy - liver failure - non-cirrhotic portal hypertension - optic nerve changes - pancreatitis (less common in children) - parotid gland enlargement - peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops) - retinal changes - rhabdomyolysis - sialadenitis

SIDE EFFECTS, FURTHER INFORMATION

- Pancreatitis. Suspend treatment if serum lipase raised (even if asymptomatic) or if symptoms of pancreatitis develop; discontinue if pancreatitis confirmed. Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (e.g. intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated.

- Lipodystrophy syndrome. Metabolic effects may occur with antiretroviral regimens containing didanosine; these include fat redistribution, insulin resistance, and dyslipidaemia—collectively termed lipodystrophy syndrome. The usual risk factors for cardiovascular disease should be taken into account before starting therapy and patients should be advised about lifestyle changes to reduce their cardiovascular risk. Plasma lipids and blood glucose should be measured before starting treatment, after 3–6 months of treatment, and then annually.

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **HEPATIC IMPAIRMENT** Insufficient information. In hepatic impairment, monitor for toxicity.

- **RENAL IMPAIRMENT** Reduce dose if eGFR less than 60 mL/minute/1.73 m²; consult product literature.

- **MONITORING REQUIREMENTS** Ophthalmological examination (including visual acuity, colour vision, and diluted fundus examination) recommended annually or if visual changes occur.

- **DIRECTIONS FOR ADMINISTRATION** Capsules should be swallowed whole and taken at least 2 hours before or 2 hours after food.

  With chewable tablets, to ensure sufficient antacid, each dose to be taken as at least 2 tablets chewed thoroughly, crushed or dispersed in water; clear apple juice may be added for flavouring; tablets to be taken 2 hours after lopinavir with ritonavir capsules and oral solution or atazanavir with ritonavir.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer didanosine capsules and chewable tablets.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  ** Chewable tablet **

  CAUTIONARY AND ADVISORY LABELS 23

  EXCIPIENTS: May contain Aspartame

  - *Videx* (Bristol-Myers Squibb Pharmaceuticals Ltd)
    - Didanosine 25 mg: *Videx* 25 mg chewable dispersible tablets sugar-free | 60 tablet PO £25.06 (Hospital only)
Emtricitabine (FDC)

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs
- **BY MOUTH USING CAPSULES**
  - Adult: 200 mg once daily
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 240 mg once daily

**DOSE EQUIVALENCE AND CONVERSION**
- 240 mg oral solution $\equiv$ 200 mg capsule; where appropriate the capsule may be used instead of the oral solution.

**INTERACTIONS** → Appendix 1 (emtricitabine).

**SIDE-EFFECTS**
- Abnormal dreams
- Hyperpigmentation
- Pruritus

**HEPATIC IMPAIRMENT**
On discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis).

**RENAL IMPAIRMENT**
- Reduce dose if eGFR less than 50 mL/minute/1.73 m²; consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral liquid formulations may include candy.

**PATIENT AND CARER ADVICE**

Missed doses
If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - Emtriva (Gilead Sciences International Ltd)
    - Emtricitabine 200 mg Emtriva 200mg capsules | 30 capsule £138.98

- **Oral solution**
  - Electrolytes: May contain Sodium
  - Emtriva (Gilead Sciences International Ltd)
    - Emtricitabine 10 mg per 1 ml Emtriva 10mg/ml oral solution sugar-free | 170 ml £39.53

Lamivudine (3TC)

**INDICATIONS AND DOSE**

EPIVIR® ORAL SOLUTION

HIV infection in combination with other antiretroviral drugs
- **BY MOUTH**
  - Adult: 150 mg every 12 hours, alternatively 300 mg once daily

Stavudine (d4T)

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs when no suitable alternative available and when prescribed for shortest period possible
- **BY MOUTH**
  - Adult (body-weight up to 60 kg): 30 mg every 12 hours, to be taken preferably at least 1 hour before food
l

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of oral liquid formulations may include cherry.

**LESS SUITABLE FOR PRESCRIBING**

Stavudine (especially in combination with didanosine) is associated with a higher risk of lipodystrophy and should be used only if alternative regimens are not suitable; it is considered to be less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **Zerit** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Stavudine 20 mg: Zerit 20mg capsules | 56 capsule POM £139.46 (Hospital only)
  - Stavudine 30 mg: Zerit 30mg capsules | 56 capsule POM £146.25 (Hospital only)
  - Stavudine 40 mg: Zerit 40mg capsules | 56 capsule POM £150.66 (Hospital only)

**Oral solution**

- **Zerit** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Stavudine 1 mg per 1 ml: Zerit 1mg/ml oral solution | 200 ml POM £22.94 (Hospital only)

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**Tenofovir disoproxil**

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**

**Chronic hepatitis B infection with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis)**

**Chronic hepatitis B infection with decompensated liver disease**

- **DOSAGE BY MOUTH**
  - Adult: 245 mg once daily

**DOSE EQUIVALENT AND CONVERSION**

- 7.5 scoops of granules contains approx. 245 mg tenofovir disoproxil (as fumarate).

**INTERACTIONS**

Appendix 1 (tenofovir).

Use with caution if concomitant or recent use of nephrotoxic drugs.

**SIDE-EFFECTS**

- **Rare** Nephrogenic diabetes insipidus - proximal renal tubulopathy - renal failure
  - **Frequency not known** Hypophosphataemia - reduced bone density

**RENAL IMPAIRMENT**

Granules: 132 mg once daily if eGFR 30–50 mL/minute/1.73 m²; 66 mg once daily if eGFR 20–30 mL/minute/1.73 m²; 33 mg once daily if eGFR 10–20 mL/minute/1.73 m².

**Tablets:** 245 mg every 2 days if eGFR 30–50 mL/minute/1.73 m²; 245 mg every 3–4 days if eGFR 10–30 mL/minute/1.73 m².

Monitor renal function — interrupt treatment if further deterioration.

**MONITORING REQUIREMENTS**

- Test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases.

- When treating chronic hepatitis B with tenofovir, monitor liver function tests every 3 months and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation — recurrent hepatitis may occur on discontinuation).

**DIRECTIONS FOR ADMINISTRATION**

Granules: mix 1 scoop of granules with 1 tablespoon of soft food (e.g. yoghurt, apple sauce) and take immediately without chewing. Do not mix granules with liquids.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer tenofovir granules.

**Missed doses**

If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

**Tenofovir disoproxil for the treatment of chronic hepatitis B** (July 2009) NICE TA173

Tenofovir is an option for the treatment of chronic hepatitis B.

[www.nice.org.uk/TA173](http://www.nice.org.uk/TA173)

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
  - **Viread** (Gilead Sciences International Ltd)
    - Tenofovir disoproxil (as Tenofovir disoproxil fumarate)
      - 123 mg: Viread 123mg tablets | 30 tablet POM £102.60
      - Tenofovir disoproxil (as Tenofovir disoproxil fumarate)
      - 163 mg: Viread 163mg tablets | 30 tablet POM £135.98
Tenofovir with cobicistat, elvitegravir and emtricitabine

The properties listed below are those particular to the combination only. For the properties of the components please consider, tenofovir disoproxil p. 599, emtricitabine p. 598, cobicistat p. 606.

### INDICATIONS AND DOSE

**HIV infection**

- **By mouth**
- **Adult:** 1 tablet once daily

### INTERACTIONS

- **Appendix 1** (cobicistat, elvitegravir, emtricitabine, tenofovir).

### SIDE-EFFECTS

- **Uncommon** Depression and suicidal ideation (in patients with a history of psychiatric illness)

### CONCEPTION AND CONTRACEPTION

Women of childbearing potential should use effective contraception (if using a hormonal contraceptive, it must contain norgestimate as the progestogen and at least 30 micrograms ethinylestradiol).

### PREGNANCY

Manufacturer advises use only if potential benefit outweighs risks.

### HEPATIC IMPAIRMENT

Avoid *Stribild*® in severe impairment.

### RENAL IMPAIRMENT

- If eGFR less than 90 mL/minute/1.73 m², only initiate *Stribild*® if other treatments cannot be used (avoid initiating *Stribild*® if eGFR less than 70 mL/minute/1.73 m²); if eGFR less than 70 mL/minute/1.73 m², continue *Stribild*® if potential benefit outweighs risk (discontinue *Stribild*® if eGFR less than 50 mL/minute/1.73 m²).

### MONITORING REQUIREMENTS

Test urine glucose before treatment, then every 4 weeks for 1 year and then every 3 months.

### DIRECTIONS FOR ADMINISTRATION

Avoid antacids 4 hours before or 4 hours after taking *Stribild*®.

### PRESCRIBING AND DISPENSING INFORMATION

Dispense in original container (contains desiccant).

### PATIENT AND CARER ADVICE

Patients or carers should be given advice on how to administer *Stribild*®.

**Missed doses**

If a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
- **Stribild** (Gilead Sciences International Ltd)
  - Cobicistat 150 mg, Elvitegravir 150 mg, Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg £879.51

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Tenofovir with efavirenz and emtricitabine

The properties listed below are those particular to the combination only. For the properties of the components please consider, tenofovir disoproxil p. 599, efavirenz p. 593, emtricitabine p. 598.

### INDICATIONS AND DOSE

**HIV infection stabilised on antiretroviral therapy for more than 3 months**

- **By mouth**
- **Adult:** 1 tablet once daily

### HEPATIC IMPAIRMENT

Manufacturer of *Atripla*® advises caution in mild impairment; avoid *Atripla*® in moderate to severe impairment.

### RENAL IMPAIRMENT

Avoid *Atripla*® if eGFR less than 50 mL/minute/1.73 m².

### PATIENT AND CARER ADVICE

**Missed doses**

If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 23, 25**
- **Atripla** (Gilead Sciences International Ltd)
  - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg, Efavirenz 600 mg £352.87

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Tenofovir with emtricitabine

The properties listed below are those particular to the combination only. For the properties of the components please consider, tenofovir disoproxil p. 599, emtricitabine p. 598.

### INDICATIONS AND DOSE

**HIV infection in combination with other antiretroviral drugs**

- **By mouth**
- **Adult:** 1 tablet once daily

### RENAL IMPAIRMENT

Use normal dose of *Truvada*® every 2 days if eGFR 30–50 mL/minute/1.73 m². Avoid *Truvada*® if eGFR less than 30 mL/minute/1.73 m².

### DIRECTIONS FOR ADMINISTRATION

Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste).

### PATIENT AND CARER ADVICE

Patients or carers should be given advice on how to administer emtricitabine with tenofovir tablets.

**Missed doses**

If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
- **Truvada** (Gilead Sciences International Ltd)
  - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg Truvada tablets £355.73
Tenofovir with emtricitabine and rilpivirine

The properties listed below are those particular to the combination only. For the properties of the components please consider, tenofovir disoproxil p. 599, emtricitabine p. 598, rilpivirine p. 595.

- **INDICATIONS AND DOSE**
  - **HIV infection in patients with plasma HIV-1 RNA concentration less than 100 000 copies/mL**
    - **BY MOUTH**
    - Adult: 1 tablet once daily

- **HEPATIC IMPAIRMENT** Manufacture of Eviplera® advises caution in moderate impairment; avoid Eviplera® in severe impairment.

- **RENAL IMPAIRMENT** Avoid Eviplera® if eGFR less than 50 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION** Avoid antacids before or 4 hours after taking Eviplera®.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer Eviplera®.

  - **Missed doses**
    - If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  
  **Tablet**
  
  CAUTIONARY AND ADVISORY LABELS 21, 25
  
  - Eviplera® (Gilead Sciences International Ltd)
    - Rilpivirine (as Rilpivirine hydrochloride) 25 mg, Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg Eviplera® 200mg/25mg/245mg tablets | 30 tablet | £525.95
    - Eviplera® 250mg/30mg/245mg tablets | 30 tablet | £525.95

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Zidovudine

(Azidothymidine; AZT)

- **INDICATIONS AND DOSE**
  - **HIV infection in combination with other antiretroviral drugs**
    - **BY MOUTH**
    - Adult: 250–300 mg twice daily
  
  **Prevention of maternal-fetal HIV transmission**
  
  - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
    - Adult: Seek specialist advice (combination therapy preferred) (consult local protocol)
  
  **HIV infection in combination with other antiretroviral drugs in patients temporarily unable to take zidovudine by mouth**
  
  - **BY INTRAVENOUS INFUSION**
    - Adult: 0.8–1 mg/kg every 4 hours usually for not more than 2 weeks, dose approximating to 1.2–1.5 mg/kg every 4 hours by mouth

- **CONTRA-INDICATIONS** Abnormally low haemoglobin concentration (consult product literature) • abnormally low neutrophil counts (consult product literature) • Acute porphyrias p. 930

- **CAUTIONS** Elderly • lactic acidosis • risk of haematological toxicity particularly with high dose and advanced disease • vitamin B₁₂ deficiency (increased risk of neutropenia)

  **CAUTIONS, FURTHER INFORMATION**
  
  - Lactic acidosis Lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with zidovudine. Use with caution in patients with hepatomegaly, hepatitis, or other risk factors for liver disease and hepatic steatosis (including obesity and alcohol abuse). Discontinue treatment if symptoms of hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function become apparent.

  **INTERACTIONS** → Appendix 1 (zidovudine).

  Increased risk of toxicity with nephrotoxic and myelosuppressive drugs—for further details consult product literature.

  **SIDE-EFFECTS** Anaemia (may require transfusion) • anxiety • chest pain • convulsions • depression • dizziness • drowsiness • gynaecomastia • influenza-like symptoms • lactic acidosis • lipodystrophy • loss of mental acuity • myopathy • neuropathy • paraesthesia • pigmentation of nails • pigmentation of oral mucosa • pigmentation of skin • pruritus • sweating • taste disturbance • urinary frequency

  **SIDE-EFFECTS, FURTHER INFORMATION**
  
  - Anaemia and myelosuppression If anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment.

  - Lipodystrophy syndrome Metabolic effects may occur with antiretroviral regimens containing zidovudine; these include fat redistribution, insulin resistance, and dyslipidaemia—collectively termed lipodystrophy syndrome. The usual risk factors for cardiovascular disease should be taken into account before starting therapy and patients should be advised about lifestyle changes to reduce their cardiovascular risk. Plasma lipids and blood glucose should be measured before starting treatment, after 3–6 months of treatment, and then annually.

  **HEPATIC IMPAIRMENT** Accumulation may occur.

  **RENAL IMPAIRMENT** Reduce oral dose to 300–400 mg daily in divided doses or intravenous dose to 1 mg/kg 3–4 times daily if eGFR is less than 10 mL/minute/1.73 m².

  **MONITORING REQUIREMENTS** Monitor full blood count after 4 weeks of treatment, then every 3 months.

  **DIRECTIONS FOR ADMINISTRATION** For intermittent intravenous infusion, dilute to a concentration of 2 mg/mL or 4 mg/mL with Glucose 5% and give over 1 hour.

  **PRESCRIBING AND DISPENSING INFORMATION** The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  
  **Capsule**
  
  - Zidovudine (non-proprietary)
    - Zidovudine 100 mg Zidovudine 100mg capsules | 60 capsule £0.50
      - Zidovudine 250 mg Zidovudine 250mg capsules | 60 capsule £96.36
    - Retrovir® (ViiV Healthcare UK Ltd)
      - Zidovudine 100 mg Retrovir 100mg capsules | 100 capsule £88.86
      - Zidovudine 250 mg Retrovir 250mg capsules | 40 capsule £88.86
  
  **Oral solution**
  
  - Retrovir® (ViiV Healthcare UK Ltd)
    - Zidovudine 10 mg per 1 ml Retrovir 50mg/5ml oral solution sugar-free | 200 ml £17.78
  
  **Solution for infusion**
  
  - Retrovir® (ViiV Healthcare UK Ltd)
    - Zidovudine 10 mg per 1 ml Retrovir IV 200mg/20ml concentrate for solution for infusion vials | 5 vial £44.61
Zidovudine with lamivudine
The properties listed below are those particular to the combination only. For the properties of the components please consider, zidovudine p. 601, lamivudine p. 598.

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**
- **BY MOUTH**
  - Adult: 1 tablet twice daily

**SIDE-EFFECTS**
- **Common or very common** Abnormal dreams · alopecia · amnesia · anxiety · arthralgia · chest pain · cholelithiasis · depression · disorientation · dry mouth · dyspnoea · gynaecomastia · haematuria · hypertension · increased appetite · mouth ulcers · nephrolithiasis · peripheral neuropathy · proteinuria · syncope · torsade de pointes · urinary frequency · weight changes
- **Rare** Abnormal gait · cholecystitis · hepatosplenomegaly · oedema · palpitation

**DIRECTIONS FOR ADMINISTRATION**
- **COMBIVIR® TABLETS** Tablets may be crushed and mixed with semi-solid food or liquid just before administration.

**MEDICINAL FORMS**
- **Tablet**
  - Zidovudine with lamivudine (Non-proprietary)
    - Lamivudine 150 mg, Zidovudine 300 mg
  - **COMBIVIR® TABLETS** Tablets may be crushed and mixed with semi-solid food or liquid just before administration.
- **Capsule**
  - Lamivudine 150 mg, Zidovudine 300 mg

**SIDE-EFFECTS, FURTHER INFORMATION**
- **Osteonecrosis** For further information see HIV infection p. 590.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment.

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs—with low-dose ritonavir**
- **BY MOUTH**
  - Adult: 300 mg once daily

**INTERACTIONS**
- **Appendix 1 (atazanavir).**
  - Caution if concomitant use with drugs that prolong PR interval. Caution with concomitant use of drugs that prolong QT interval.

**SIDE-EFFECTS**
- **Uncommon** Abnormal dreams · alopecia · amnesia · anxiety · arthralgia · chest pain · cholelithiasis · depression · disorientation · dry mouth · dyspnoea · gynaecomastia · haematuria · hypertension · increased appetite · mouth ulcers · nephrolithiasis · peripheral neuropathy · proteinuria · syncope · torsade de pointes · urinary frequency · weight changes

**RENAL IMPAIRMENT**
- Avoid if eGFR less than 50 mL/minute/1.73 m² (consult product literature).

**DIRECTIONS FOR ADMINISTRATION**
- **COMBIVIR® TABLETS** Tablets may be crushed and mixed with semi-solid food or liquid just before administration.

**MEDICINAL FORMS**
- **Tablet**
  - **Zidovudine with lamivudine (Non-proprietary)**
    - Lamivudine 150 mg, Zidovudine 300 mg
  - **COMBIVIR® TABLETS** Tablets may be crushed and mixed with semi-solid food or liquid just before administration.
  - **Capsule**
    - Lamivudine 150 mg, Zidovudine 300 mg

**SIDE-EFFECTS, FURTHER INFORMATION**
- **Osteonecrosis** For further information see HIV infection p. 590.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment.

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs—in patients previously treated with antiretroviral therapy—with low-dose ritonavir**
- **BY MOUTH**
  - Adult: 300 mg once daily, dose appropriate if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells $\times 10^3$ litre

**INTERACTIONS**
- **Appendix 1 (darunavir).**
- **SIDE-EFFECTS**
  - **Common or very common** Peripheral neuropathy · rash
  - **Uncommon** Abnormal dreams · acne · alopecia · angina · anxiety · arthralgia · conjunctival hyperaemia · cough
depression · dry eyes · dry mouth · dyspnoea · dysuria · eczema · erectile dysfunction · flushing · gynaecomastia · hypertension · hypothyroidism · increased appetite · increased sweating · memory impairment · myocardial infarction · nail discoloration · nephrolithiasis · osteoporosis · peripheral oedema · polyuria · pyrexia · QT interval prolongation · reduced libido · renal failure · severe skin rash · Stevens-Johnson syndrome · stomatitis · tachycardia · throat irritation · toxic epidermal necrolysis · weight changes

- Rare Bradycardia · confusion · convulsions · haematemeses · palpitation · rhinorrhea · seborrhoeic dermatitis · syncope · visual disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

- Rash Mild to moderate rash occurs commonly, usually within the first 4 weeks of therapy and resolves without stopping treatment. Severe skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) occurs less frequently and may be accompanied by fever, malaise, arthralgia, myalgia, oral lesions, conjunctivitis, hepatitis, or eosinophilia; treatment should be stopped if severe rash develops.

- **ALLERGY AND CROSS-SENSITIVITY** Use with caution in patients with sulfonamide sensitivity.

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk; if required, use the twice daily dose regimen.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment—no information available.

- **MONITORING REQUIREMENTS** Monitor liver function before and during treatment.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include strawberry.

- **PATIENT AND CARER ADVICE**

  - Missed doses
  
  If a dose is more than 6 hours late on the twice daily regimen (or more than 12 hours late on the once daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  
  CAUTIONARY AND ADVISORY LABELS 21

  - **Prezista** (Janssen-Cilag Ltd)
    
    Darunavir (as Darunavir ethanolate) 75 mg Prezista 75mg tablets | 480 tablet [Rx] £446.70
    
    Darunavir (as Darunavir ethanolate) 150 mg Prezista 150mg tablets | 240 tablet [Rx] £446.70
    
    Darunavir (as Darunavir ethanolate) 400 mg Prezista 400mg tablets | 60 tablet [Rx] £297.80
    
    Darunavir (as Darunavir ethanolate) 600 mg Prezista 600mg tablets | 60 tablet [Rx] £446.70
    
    Darunavir (as Darunavir ethanolate) 800 mg Prezista 800mg tablets | 30 tablet [Rx] £297.80

  **Oral suspension**
  
  CAUTIONARY AND ADVISORY LABELS 21

  - **Prezista** (Janssen-Cilag Ltd)
    
    Darunavir (as Darunavir ethanolate) 100 mg per 1 ml Prezista 100mg/ml oral suspension sugar-free | 200 ml [Rx] £248.17

**Fosamprenavir**

- **DRUG ACTION** Fosamprenavir is a pro-drug of amprenavir.

- **INDICATIONS AND DOSE**

  HIV infection in combination with other antiretroviral drugs—with low-dose ritonavir

  - **BY MOUTH**
    
    Adult: 700 mg twice daily

  **DOSE EQUIVALENCE AND CONVERSION**

  - 700 mg fosamprenavir is equivalent to approximately 600 mg amprenavir.

- **INTERACTIONS** → Appendix 1 (fosamprenavir).

- **SIDE-EFFECTS**

  - Rare Stevens-Johnson syndrome
  
  - Frequency not known Rash

  **SIDE-EFFECTS, FURTHER INFORMATION**

  - Rash Rash may occur, usually in the second week of therapy; discontinue permanently if severe rash with systemic or allergic symptoms or, mucosal involvement; if rash mild or moderate, may continue without interruption—usually resolves within 2 weeks and may respond to antihistamines.

- **PREGNANCY** Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk.

- **HEPATIC IMPAIRMENT** Reduce dose to 450 mg twice daily in moderate impairment; reduce dose to 300 mg twice daily in severe impairment. Manufacturer advises caution in mild impairment.

- **DIRECTIONS FOR ADMINISTRATION** In adults, oral suspension should be taken on an empty stomach.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include grape, bubblegum, or peppermint.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer fosamprenavir oral suspension.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - Telzir (ViiV Healthcare UK Ltd)
    
    Fosamprenavir (as Fosamprenavir calcium) 700 mg Telzir 700mg tablets | 60 tablet [Rx] £220.13

  **Oral suspension**

  EXCipients: May contain Propylene glycol

  - Telzir (ViiV Healthcare UK Ltd)
    
    Fosamprenavir (as Fosamprenavir calcium) 50 mg per 1 ml Telzir 50mg/ml oral suspension | 225 ml [Rx] £58.70

**Indinavir**

- **INDICATIONS AND DOSE**

  HIV infection in combination with nucleoside reverse transcriptase inhibitors

  - **BY MOUTH**
    
    Adult: Seek specialist advice

- **CAUTIONS**

  Ensure adequate hydration (risk of nephrolithiasis) · patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%) · patients at risk of nephrolithiasis (monitor for nephrolithiasis)

- **INTERACTIONS** → Appendix 1 (indinavir).

- **SIDE-EFFECTS**

  - Alopecia · crystalluria · dry mouth · dry skin · dysuria · haematuria · haemolytic anaemia · hyperpigmentation · hypoaeesthesia · interstitial nephritis (with medullary calcification and cortical atrophy in...
asymptomatic severe leucocyturia) • nephrolithiasis (may require interruption or discontinuation) • paronychia • proteinuria • pyelonephritis

- **PREGNANCY** Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia and renal stones in neonate if used at term.

- **HEPATIC IMPAIRMENT** Reduce dose in mild to moderate impairment. Not studied in severe impairment. Increased risk of nephrolithiasis.

- **RENAL IMPAIRMENT** Use with caution. In patients with renal impairment, monitor for nephrolithiasis.

- **DIRECTIONS FOR ADMINISTRATION** Administer 1 hour before or 2 hours after a meal; may be administered with a low-fat light meal; in combination with didanosine tablets, allow 1 hour between each drug (antacids in didanosine tablets reduce absorption of indinavir); in combination with low-dose ritonavir, give with food.

- **PRESCRIBING AND DISPENSING INFORMATION** Dispense in original container (contains desiccant).

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer indinavir capsules.

- **LESS SUITABLE FOR PRESCRIBING** Indinavir is rarely used in the treatment of HIV-infection because it is associated with nephrolithiasis; it is considered to be less suitable for prescribing.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **Capsule**

  - **INDICATIONS AND DOSE**
  HIV infection in combination with other antiretroviral drugs

  - **BY MOUTH USING TABLETS**
  > Adult: 400/100 mg twice daily, alternatively 800/200 mg once daily, once daily dose to be used only in adults with a HIV strain that has less than 3 mutations to protease inhibitors

  - **BY MOUTH USING ORAL SOLUTION**
  > Adult: 5 mL twice daily, to be taken with food, oral solution contains 400 mg lopinavir, 100 mg ritonavir/5 mL

- **CAUTIONS** Cardiac conduction disorders • pancreatitis • patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%) • structural heart disease

- **INTERACTIONS** → Appendix 1 (lopinavir, ritonavir). Caution if concomitant use with drugs that prolong QT or PR interval.

- **SIDE-EFFECTS**

  - **Common or very common** Amenorrhoea • anxiety • arthralgia • colitis • hypertension • menstruation • neuropathy • night sweats • sexual dysfunction • weight changes

  - **Uncommon** Abnormal dreams • alopecia • AV block • cerebrovascular accident • convulsions • deep vein thrombosis • dry mouth • gastro-intestinal ulcer • haematuria • myocardial infarction • nephritis • rectal bleeding • stomatitis • tinnitus • tremor • visual disturbances

- **SIDE-EFFECTS, FURTHER INFORMATION**

  - **Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

  - **PREGNANCY** Avoid oral solution due to high propylene glycol content; use tablets only if potential benefit outweighs risk (toxicity in animal studies).

- **HEPATIC IMPAIRMENT** Avoid oral solution due to high propylene glycol content. Use tablets with caution in severe impairment.

- **RENAL IMPAIRMENT** Avoid oral solution due to high propylene glycol content. Use tablets in severe impairment.

- **MONITORING REQUIREMENTS** Monitor liver function before and during treatment.

- **PATIENT AND CARER ADVICE** Oral solution tastes bitter.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**

  - **INDICATIONS AND DOSE**
  HIV infection in combination with other antiretroviral drugs (high-dose ritonavir)

  - **BY MOUTH**
  > Adult: Initially 300 mg every 12 hours for 3 days, increased in steps of 100 mg every 12 hours over not longer than 14 days; increased to 600 mg every 12 hours

  - **Low-dose booster to increase effect of other protease inhibitors**
  > **BY MOUTH**
  > Adult: 100–200 mg 1–2 times a day

  - **CAUTIONS** Cardiac conduction disorders • pancreatitis • structural heart disease

  - **INTERACTIONS** → Appendix 1 (ritonavir). Caution if concomitant use with drugs that prolong PR interval.

  - **SIDE-EFFECTS**

    - **Common or very common** Acne • anxiety • arthralgia • blood pressure changes • blurred vision • confusion • cough • decreased blood thyroxine concentration • fever • flushing • gastro-intestinal haemorrhage • menorrhagia • mouth ulcers • oedema • peripheral neuropathy • pharyngitis • renal impairment • seizures • syncope

    - **Uncommon** Electrolyte disturbances • myocardial infarction

    - **Rare** Toxic epidermal necrolysis

    - **SIDE-EFFECTS, FURTHER INFORMATION**

    - **Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed.

    - **PREGNANCY** Only use low-dose booster to increase the effect of other protease inhibitors.

## Lopinavir with ritonavir

- **INDICATIONS AND DOSE**

  HIV infection in combination with other antiretroviral drugs

  - **BY MOUTH USING TABLETS**
  > Adult: 400/100 mg twice daily, alternatively 800/200 mg once daily, once daily dose to be used only in adults with a HIV strain that has less than 3 mutations to protease inhibitors

  - **BY MOUTH USING ORAL SOLUTION**
  > Adult: 5 mL twice daily, to be taken with food, oral solution contains 400 mg lopinavir, 100 mg ritonavir/5 mL

- **CAUTIONS** Cardiac conduction disorders • pancreatitis • patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%) • structural heart disease

- **INTERACTIONS** → Appendix 1 (lopinavir, ritonavir). Caution if concomitant use with drugs that prolong QT or PR interval.

- **SIDE-EFFECTS**

  - **Common or very common** Amenorrhoea • anxiety • arthralgia • colitis • hypertension • menstruation • neuropathy • night sweats • sexual dysfunction • weight changes

  - **Uncommon** Abnormal dreams • alopecia • AV block • cerebrovascular accident • convulsions • deep vein thrombosis • dry mouth • gastro-intestinal ulcer • haematuria • mycardial infarction • nephritis • rectal bleeding • stomatitis • tinnitus • tremor • visual disturbances

- **SIDE-EFFECTS, FURTHER INFORMATION**

  - **Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

  - **PREGNANCY** Avoid oral solution due to high propylene glycol content; use tablets only if potential benefit outweighs risk (toxicity in animal studies).

  - **HEPATIC IMPAIRMENT** Avoid oral solution due to high propylene glycol content. Use tablets with caution in severe impairment.

  - **RENAL IMPAIRMENT** Avoid oral solution due to high propylene glycol content. Use tablets in severe impairment.

  - **MONITORING REQUIREMENTS** Monitor liver function before and during treatment.

  - **PATIENT AND CARER ADVICE** Oral solution tastes bitter.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**

  - **CAUTIONARY AND ADVISORY LABELS**

  - **INDICATIONS AND DOSE**
  HIV infection in combination with other antiretroviral drugs (high-dose ritonavir)

  - **BY MOUTH**
  > Adult: Initially 300 mg every 12 hours for 3 days, increased in steps of 100 mg every 12 hours over not longer than 14 days; increased to 600 mg every 12 hours

  - **Low-dose booster to increase effect of other protease inhibitors**
  > **BY MOUTH**
  > Adult: 100–200 mg 1–2 times a day

  - **CAUTIONS** Cardiac conduction disorders • pancreatitis • structural heart disease

  - **INTERACTIONS** → Appendix 1 (ritonavir). Caution if concomitant use with drugs that prolong PR interval.

  - **SIDE-EFFECTS**

    - **Common or very common** Acne • anxiety • arthralgia • blood pressure changes • blurred vision • confusion • cough • decreased blood thyroxine concentration • fever • flushing • gastro-intestinal haemorrhage • menorrhagia • mouth ulcers • oedema • peripheral neuropathy • pharyngitis • renal impairment • seizures • syncope

    - **Uncommon** Electrolyte disturbances • myocardial infarction

    - **Rare** Toxic epidermal necrolysis

    - **SIDE-EFFECTS, FURTHER INFORMATION**

    - **Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed.

    - **PREGNANCY** Only use low-dose booster to increase the effect of other protease inhibitors.
Tipranavir

- **INDICATIONS AND DOSE**
  HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in patients previously treated with antiretrovirals—with low-dose ritonavir
  - **BY MOUTH USING CAPSULES**
    - Adult: 500 mg twice daily

- **DOSE EQUIVALENCE AND CONVERSION**
  - The bioavailability of tipranavir oral solution is higher than that of the capsules; the oral solution is not interchangeable with the capsules on a milligram-for-milligram basis.

- **CAUTIONS**
  Patients at risk of increased bleeding from trauma, surgery or other pathological conditions

- **INTERACTIONS**
  - **Appendix 1 (saquinavir).** Caution with concomitant use of drugs that increase risk of bleeding.

- **SIDE-EFFECTS**
  - **Rare** Dehydration
  - **Frequency not known** Anorexia · dyspnoea · influenza-like symptoms · peripheral neuroathy · photosensitivity · renal impairment

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Hepatotoxicity Potentially life-threatening hepatotoxicity reported. Discontinue if signs or symptoms of hepatitis develop or if liver-function abnormality develops (consult product literature).

- **PREGNANCY**
  Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in mild impairment; avoid in moderate or severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  Monitor liver function before treatment then every 2 weeks for 1 month, then every 3 months.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Flavours of oral liquid formulations may include toffee and mint.

- **PATIENT AND CARER ADVICE**
  Patients or carers should be told to observe the oral solution for crystallisation; the bottle should be replaced if more than a thin layer of crystals form (doses should continue to be taken at the normal time until the bottle is replaced).

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - Cautionary and advisory labels: 5, 21
    - Excipients: May contain Ethanol
    - Tipranavir 250 mg Aptivus 250 mg capsules | 120 capsule £41.00
606 Viral infection

ANTIVIRALS ≥ OTHER

Maraviroc

- **DRUG ACTION**: Maraviroc is an antagonist of the CCR5 chemokine receptor.

- **INDICATIONS AND DOSE**: CCR5-tropic HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretrovirals
  - **BY MOUTH**
  - Adult: 300 mg twice daily

- **CAUTIONS**: Cardiovascular disease

- **INTERACTIONS**: → Appendix 1 (maraviroc).

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain, anaemia, anorexia, depression, diarrhoea, flatulence, headache, insomnia, malaise, nausea, rash
  - Uncommon: Myositis, proteinuria, renal failure, seizures
  - Rare: Angina, granulocytopenia, hepatitis, pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Frequency not known: Eosinophilia, fever, hepatic reactions, hypersensitivity reactions, osteonecrosis, rash

- **SIDE-EFFECTS, FURTHER INFORMATION**: Osteonecrosis For further information see HIV infection p. 590.

- **PREGNANCY**: Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

- **HEPATIC IMPAIRMENT**: Manufacturer advises caution in hepatic impairment, including patients with chronic hepatitis B or C.

- **RENAL IMPAIRMENT**: If eGFR less than 80 mL/minute/1.73 m², consult product literature.

- **NATIONAL FUNDING/ACCESS DECISIONS**: Scottish Medicines Consortium (SMC) Decisions The Scottish Medicines Consortium has advised (March 2008) that maraviroc (Celsentri®) is not recommended for use within NHS Scotland.

- **MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**: Celsentri (ViiV Healthcare UK Ltd)
    - Maraviroc 150 mg Celsentri 150mg tablets | 60 tablet PoD £441.27
    - Maraviroc 300 mg Celsentri 300mg tablets | 60 tablet PoD £441.27

PHARMACOKINETIC ENHANCERS

Cobicistat

- **INDICATIONS AND DOSE**: Pharmacokinetic enhancer used to increase the effect of atazanavir or darunavir
  - **BY MOUTH**
  - Adult: 150 mg once daily

- **INTERACTIONS**: → Appendix 1 (cobicistat).

- **PREGNANCY**: Manufacturer advises avoid unless essential.

- **HEPATIC IMPAIRMENT**: Manufacturer advises avoid in severe impairment—no information available.

- **RENAL IMPAIRMENT**: No dose adjustment required; inhibits tubular secretion of creatinine; when any co-administered drug requires dose adjustment based on renal function, avoid initiating cobicistat if eGFR less than 70 mL/minute/1.73 m².

- **PRESCRIBING AND DISPENSING INFORMATION**: Dispense in original container (contains desiccant).

- **PATIENT AND CARER ADVICE**: Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**: Cautionary and Advisory Labels 21
    - Tybost (Gilead Sciences International Ltd) ▼
    - Cobicistat 150 mg Tybost 150mg tablets | 30 tablet PoD £21.38

  Combinations available: Tenofovir with cobicistat, elvitegravir and emtricitabine, p. 600

6.5 Influenza

Influenza

Management

Oseltamivir p. 607 and zanamivir p. 608 are most effective for the treatment of influenza if started within a few hours of the onset of symptoms; they are licensed for use within 48 hours of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. Oseltamivir or zanamivir can reduce the risk of complications from influenza in the elderly and in patients with chronic disease.

Oseltamivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza. However, in patients with severe influenza or in those who are immunocompromised, antivirals may still be effective after this time if viral shedding continues [unlicensed use]. Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

There is evidence that some strains of influenza A virus have reduced susceptibility to oseltamivir, but may retain susceptibility to zanamivir. Resistance to oseltamivir may be greater in severely immunocompromised patients.

Zanamivir should be reserved for patients who are severely immunocompromised, or when oseltamivir cannot be used, or when resistance to oseltamivir is suspected. For those unable to use the dry powder for inhalation, zanamivir is available as a solution that can be administered by nebuliser or intravenously [unlicensed].

Amantadine hydrochloride p. 390 is licensed for prophylaxis and treatment of influenza A but it is no longer recommended.

Information on pandemic influenza, avian influenza, and swine influenza may be found at www.gov.uk/phe.

Immunisation against influenza is recommended for persons at high risk, and to reduce transmission of infection.

Oseltamivir in children under 1 year of age

Data on the use of oseltamivir in children under 1 year of age is limited. Furthermore, oseltamivir may be ineffective in neonates because they may not be able to metabolise oseltamivir to its active form. However, oseltamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age. The Department of Health has advised (May 2009) that during a pandemic, treatment with oseltamivir can be
overseen by healthcare professionals experienced in assessing children.

**ANTIVIRALS**

**NEURAMINIDASE INHIBITORS**

Oseltamivir

**DRUG ACTION** Reduces replication of influenza A and B viruses by inhibiting viral neuraminidase.

**INDICATIONS AND DOSE**

**Prevention of influenza**

- **BY MOUTH**
  - Child 1-11 months: 3 mg/kg once daily for 10 days for post-exposure prophylaxis
  - Child 1-12 years (body-weight 10-15 kg): 30 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
  - Child 1-12 years (body-weight 15-23 kg): 45 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
  - Child 1-12 years (body-weight 23-40 kg): 60 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
  - Child 1-12 years (body-weight 40 kg and above): 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
  - Child 13-17 years: 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
  - Adult: 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

**Treatment of influenza**

- **BY MOUTH**
  - Child 1-11 months: 3 mg/kg twice daily for 5 days
  - Child 1-12 years (body-weight 10-15 kg): 30 mg twice daily for 5 days
  - Child 1-12 years (body-weight 15-23 kg): 45 mg twice daily for 5 days
  - Child 1-12 years (body-weight 23-40 kg): 60 mg twice daily for 5 days
  - Child 1-12 years (body-weight 40 kg and above): 75 mg twice daily for 5 days
  - Child 13-17 years: 75 mg twice daily for 5 days
  - Adult: 75 mg twice daily for 5 days

**UNLICENSED USE** Not licensed for use in premature infants.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, dyspepsia, headache, nausea, vomiting
- **Uncommon** Altered consciousness (usually in children and adolescents), arrhythmias, convulsions, eczema, rash
- **Rare** Gastro-intestinal bleeding, hepatitis, neuropsychiatric disorders (usually in children and adolescents), Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, visual disturbances

**PREGNANCY** Although safety data are limited, oseltamivir can be used in women who are pregnant when the potential benefit outweighs the risk (e.g. during a pandemic). Use only if potential benefit outweighs risk (e.g. during a pandemic).

**BREAST FEEDING** Although safety data are limited, oseltamivir can be used in women who are breast-feeding when the potential benefit outweighs the risk (e.g. during a pandemic). Oseltamivir is the preferred drug in women who are breast-feeding. Amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic).

**RENAL IMPAIRMENT**

- In adults For treatment, use 30 mg twice daily if eGFR 30–60 mL/minute/1.73 m² (30 mg once daily if eGFR 10–30 mL/minute/1.73 m²). For prevention, use 30 mg once daily if eGFR 30–60 mL/minute/1.73 m² (30 mg every 48 hours if eGFR 10–30 mL/minute/1.73 m²). Avoid for treatment and prevention if eGFR less than 10 mL/minute/1.73 m².
- In children For treatment, use 40% of normal dose twice daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose once daily if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²). For prevention, use 40% of normal dose once daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose every 48 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²). Avoid for treatment and prevention if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** If suspension not available, capsules can be opened and the contents mixed with a small amount of sweetened food, such as sugar water or chocolate syrup, just before administration.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include tutti-frutti.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Oseltamivir for influenza (flu) www.medicinesforchildren.org.uk/oseltamivir-for-influenza

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) NICE TA158
  - Oseltamivir is **not** a substitute for vaccination, which remains the most effective way of preventing illness from influenza.
  - Oseltamivir is **not** recommended for seasonal prophylaxis against influenza.

- When influenza is circulating in the community, oseltamivir is an option recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Oseltamivir should be given within 48 hours of exposure to influenza. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.)

- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, oseltamivir may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At risk patients include those aged over 65 years or those who have one or more of the following conditions:

- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.
This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/TA158

Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009) NICE TA168

Oseltamivir is not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

- When influenza is circulating in the community, oseltamivir is an option recommended (in accordance with UK licensing) for the treatment of influenza in at-risk patients who can start treatment within 48 hours of the onset of symptoms. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.)
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, oseltamivir may be used for treatment in at-risk patients living in long-term residential or nursing homes.
- At risk patients include those aged over 65 years or those who have one or more of the following conditions:
  - chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
  - chronic heart disease;
  - chronic renal disease;
  - chronic liver disease;
  - chronic neurological disease;
  - immunosuppression;
  - diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/TA168

NHS restrictions Except for the treatment and prophylaxis of influenza as indicated in the NICE guidance; endorse prescription ‘SLS’.

- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

- CAUTIONARY AND ADVISORY LABELS 9
  - **Tamiflu** (Roche Products Ltd)
  - **Oseltamivir** (as Oseltamivir phosphate) 30 mg Tamiflu 30 mg capsules | 10 capsules [POM] £7.71
  - **Oseltamivir** (as Oseltamivir phosphate) 45 mg Tamiflu 45 mg capsules | 10 capsules [POM] £15.41
  - **Oseltamivir** (as Oseltamivir phosphate) 75 mg Tamiflu 75 mg capsules | 10 capsules [POM] £15.41

**Oral suspension**

- CAUTIONARY AND ADVISORY LABELS 9
  - **Tamiflu** (Roche Products Ltd)
  - **Oseltamivir** (as Oseltamivir phosphate) 6 mg per 1 ml Tamiflu 6 mg/ml oral suspension sugar-free | 65 ml [POM] £10.27

**Oral solution**

- CAUTIONARY AND ADVISORY LABELS 9
  - **Oseltamivir** (Non-proprietary)
  - **Oseltamivir** (as Oseltamivir phosphate) 15 mg per 1 ml Oseltamivir 15 mg/ml oral solution sugar free sugar-free | 20 ml [POM] £10.00

**Zanamivir**

- **Drug action** Reduces replication of influenza A and B viruses by inhibiting viral neuraminidase.

- **Indications and dose**
  - **Post-exposure prophylaxis of influenza**
    - BY INHALATION OF POWDER
    - Child 5-17 years: 10 mg once daily for 10 days
    - Adult: 10 mg once daily for 10 days
  - **Prevention of influenza during an epidemic**
    - BY INHALATION OF POWDER
    - Child 5-17 years: 10 mg once daily for up to 28 days
    - Adult: 10 mg once daily for up to 28 days

- **Treatment of influenza**
  - BY INHALATION OF POWDER
  - Child 5-17 years: 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)
  - Adult: 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)

- **Unlicensed use** Use of zanamivir for up to 10 days if resistance to oseltamivir suspected is an unlicensed duration.

- **Caution** Asthma, chronic pulmonary disease, uncontrolled chronic illness

- **Further information**
  - Asthma and chronic pulmonary disease Risk of bronchospasm—short-acting bronchodilator should be available.
  - Avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm.

- **Side-effects**
  - Common or very common Rash
  - Uncommon Angioedema, bronchospasm, dyspnoea, urticaria
  - Rare Neuropsychiatric disorders (especially in children and adolescents), Stevens-Johnson syndrome, toxic epidermal necrolysis

- **Pregnancy** Although safety data are limited, zanamivir can be used in women who are pregnant when the potential benefit outweighs the risk (e.g. during a pandemic). Use only if potential benefit outweighs risk (e.g. during a pandemic).

- **Breastfeeding** Although safety data are limited, zanamivir can be used in women who are breastfeeding when the potential benefit outweighs the risk (e.g. during a pandemic). Amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic).

- **Directions for administration** Other inhaled drugs should be administered before zanamivir.

- **Prescribing and dispensing information** Except for the treatment and prophylaxis of influenza as indicated in the NICE guidance; endorse prescription ‘SLS’.

- **National funding/access decisions**
  - NICE technology appraisals (TAs)
    - Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) NICE TA158
    - Zanamivir is not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.
    - Zanamivir is not recommended for seasonal prophylaxis against influenza.
    - When influenza is circulating in the community, zanamivir is an option recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the
same household or residential setting. Amantadine should be given within 36 hours of exposure to influenza. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.)

- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, amantadine may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At-risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at-risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza.

At-risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at-risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/TA158

Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009) NICE TA168

Zanamivir is not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

- When influenza is circulating in the community, zanamivir is an option recommended (in accordance with UK licensing) for the treatment of influenza in at-risk patients who can start treatment within 48 hours (within 36 hours for zanamivir in children) of the onset of symptoms. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.)

- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, zanamivir may be used for treatment in at-risk patients living in long-term residential or nursing homes.

At-risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at-risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/TA168

6.6 Respiratory syncytial virus

Respiratory syncytial virus

Management in adults

Ribavirin p. 578 inhibits a wide range of DNA and RNA viruses. It is given by mouth for the treatment of chronic hepatitis C infection, in double therapy with peginterferon alfa p. 576, interferon alfa p. 850, or sofosbuvir p. 580, or in triple therapy with peginterferon alfa and one protease inhibitor (i.e. boceprevir p. 581, telaprevir p. 583 or simeprevir p. 582) or sofosbuvir. Ribavirin is also effective in Lassa fever [unlicensed indication].

Management in children

Ribavirin is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases. However, there is no evidence that ribavirin produces clinically relevant benefit in RSV bronchiolitis.

Palivizumab is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease; it should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation.

Palivizumab is recommended for:
- children under 9 months of age with chronic lung disease (defined as requiring oxygen for at least 28 days from birth) and who were born preterm;
- children under 6 months of age with haemodynamically significant, acyanotic congenital heart disease who were born preterm.

Palivizumab should be considered for:
- children under 2 years of age with severe combined immunodeficiency syndrome;
- children under 1 year of age who require long-term ventilation;
- children 1–2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension).

For details of the preterm age groups included in the recommendations, see Immunisation against Infectious Disease (2006), available at www.gov.uk/dh.

www.gov.uk/dh
Chapter 6
Endocrine system

1 Antidiuretic hormone disorders

Posterior pituitary hormones and antagonists

Posterior pituitary hormones

Diabetes insipidus

Vasopressin p. 613 (antidiuretic hormone, ADH) is used in the treatment of pituitary (‘cranial’) diabetes insipidus as is its analogue desmopressin p. 611. Dosage is tailored to produce a slight diuresis every 24 hours to avoid water intoxication. Treatment may be required for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus. Following a dose intramuscularly or intranasally, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of cranial diabetes insipidus. Failure to respond occurs in nephrogenic diabetes insipidus.

In nephrogenic and partial pituitary diabetes insipidus benefit may be gained from the paradoxical antidiuretic effect of thiazides.

Carbamazepine p. 291 is sometimes useful in partial pituitary diabetes insipidus [unlicensed]; it may act by sensitising the renal tubules to the action of remaining endogenous vasopressin.

Other uses

Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand’s disease; it is also used to test fibrinolytic response. Desmopressin may also have a role in nocturnal enuresis.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, prior to more definitive treatment and with variable results. Terlipressin acetate, a derivative of vasopressin with reportedly less pressor and antidiuretic activity, is used similarly.

Oxytocin p. 753, another posterior pituitary hormone, is indicated in obstetrics.

Antidiuretic hormone antagonists

Demeclocycline hydrochloride p. 521 can be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable. Demeclocycline hydrochloride is thought to act by directly blocking the renal tubular effect of antidiuretic hormone.

Tolvaptan p. 613 is a vasopressin V$_2$-receptor antagonist licensed for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion; treatment duration with tolvaptan is determined by the underlying disease and its treatment.

Rapid correction of hyponatraemia during tolvaptan therapy can cause osmotic demyelination, leading to serious neurological events; close monitoring of serum sodium concentration and fluid balance is essential.

1.1 Diabetes insipidus

Other drugs used for Diabetes insipidus: Chlortalidone, p. 219
Desmopressin

**DRUG ACTION** Desmopressin is an analogue of vasopressin.

**INDICATIONS AND DOSE**

**Diabetes insipidus, treatment**

- **BY MOUTH**
  - Child 1-23 months: Initially 10 micrograms 2-3 times a day, adjusted according to response; usual dose 30–150 micrograms daily
  - Child 2-11 years: Initially 50 micrograms 2–3 times a day, adjusted according to response; usual dose 100–800 micrograms daily
  - Child 12-17 years: Initially 100 micrograms 2–3 times a day, adjusted according to response; usual dose 0.2–1.2 mg daily
  - Adult: Initially 100 micrograms 3 times a day; maintenance 100–200 micrograms 3 times a day; usual dose 0.2–1.2 mg daily
- **BY SUBLINGUAL ADMINISTRATION**
  - Child 2-17 years: Initially 60 micrograms 3 times a day, adjusted according to response; usual dose 40–240 micrograms 3 times a day
  - Adult: Initially 60 micrograms 3 times a day, adjusted according to response; usual dose 40–240 micrograms 3 times a day
- **BY INTRanasAL ADMINISTRATION**
  - Child 1-23 months: Initially 2.5–5 micrograms 1-2 times a day, adjusted according to response
  - Child 2-11 years: Initially 5–20 micrograms 1-2 times a day, adjusted according to response
  - Child 12-17 years: Initially 10–20 micrograms 1–2 times a day, adjusted according to response
  - Adult: 10–40 micrograms daily in 1–2 divided doses
- **BY SUBCUTaneous INJECTION, OR BY INTRanasAL INJECTION, OR BY INTRamuscular INJECTION**
  - Adult: 1–4 micrograms daily

**Primary nocturnal enuresis**

- **BY MOUTH**
  - Child 5-17 years: 200 micrograms once daily, only increased to 400 micrograms if lower dose not effective; withdraw for at least 1 week for reassessment after 3 months, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration
  - Adult 18-65 years: 200 micrograms once daily, only increased to 400 micrograms if lower dose not effective; withdraw for at least 1 week for reassessment after 3 months, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration
- **BY SUBLINGUAL ADMINISTRATION**
  - Child 5-17 years: 120 micrograms once daily, increased if necessary to 240 micrograms once daily, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration, dose to be increased only if lower dose not effective, reassess after 3 months by withdrawing treatment for at least 1 week
  - Adult 18-65 years: 120 micrograms once daily, increased if necessary to 240 micrograms once daily, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration, dose to be increased only if lower dose not effective, reassess after 3 months by withdrawing treatment for at least 1 week

**Postoperative polyuria or polydipsia**

- **BY MOUTH**
  - Adult: Dose to be adjusted according to urine osmolality

**Polyuria or polydipsia after hypophysectomy**

- **BY SUBLINGUAL ADMINISTRATION**
  - Adult: Dose to be adjusted according to urine osmolality

**Idiopathic nocturnal polyuria in females**

- **BY SUBLINGUAL ADMINISTRATION**
  - Adult: 25 micrograms daily, to be taken 1 hour before bedtime

**Idiopathic nocturnal polyuria in males**

- **BY SUBLINGUAL ADMINISTRATION**
  - Adult: 50 micrograms daily, to be taken 1 hour before bedtime

**Diabetes insipidus, diagnosis (water deprivation test)**

- **BY INTRanasAL ADMINISTRATION**
  - Adult: 20 micrograms, limit fluid intake to 500 mL from 1 hour before until 8 hours after administration
  - **BY INTRamuscular INJECTION, OR BY INTRanasAL INJECTION**
  - Adult: 2 micrograms for 1 dose, limit fluid intake to 500 mL from 1 hour before to 8 hours after administration

**Nocturia associated with multiple sclerosis (when other treatments have failed)**

- **BY INTRanasAL ADMINISTRATION**
  - Adult 18–65 years: 10–20 micrograms once daily, to be taken at bedtime, dose not to be repeated within 24 hours, limit fluid intake from 1 hour before to 8 hours after administration

**Renal function testing**

- **BY INTRanasAL ADMINISTRATION**
  - Adult: 40 micrograms, empty bladder at time of administration and limit fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload
  - **BY SUBCUTaneous INJECTION, OR BY INTRamuscular INJECTION**
  - Adult: 2 micrograms, empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload

**Mild to moderate haemophilia and von Willebrand’s disease**

- **BY INTRanasAL ADMINISTRATION**
  - Adult: 300 micrograms every 12 hours if required, one 150 microgram spray into each nostril, 30 minutes before surgery or when bleeding, dose may alternatively be repeated at intervals of at least 3 days, if self-administered
  - **BY INTRanasAL INJECTION, OR BY SUBCUTaneous INJECTION**
  - Adult: 300 nanograms/kg for 1 dose, to be administered immediately before surgery or after trauma; may be repeated at intervals of 12 hours

**Fibrinolytic response testing**

- **BY INTRanasAL ADMINISTRATION**
  - Adult: 300 micrograms, blood to be sampled after 1 hour for fibrinolytic activity, one 150 microgram spray to be administered into each nostril
  - **BY SUBCUTaneous INJECTION, OR BY INTRanasAL INJECTION**
  - Adult: 300 nanograms/kg for 1 dose, blood to be sampled after 20 minutes for fibrinolytic activity

**Lumbar-puncture-associated headache**

- **BY INTRamuscular INJECTION, OR BY SUBCUTaneous INJECTION**
  - Adult: (consult product literature)
PRESCRIBING AND DISPENSING INFORMATION

RENAL IMPAIRMENT

PREGNANCY

SIDE-EFFECTS

INTERACTIONS

CAUTIONS

GENERAL CAUTIONS

Asthma • avoid fluid overload • cardiovascular disease (not indicated for nocturnal enuresis or nocturia) • conditions which might be aggravated by water retention • cystic fibrosis • elderly (avoid for primary nocturnal enuresis and nocturia associated with multiple sclerosis in those over 65 years) • epilepsy • heart failure • hypertension (not indicated for nocturnal enuresis or nocturia) • migraine • nocturia • limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards • nocturnal enuresis—limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards

SPECIFIC CAUTIONS

With intranasal use should not be given intranasally for nocturnal enuresis due to an increased incidence of side-effects

CAUTIONS, FURTHER INFORMATION

Elderly patients are at increased risk of hyponatraemia and renal impairment—manufacturer advises measure baseline serum sodium concentration, then monitor regularly during treatment; discontinue treatment if levels fall below the normal range. Review treatment if no therapeutic benefit after 3 months.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Hyponatraemia (in more serious cases with convulsions) on administration without restricting fluid intake • nausea

Frequency not known Allergic reactions • emotional disturbance in children • epistaxis • fluid retention • headache • nasal congestion • stomach pain • vomiting

SPECIFIC SIDE-EFFECTS

With intranasal use Rhinitis

SIDE-EFFECTS, FURTHER INFORMATION

Hyponatraemic convulsions The risk of hyponatraemic convulsions can be minimised by keeping to the recommended starting doses and by avoiding concomitant use of drugs which increase secretion of vasopressin (e.g. tricyclic antidepressants).

PREGNANCY Small oxytocic effect in third trimester; increased risk of pre-eclampsia.

BREAST FEEDING Amount too small to be harmful.

RENAL IMPAIRMENT Use with caution; antidiuretic effect

MONITORING REQUIREMENTS In nocturia, periodic blood pressure and weight checks are needed to monitor for fluid overload.

DIRECTIONS FOR ADMINISTRATION

DDAVP® and Desmotabs® tablets may be crushed. DDAVP® intranasal solution may be diluted with Sodium Chloride 0.9% to a concentration of 10 micrograms/mL. DDAVP® injection may be administered orally.

Desmopressin oral lyophilisates are for sublingual administration.

For intravenous infusion (DDAVP®, Octim®), give intermittently in Sodium chloride 0.9%; dilute with 50 mL and give over 20 minutes.

PRESCRIBING AND DISPENSING INFORMATION Oral, intranasal, intravenous, subcutaneous and intramuscular doses are expressed as desmopressin acetate; sublingual doses are expressed as desmopressin base.

Children requiring an intranasal dose of less than 10 micrograms should be given DDAVP® intranasal solution.

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Desmopressin for bedwetting

www.medicinesforchildren.org.uk/desmopressin-bedwetting

Hyponatraemic convulsions Patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution, spray, nasal drops

Tablet

Desmopressin (Non-proprietary)

Desmopressin acetate 100 microgram

Desmopressin 100microgram tablets | 90 tablet (PoT) £76.62 DT price = £63.08

Desmopressin acetate 200 microgram

Desmopressin 200microgram tablets | 30 tablet (PoT) £35.23 DT price = £7.41 | 90 tablet (PoT) £87.50

DDAVP (Ferring Pharmaceuticals Ltd)

Desmopressin acetate 100 microgram

DDAVP 0.1mg tablets | 90 tablet (PoT) £84.12 DT price = £63.08

Desmopressin acetate 200 microgram

DDAVP 0.2mg tablets | 90 tablet (PoT) £88.23

Desmotabs (Ferring Pharmaceuticals Ltd)

Desmopressin acetate 200 microgram

Desmotabs 0.2mg tablets | 30 tablet (PoT) £29.43 DT price = £7.41

Oral solution

Desmopressin (Non-proprietary)

Desmopressin (as Desmopressin acetate) 360 microgram per 1 ml

Desmopressin 360micrograms/ml oral solution | 15 ml (PoT) £30.00 DT price = £30.00

Oral lyophilisate

CAUTIONARY AND ADVISORY LABELS

Desmopressin (as Desmopressin acetate) 120 microgram

Desmopressin 120microgram oral lyophilisates sugar free sugar-free | 30 tablet (PoT) no price available DT price = £30.34

Desmopressin (as Desmopressin acetate) 240 microgram

Desmopressin 240microgram oral lyophilisates sugar free sugar-free | 30 tablet (PoT) no price available DT price = £60.68

DDAVP (Ferring Pharmaceuticals Ltd)

Desmopressin (as Desmopressin acetate) 60 microgram

DDAVP Melt 60microgram oral lyophilisates sugar-free sugar-free | 100 tablet (PoT) £50.53 DT price = £50.53

Desmopressin (as Desmopressin acetate) 120 microgram

DDAVP Melt 120microgram oral lyophilisates sugar-free sugar-free | 100 tablet (PoT) £101.07 DT price = £101.07

Desmopressin (as Desmopressin acetate) 240 microgram

DDAVP Melt 240microgram oral lyophilisates sugar-free sugar-free | 100 tablet (PoT) £202.14

DesmoMelt (Ferring Pharmaceuticals Ltd)

Desmopressin (as Desmopressin acetate) 120 microgram

DesmoMelt 120microgram oral lyophilisates sugar-free sugar-free | 30 tablet (PoT) £30.34 DT price = £30.34

Desmopressin (as Desmopressin acetate) 240 microgram

DesmoMelt 240microgram oral lyophilisates sugar-free sugar-free | 30 tablet (PoT) £60.68 DT price = £60.68

Noqdirna (Ferring Pharmaceuticals Ltd)

Desmopressin (as Desmopressin acetate) 25 microgram

Noqdirna 25microgram oral lyophilisates sugar-free sugar-free | 30 tablet (PoT) £15.16

Desmopressin (as Desmopressin acetate) 50 microgram

Noqdirna 50microgram oral lyophilisates sugar-free sugar-free | 30 tablet (PoT) £30.34

Solution for injection

DDAVP (Ferring Pharmaceuticals Ltd)

Desmopressin acetate 4 microgram per 1 ml

DDAVP 4micrograms/1ml solution for injection ampoules | 10 ampoule (PoT) £13.16
SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

1.2 Syndrome of inappropriate antidiuretic hormone secretion

Other drugs used for Syndrome of inappropriate antidiuretic hormone secretion Demeclocycline hydrochloride, p. 521

DIURETICS > SELECTIVE VASOPRESSIN V2-RECEPTOR ANTAGONISTS

Tolvaptan

- **DRUG ACTION** Tolvaptan is a vasopressin V2-receptor antagonist.

- **INDICATIONS AND DOSE**
  
<table>
<thead>
<tr>
<th>JINARC®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant polycystic kidney disease in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (initiated by a specialist)</td>
</tr>
</tbody>
</table>

- **BY MOUTH**
  - Adult: Initially 60 mg daily in 2 divided doses for at least a week, 45 mg in the morning before breakfast, and then 15 mg taken 8 hours later; increased to 90 mg daily in 2 divided doses for at least a week, 60 mg in the morning before breakfast, and then 30 mg taken 8 hours later, then increased if tolerated to 120 mg daily in 2 divided doses, 90 mg in the morning before breakfast, and then 30 mg taken 8 hours later, dose titration should be performed cautiously; patients may down-titrate to lower doses based on tolerability

- **SAMSCA®**

**Treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion**

- **BY MOUTH**
  - Adult: 15 mg once daily, increased if necessary up to 60 mg daily; treatment duration is determined by the underlying disease and its treatment

- **CONTRA-INDICATIONS** Anuria · hypernatraemia · hypovolaemic or hypophaesmin · impaired perception of thirst · volume depletion

- **CAUTIONS** Alcoholism (increased risk of demyelination syndrome if rapid correction of hyponatraemia) · diabetes mellitus · ensure adequate fluid intake · hypoxia (increased risk of demyelination syndrome if rapid correction of hyponatraemia) · malnutrition (increased risk of demyelination syndrome if rapid correction of hyponatraemia) · pseudohyponatraemia associated with diabetes mellitus (exclude before treatment)

- **INTERACTIONS** Appendix 1 (tolvaptan). Avoid concomitant drugs that increase serum-sodium concentration.

- **SIDE-EFFECTS**
  - Common or very common Constipation · decreased appetite · dehydration · dry mouth · ecchymosis · fever · hyperglycaemia · hyperkalaemia · increased blood creatinine · malaise · nausea · neurological disturbance (following rapid correction of hyponatraemia) · postural hypotension · pruritus · thirst · urinary frequency
  - Uncommon Renal impairment · taste disturbance
  - Frequency not known Dizziness · hepatic impairment (discontinue) · hypernatraemia · hyperuricaemia · hypoglycaemia · syncope

---

**1.2 Syndrome of inappropriate antidiuretic hormone secretion**

**Vasopressin**

- **INDICATIONS AND DOSE**
  - Pituitary diabetes insipidus
    - By intramuscular injection, or by subcutaneous injection
    - Adult: 5–20 units every 4 hours
  - Initial control of oesophageal variceal bleeding
    - By intravenous infusion
    - Adult: 20 units, dose to be administered over 15 minutes

- **CONTRA-INDICATIONS** Chronic nephritis (until reasonable blood nitrogen concentrations attained) · vascular disease (especially disease of coronary arteries) unless extreme caution

- **CAUTIONS** Asthma · avoid fluid overload · conditions which might be aggravated by water retention · epilepsy · heart failure · hypertension · migraine

- **SIDE-EFFECTS**
  - Rare Gangrene
  - Frequency not known Abdominal cramps · anaphylaxis · anginal attacks · delirium · constriction of coronary arteries · desire to defaecate · fluid retention · headache · hypersensitivity reactions · myocardial ischaemia · nausea · pallor · peripheral ischaemia · sweating · tremor · vertigo · vomiting

- **PREGNANCY** Oxytocic effect in third trimester.

- **BREAST FEEDING** Not known to be harmful.

- **DIRECTIONS FOR ADMINISTRATION**
  For intravenous infusion (arginpressin), give intermittently in Glucose 5%; suggested concentration 20 units/100mL given over 15 minutes.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Vasopressin (Non-proprietary)**

  *Argipressin 20 unit per 1 ml Argipressin 20units/1ml solution for injection ampoules | 10 ampoule £800.00 (Hospital only)*
SIDE-EFFECTS, FURTHER INFORMATION

- Hepatic impairment: Discontinue and perform liver-function tests promptly if symptoms of hepatic impairment (anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, dark urine, pruritus).
- PREGNANCY: Avoid—toxicity in animal studies.
- BREAST FEEDING: Avoid—present in milk in animal studies.
- HEPATIC IMPAIRMENT: Use with caution in severe impairment—no information available.
- RENAL IMPAIRMENT: No information available in severe impairment.
- MONITORING REQUIREMENTS:
  - Monitor for dehydration in patients who are fluid-restricted.
  - Monitor serum-sodium concentration and fluid balance no later than 6 hours after initiating treatment and every 6 hours during the first 1–2 days of treatment and until dose stabilised. Discontinue if rapid rise in serum-sodium concentration (greater than 12 mmol/litre in 24 hours or 18 mmol/litre in 48 hours).
- PATIENT AND CARER ADVICE: For Jinarc®, morning dose to be taken 30 minutes before food, second dose can be taken with or without food.
- NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Tolvaptan for treating autosomal dominant polycystic kidney disease (October 2015) NICE TA358
  Tolvaptan (Jinarc®) is recommended as an option for the treatment of autosomal dominant polycystic kidney disease in adults if:
  - the patient has chronic kidney disease stage 2 or 3 at the start of treatment and
  - there is evidence of rapidly progressing disease
  - and the manufacturer provides tolvaptan with the discount agreed in the patient access scheme

Patients currently receiving tolvaptan (Jinarc®) whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA358

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Jinarc (Otsuka Pharmaceuticals (U.K.) Ltd)
  - Tolvaptan 15 mg: Jinarc 15mg tablets | 7 tablet (Pom) £302.05
  - Tolvaptan 30 mg: Jinarc 30mg tablets | 7 tablet (Pom) £302.05
  - Tolvaptan 45 mg: Jinarc 45mg tablets | 7 tablet (Pom) no price available
  - Tolvaptan 60 mg: Jinarc 60mg tablets | 7 tablet (Pom) no price available
  - Tolvaptan 90 mg: Jinarc 90mg tablets | 7 tablet (Pom) no price available
  - Jinarc 45mg tablets and Jinarc 15mg tablets | 56 tablet (Pom) £1,208.20
  - Jinarc 60mg tablets and Jinarc 30mg tablets | 56 tablet (Pom) £1,208.20
  - Jinarc 90mg tablets and Jinarc 30mg tablets | 56 tablet (Pom) £1,208.20
- Samsca (Otsuka Pharmaceuticals (U.K.) Ltd)
  - Tolvaptan 15 mg: Samsca 15mg tablets | 10 tablet (Pom) £746.80
  - Tolvaptan 30 mg: Samsca 30mg tablets | 10 tablet (Pom) £746.80

2 Corticosteroid responsive conditions

CORTICOSTEROIDS

Corticosteroids, general use

Overview

Dosages of corticosteroids vary widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.

When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.

When potentially less harmful measures are ineffective corticosteroids are used topically for the treatment of inflammatory conditions of the skin. Corticosteroids should be avoided or used only under specialist supervision in psoriasis.

Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn’s disease. They are also included in locally applied creams for haemorrhoids.

Use can be made of the mineralocorticoid activity of fludrocortisone acetate p. 619 to treat postural hypotension in autonomic neuropathy.

High-dose corticosteroids should be avoided for the management of septic shock. However, there is evidence that administration of lower doses of hydrocortisone p. 620 and fludrocortisone acetate is of benefit in adrenocortical insufficiency resulting from septic shock.

Dexamethasone p. 618 and betamethasone p. 618 have little if any mineralocorticoid action and their long duration of action makes them particularly suitable for suppressing corticotropin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and by measurement of adrenal androgens and 17-hydroxyprogesterone. In common with all glucocorticoids their suppressive action on the hypothalamic–pituitary–adrenal axis is greatest and most prolonged when they are given at night. In most individuals a single dose of dexamethasone at night, is sufficient to inhibit corticotropin secretion for 24 hours. This is the basis of the ‘overnight dexamethasone suppression test’ for diagnosing Cushing’s syndrome.

Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.

A corticosteroid may be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy (see Prescribing in palliative care p. 22); high doses of betamethasone or dexamethasone are generally used. However, a corticosteroid should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

In acute hypersensitivity reactions, such as angioedema of the upper respiratory tract and anaphylaxis, corticosteroids are indicated as an adjunct to emergency treatment with adrenaline/epinephrine p. 211. In such cases hydrocortisone (as sodium succinate) by intravenous injection may be required.

Corticosteroids are preferably used by inhalation in the management of asthma but systemic therapy in association
with bronchodilators is required for the emergency treatment of severe acute asthma.

Corticosteroids may also be useful in conditions such as autoimmune hepatitis, rheumatoid arthritis and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia, and some cases of the nephrotic syndrome (particularly in children) and thrombocytopenic purpura.

Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis, and polyarteritis nodosa; the effects of the disease process may be suppressed and symptoms relieved, but the underlying condition is not cured, although it may ultimately remit. It is usual to begin therapy in these conditions at fairly high dose, and then to reduce the dose to the lowest commensurate with disease control.

For other references to the use of corticosteroids see: Prescribing in Palliative Care, immunosuppression, rheumatic diseases, eye, otitis externa allergic rhinitis, and aphthous ulcers.

### Side-effects

Overdosage or prolonged use can exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects.

#### Mineralocorticoid side effects
- Hypertension
- Sodium retention
- Water retention
- Potassium loss
- Calcium loss

Mineralocorticoid side effects are most marked with fludrocortisone, but are significant with hydrocortisone, corticotropin, and tetracosactide. Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.

#### Glucocorticoid side effects
- Diabetes
- Osteoporosis, which is a danger, particularly in the elderly, as it can result in osteoporotic fractures for example of the hip or vertebrae;
- In addition high doses are associated with avascular necrosis of the femoral head.
- Muscle wasting (proximal myopathy) can also occur.
- Corticosteroid therapy is also weakly linked with peptic ulceration and perforation.
- Psychiatric reactions may also occur.

### Managing side-effects

Side-effects can be minimised by using lowest effective dose for minimum period possible. The suppressive action of a corticosteroid on cortisol secretion is least when it is given as a single dose in the morning. In an attempt to reduce pituitary-adrenal suppression further, the total dose for two days can sometimes be taken as a single dose on alternate days; alternate-day administration has not been very successful in the management of asthma. Pituitary-adrenal suppression can also be reduced by means of intermittent therapy with short courses. In some conditions it may be possible to reduce the dose of corticosteroid by adding a small dose of an immunosuppressive drug.

Whenever possible local treatment with creams, intra-articular injections, inhalations, eye-drops, or enemas should be used in preference to systemic treatment.

Inhaled corticosteroids have considerably fewer systemic effects than oral corticosteroids, but adverse effects including adrenal suppression have been reported. Use of other corticosteroid therapy (including topical) or concurrent use of drugs which inhibit corticosteroid metabolism should be taken into account when assessing systemic risk. In children, growth restriction associated with systemic corticosteroid therapy does not seem to occur with recommended doses of inhaled therapy; although initial growth velocity may be reduced, there appears to be no effect on achieving normal adult height. Large-volume spacer devices should be used for administering inhaled corticosteroids in children under 15 years; they are also useful in older children and adults, particularly if high doses are required. Spacer devices increase airway deposition and reduce oropharyngeal deposition.

### Corticosteroids, replacement therapy

#### Overview

The adrenal cortex normally secretes hydrocortisone p. 620 (cortisol) which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best achieved with a combination of hydrocortisone and the mineralocorticoid hydrocortisone acetate p. 618; hydrocortisone alone does not usually provide sufficient mineralocorticoid activity for complete replacement.

In Addison’s disease or following adrenalectomy, hydrocortisone by mouth is usually required. This is given in 2 doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The optimum daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone acetate.

In acute adrenocortical insufficiency, hydrocortisone is given intravenously (preferably as sodium succinate) every 6 to 8 hours in sodium chloride intravenous infusion 0.9% p. 914.

In hypopituitarism, glucocorticoids should be given as in adrenocortical insufficiency, but since production of aldosterone is also regulated by the renin-angiotensin system a mineralocorticoid is not usually required.

Additional replacement therapy with levothyroxine sodium p. 708 and sex hormones should be given as indicated by the pattern of hormone deficiency.

### Glucocorticoid therapy

#### Glucocorticoid and mineralocorticoid activity

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory (glucocorticoid) effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids). The mineralocorticoid activity of fludrocortisone acetate p. 619 is so high that its anti-inflammatory activity is of no clinical relevance.

<table>
<thead>
<tr>
<th>Equivalent anti-inflammatory doses of corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action</td>
</tr>
<tr>
<td>Prednisolone 5 mg</td>
</tr>
<tr>
<td>Betamethasone 750 micrograms</td>
</tr>
<tr>
<td>Deflazacort 6 mg</td>
</tr>
<tr>
<td>Dexamethasone 750 micrograms</td>
</tr>
<tr>
<td>Hydrocortisone 20 mg</td>
</tr>
<tr>
<td>Methylprednisolone 4 mg</td>
</tr>
<tr>
<td>Prednisone 5 mg</td>
</tr>
<tr>
<td>Triamcinolone 4 mg</td>
</tr>
</tbody>
</table>
The relatively high mineralocorticoid activity of hydrocortisone p. 620, and the resulting fluid retention, makes it unsuitable for disease suppression on a long-term basis. However, hydrocortisone can be used for adrenal replacement therapy. Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked.

Prednisolone p. 622 and prednisone p. 623 have predominantly glucocorticoid activity. Prednisolone is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone p. 618 and dexamethasone p. 618 have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage.

Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid action makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion (e.g. congenital adrenal hyperplasia).

Some esters of betamethasone and of beclometasone dipropionate p. 40 (beclomethasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations).

Delfazacort p. 618 has a high glucocorticoid activity; it is derived from prednisolone.

**Corticosteroids (systemic)**

- **CONTRA-INDICATIONS** Avoid injections containing benzyl alcohol in neonates • avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished) • systemic infection (unless specific therapy given)

**CONTRA-INDICATIONS, FURTHER INFORMATION**

For further information on contra-indications associated with intra-articular, intradermal and intralesional preparations, consult product literature.

- **CAUTIONS** Congestive heart failure • diabetes mellitus (including a family history of) • diverticulitis • epilepsy • glaucoma (including a family history of or susceptibility to) • history of steroid myopathy • history of tuberculosis or X-ray changes (frequent monitoring required) • hypertension • hypothyroidism • infection (particularly untreated) • myasthenia gravis • ocular herpes simplex (risk of corneal perforation) • osteoporosis (in children) • osteoporosis (post-menopausal women and the elderly at special risk) • peptic ulcer • psychiatric reactions • recent intestinal anastomoses • recent myocardial infarction (rupture reported) • severe affective disorders (particularly if history of steroid-induced psychosis) • should not be used long-term • thromboembolic disorders • ulcerative colitis

**CAUTIONS, FURTHER INFORMATION**

- With intra-articular use or intradermal use or intralesional use For further information on cautions associated with intra-articular, intradermal and intralesional preparations, consult product literature.

- **INTERACTIONS** → Appendix 1 (corticosteroids).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

Abdominal distension • acute pancreatitis • aggravation of epilepsy • aggravation of schizophrenia • anorexia • anaphylaxis (in children) • bruising • candidiasis • congestive heart failure • corneal thinning • Cushing’s syndrome (with moon face, striae and acne) • dyspepsia • ecchymoses • exacerbation of ophthalmic fungal disease • exacerbation of ophthalmic viral disease • exophthalmos • facial erythema • glaucoma • headache • hiccups • hirsutism • hypercholesterolaemia • hyperglycaemia • hyperhidrosis • hyperlipidaemia • hypersensitivity reactions (in children) • impaired healing • increased appetite • increased intraocular pressure • increased intracranial pressure with papilloedema (usually after withdrawal) (in children) • increased susceptibility to and severity of infection • insomnia • leucocytosis • long bone fractures • malaise • menstrual irregularities • muscle weakness • myocardial rupture following recent myocardial infarction • nausea • negative calcium balance • negative nitrogen balance • oesophageal ulceration • papilloedema (in adults) • petechiae • posterior subcapsular cataracts • potassium loss • psychological dependence • reactivation of dormant tuberculosis • scleral thinning • skin atrophy • sodium retention • suppression of growth (in children) • telangiectasia • tendon rupture • thromboembolism • urticaria • vertebral fractures • vertigo • water retention • weight gain

**SPECIFIC SIDE-EFFECTS**

- With intra-articular use Flushing • may affect the hyaline cartilage

**SIDE-EFFECTS, FURTHER INFORMATION**

For further information on side-effects associated with intra-articular, intradermal and intralesional preparations, consult product literature.

Side effects can be managed by choice of route and duration of course. For further detail see Corticosteroids, general use p. 614

- **Adrenal suppression** During prolonged therapy with corticosteroids, particularly with systemic use, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension, or death.

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary reintroduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period, anaesthetists must know whether a patient is taking or has been taking a corticosteroid. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- **Minor surgery under general anaesthesia**—usual oral corticosteroid dose on the morning of surgery or hydrocortisone (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery.

- **Moderate or major surgery**—usual oral corticosteroid dose on the morning of surgery and hydrocortisone intravenously at induction, followed by hydrocortisone 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections.

Patients on long-term corticosteroid treatment should carry a steroid treatment card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.
Infections  Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. sepsicaemia and tuberculosis may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral infections may also be exacerbated.

Chickenpox  Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox (see Steroid Treatment Card). Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non–immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.

Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

Measles  Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Psychiatric reactions  Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. A serious paranoid state or depression with risk of suicide can be induced, particularly, in patients with a history of mental disorder. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Patients should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment.

Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid–induced psychosis, or who have a personal or family history of psychiatric disorders.

Pregnancy  The benefit of treatment with corticosteroids during pregnancy outweighs the risk. Corticosteroid cover is required during labour. Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM (May 1998) concluded that corticosteroids vary in their ability to cross the placenta but there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip. When administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome). Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important.

Pregnant women with fluid retention should be monitored closely when given systemic corticosteroids.

Breast feeding  The benefit of treatment with corticosteroids during breast-feeding outweighs the risk.

Hepatic impairment  The plasma–drug concentration may be increased (particularly on systemic use). Oral and parenteral use should be undertaken with caution.

Renal impairment  Use by oral and injectable routes should be undertaken with caution.

Monitoring requirements  The height and weight of children receiving prolonged treatment with corticosteroids should be monitored annually; if growth is slowed, referral to a paediatrician should be considered.

Effect on laboratory tests  Suppression of skin test reactions.

Treatment cessation  In adults  Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death. Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss. The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case–by–case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteroid treatment. Gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:

- received more than 40 mg prednisolone (or equivalent) daily for more than 1 week;
- been given repeat doses in the evening;
- received more than 3 weeks' treatment;
- recently received repeated courses (particularly if taken for longer than 3 weeks);
- taken a short course within 1 year of stopping long-term therapy;
- other possible causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

In children  The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case–by–case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteroid treatment. Gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:

- received more than 40 mg prednisolone (or equivalent) daily for more than 1 week or 2 mg/kg daily for 1 week or 1 mg/kg daily for 1 month;
- been given repeat doses in the evening;
- received more than 3 weeks' treatment;
- recently received repeated courses (particularly if taken for longer than 3 weeks);
- taken a short course within 1 year of stopping long-term therapy;
- other possible causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 2–2.5 mg/m² daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.
PATIENT AND CARER ADVICE

Patients on long-term corticosteroid treatment should carry a Steroid Treatment Card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment. A patient information leaflet should be supplied to every patient when a systemic corticosteroid is prescribed. Patients should especially be advised of the following:

● Immunosuppression Prolonged courses of corticosteroids can increase susceptibility to infection and serious infections can go unrecognised. Unless already immune, patients are at risk of severe chickenpox and should avoid close contact with people who have chickenpox or shingles. Similarly, precautions should also be taken against contracting measles;

● Adrenal suppression If the corticosteroid is given for longer than 3 weeks, treatment must not be stopped abruptly. Adrenal suppression can last for a year or more after stopping treatment and the patient must mention the course of corticosteroid when receiving treatment for any illness or injury;

● Mood and behaviour changes Corticosteroid treatment, especially with high doses, can alter mood and behaviour early in treatment—the patient can become confused, irritable and suffer from delusion and suicidal thoughts. These effects can also occur when corticosteroid treatment is being withdrawn. Medical advice should be sought if worrying psychological changes occur;

● Other serious effects Serious gastro-intestinal, musculoskeletal, and ophthalmic effects which require medical help can also occur. Steroid treatment cards should be issued where appropriate. Consider giving a ‘steroid card’ to support communication of the risks associated with treatment, and specific written advice to consider corticosteroid replacement during an episode of stress, such as severe intercurrent illness or an operation, to patients using greater than maximum licensed doses of inhaled corticosteroids. Steroid treatment cards are available for purchase from the NHS Print online ordering portal www.nhsforms.co.uk

GP practices can obtain supplies through Primary Care Support England. NHS Trusts can order supplies via the online ordering portal. In Scotland, steroid treatment cards can be obtained from APS Group Scotland by emailing stockorders.dppas@apsgroup.co.uk or by fax on 0131 629 9967.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Soluble tablet

CAUTIONARY AND ADVISORY LABELS 10, 13, 21 (not for use as mouthwash for oral ulceration)

● Betamethasone (Non-proprietary)

Betamethasone (as Betamethasone sodium phosphate) 500 microgram Betamethasone 500microgram soluble tablets sugar free sugar-free 100 tablet (Pack) £42.60 DT price = £42.57

Solution for injection

CAUTIONARY AND ADVISORY LABELS 10

● Betamethasone (Non-proprietary)

Betamethasone (as Betamethasone sodium phosphate) 4 mg per 1 ml Betamethasone 4mg/1ml solution for injection ampoules | 5 ampoule (Pack) £13.06-£15.68

Deflazacort

INDICATIONS AND DOSE

Suppression of inflammatory and allergic disorders

● BY MOUTH

● Adult: Maintenance 3–18 mg daily

Suppression of inflammatory and allergic disorders (acute disorders)

● BY MOUTH

● Adult: Initially up to 120 mg daily

Inflammatory and allergic disorders

● BY MOUTH

● Child 1 month–11 years: 0.25–1.5 mg/kg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations

● Child 12–17 years: 3–18 mg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations

RENAL IMPAIRMENT Use with caution.

PATIENT AND CARER ADVICE Patient counselling is advised for deflazacort tablets (steroid card).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

tablet

CAUTIONARY AND ADVISORY LABELS 5, 10

● Calcort (Sanofi)

Deflazacort 6 mg Calcort 6mg tablets | 60 tablet (Pack) £15.82

Dexamethasone

INDICATIONS AND DOSE

Suppression of inflammatory and allergic disorders

● BY MOUTH

● Adult: 0.5–10 mg daily

Mild croup

● BY MOUTH

● Child: 150 micrograms/kg for 1 dose

Severe croup (or mild croup that might cause complications)

● INITIALLY BY MOUTH

● Child: Initially 150 micrograms/kg for 1 dose, to be given before transfer to hospital, then (by mouth or by intravenous injection) 150 micrograms/kg, then (by mouth or by intravenous injection) 150 micrograms/kg after 12 hours if required

Inflammatory and allergic disorders (acute disorders)

● BY MOUTH

● Adult: Maintenance 3–18 mg daily

Suppression of inflammatory and allergic disorders

● BY MOUTH

● Adult: Initially up to 120 mg daily

DIABETES MELLITUS, Glucose intolerance

● BY MOUTH

● Adult: Initially up to 120 mg daily

PREGNANCY Readily crosses the placenta. Transient effect on fetal movements and heart rate.

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (as sodium phosphate) (Betnesol®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.

PATIENT AND CARER ADVICE Patient counselling is advised for dexamethasone soluble tablets (steroid card).
With intravenous use in adults

- **Overnight dexamethasone suppression test**
- **BY MOUTH**
- Adult: 1 mg for 1 dose, to be given at night

**Adju nctive treatment of bacterial meningitis (starting before or with first dose of antibacterial)**
- **BY INTRAVENOUS INJECTION**
- Adult: 8.3 mg every 6 hours for 4 days

**Symptom control of anorexia (in palliative care)**
- Adult: 2–4 mg daily

**Obstruction due to tumour (dysphagia in palliative care)**
- Adult: 8 mg daily

**Bronchospasm or partial obstruction (dyspnoea in palliative care)**
- Adult: 4–8 mg daily

**Nausea and vomiting (adjunct in palliative care)**
- **BY MOUTH**
- Adult: 8–16 mg daily

**Headaches due to raised intracranial pressure (in palliative care)**
- Adult: 16 mg daily for 4–5 days, then reduced to 4–6 mg daily, reduce dose if possible. To be given before 6 pm to reduce the risk of insomnia

**Pain due to nerve compression (in palliative care)**
- Adult: 8 mg daily

**Cerebral oedema associated with malignancy**
- **BY MOUTH**
- Adult: 0.5–10 mg daily

**Cerebral oedema**
- **INITIALLY BY INTRAVENOUS INJECTION**
- Adult: Initially 8–16 mg for 1 dose, then (by intramuscular injection or by intravenous injection) 5 mg every 6 hours until adequate response achieved then taper-off gradually, use the 3.8 mg/mL injection preparation for this dose

**Cerebral oedema associated with malignancy**
- **INITIALLY BY INTRAVENOUS INJECTION**
- Adult: Initially 8.3 mg for 1 dose, then (by intramuscular injection) 3.3 mg every 6 hours as required for 2–4 days, subsequently, reduce dose gradually and stop over 5–7 days, use the 3.3 mg/mL injection preparation for this dose

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### Medicinal forms

**Medicines for Children leaflet: Dexamethasone for croup**

- www.medicinesforchildren.org.uk/dexamethasone-croup

### Indications and dose

#### Neuropathic postural hypoten sion
- **BY MOUTH**
- Adult: 100–400 micrograms daily

#### Mineralocorticoid replacement in adrenocortical insufficiency
- **BY MOUTH**
- Adult: 50–300 micrograms once daily

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**Fludrocortisone acetate**

#### Indications and dose

**Neuropathic postural hypotension**
- **BY MOUTH**
- Adult: 100–400 micrograms daily

**Mineralocorticoid replacement in adrenocortical insufficiency**
- **BY MOUTH**
- Adult: 50–300 micrograms once daily

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**Patient and carer advice**

Patient counselling is advised for dexamethasone tablet, oral solution and injection (steroid card).
Hydrocortisone

**INDICATIONS AND DOSE**

**Thyrotoxic crisis (thyroid storm)**
- **By intravenous injection**
  - Adult: 100 mg every 6 hours, to be administered as sodium succinate

**Adrenocortical insufficiency resulting from septic shock**
- **By intravenous injection**
  - Adult: 50 mg every 6 hours, given in combination withfludrocortisone

**Acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylaxis (adjunct to adrenaline)**
- **By intravenous injection**
  - Adult: 100–300 mg, to be administered as sodium succinate

**Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of minor surgery under general anaesthesia**
- **By intravenous injection, or by intravenous infusion**
  - Adult: Initially 25–50 mg, to be administered atinduction of surgery, the patient’s usual oral corticosteroid dose is recommenced after surgery

**Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of moderate or major surgery**
- **By intravenous injection, or by intravenous infusion**
  - Adult: Initially 25–50 mg, to be administered atinduction of surgery (following usual oral corticosteroid dose on the morning of surgery), followed by 25–50 mg 3 times a day for 24 hours aftermoderate surgery and for 48–72 hours after major surgery

**Adrenocortical insufficiency in Addison’s disease or following adrenalectomy**
- **By mouth using immediate-release medicines**
  - Adult: 20–30 mg daily in 2 divided doses, the largerdose to be given in the morning and the smaller in the evening,mimicking the normal diurnal rhythm ofcortisol secretion, the optimum daily dose is determined on the basis of clinical response

**Adrenocortical insufficiency**
- **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
  - Adult: 100–500 mg 3–4 times a day or when required

**Severe inflammatory bowel disease**
- **By slow intravenous injection, or by intravenous infusion**
  - Adult: 100–500 mg 3–4 times a day or when required

**Replacement in adrenocortical insufficiency**
- **By mouth using modified-release medicines**
  - Adult: 20–30 mg once daily, adjusted according toresponse, dose to be taken in the morning
- **By mouth using immediate-release medicines**
  - Adult: 20–30 mg daily in divided doses, adjustedaccording to response

**Ulcerative colitis | Proctitis | Proctosigmoiditis**
- **By rectum using rectal foam**
  - Adult: Initially 1 metered application 1–2 times a dayfor 2–3 weeks, then reduced to 1 metered applicationonce daily on alternate days, to be inserted into therectum

**Acute hypersensitivity reactions | Angioedema**
- **By intramuscular injection, or by intravenous injection**
  - Child 1–5 months: Initially 25 mg 3 times a day, adjustedaccording to response
- Child 6 months–5 years: Initially 50 mg 3 times a day,adjusted according to response
- Child 6–11 years: Initially 100 mg 3 times a day, adjustedaccording to response
- Child 12–17 years: Initially 200 mg 3 times a day, adjustedaccording to response

**Severe acute asthma | Life-threatening acute asthma**
- **By intravenous injection**
  - Child 1 month–1 year: 4 mg/kg every 6 hours (max. per dose100 mg), alternatively 25 mg every 6 hours untilconversion to oral prednisolone is possible, dose given,preferably, as sodium succinate
  - Child 2–4 years: 4 mg/kg every 6 hours (max. per dose100 mg), alternatively 50 mg every 6 hours untilconversion to oral prednisolone is possible, dose given,preferably, as sodium succinate
  - Child 5–11 years: 4 mg/kg every 6 hours (max. per dose100 mg), alternatively 100 mg every 6 hours untilconversion to oral prednisolone is possible, dose given,preferably, as sodium succinate
  - Child 12–17 years: 4 mg/kg every 6 hours (max. per dose100 mg), alternatively 100 mg every 6 hours untilconversion to oral prednisolone is possible, dose given,preferably, as sodium succinate
  - Adult: 100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate

**DOSE EQUIVALEANCE AND CONVERSION**
When switching from immediate-release hydrocortisone tablets to modified release Plenadren® use same total dailydose. Bioavailability of Plenadren® lower than immediate releasetablets—monitor clinical response.

**CONTRA-INDICATIONS**
- With rectal use Bowel perforation · extensive fistulas ·intestinal obstruction · recent intestinal anastomoses

**CAUTIONS**
- With rectal use Systemic absorption may occur

**SIDE-EFFECTS**
- With intravenous use Phosphate ester associated with painand paraesthesia (particularly in the perineal region)
- With rectal use Local irritation

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use in children For intravenousadministration, dilute with Glucose 5% or Sodium Chloride0.9%. For intermittent infusion give over 20–30 minutes.
- With intravenous use in adults For intravenous infusion(SoluCortef®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.
PATIENT AND CARER ADVICE
Patient counselling is advised for hydrocortisone tablets and injections (steroid card).

LESS SUITABLE FOR PRESCRIBING
- With intravenous use Hydrocortisone as the sodium phosphate is less suitable for prescribing as paraesthesia and pain (particularly in the perineal region) may follow intravenous injection.

EXCEPTIONS TO LEGAL CATEGORY
- With intramuscular use or intravenous use Prescription only medicine restriction does not apply where administration is for saving life in emergency.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 10, 21</th>
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<tbody>
<tr>
<td>Hydrocortisone 10 mg</td>
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<tr>
<td>Hydrocortisone 20 mg</td>
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Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 10, 22, 25
- Plenadren (Shire Pharmaceuticals Ltd) Hydrocortisone 5 mg Plenadren 5mg modified-release tablets | 50 tablet £242.50 |
- Hydrocortisone 20 mg Plenadren 20mg modified-release tablets | 50 tablet £400.00 |

Solution for injection
CAUTIONARY AND ADVISORY LABELS 10
- Hydrocortisone (Non-proprietary) Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg per 1 ml Hydrocortisone sodium phosphate 100mg/1ml solution for injection ampoules | 5 ampoule £8.33 |
- Hydrocortisone sodium phosphate 500mg/5ml solution for injection ampoules | 5 ampoule £36.45 |

Powder for solution for injection
- Solu-Cortef (Pfizer Ltd) Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg | Solu-Cortef 100mg powder for solution for injection vials | 10 vial £3.88 |
- Solu-Cortef (Pfizer Ltd) Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg | Solu-Cortef 100mg powder for solution for injection vials | 1 vial £1.16 DT price = £1.16 |

Powder and solvent for solution for injection
CAUTIONARY AND ADVISORY LABELS 10
- Solu-Cortef (Pfizer Ltd) Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg | Solu-Cortef 100mg powder and solvent for injection vials | 1 vial £1.16 DT price = £1.16 |

Foam
EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), propylene glycol
- Colifoam (Mead Pharmaceuticals Ltd) Hydrocortisone acetate 100 mg per 1 gram | Colifoam10% aerosol | 14 dose £9.33 DT price = £9.33 |

Methylprednisolone

INDICATIONS AND DOSE
Suppression of inflammatory and allergic disorders | Cerebral oedema associated with malignancy
- BY MOUTH
  - Adult: Usual dose 2–40 mg daily
  - BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
  - Adult: Initially 10–500 mg

Treatment of graft rejection reactions
- BY INTRAVENOUS INFUSION
  - Adult: Up to 1 g daily for up to 3 days

CAUTIONS
- With intravenous use Rapid intravenous administration of large doses associated with cardiovascular collapse

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (as sodium succinate) (Solu-Medrone®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially with water for injections; doses up to 250 mg should be given over at least 5 minutes, high doses over at least 30 minutes.

PATIENT AND CARER ADVICE
Patient counselling is advised for methylprednisolone tablets and injections (steroid card).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

<table>
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<tr>
<th>Tablet</th>
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<tbody>
<tr>
<td>Methylprednisolone 2 mg</td>
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<tr>
<td>Methylprednisolone 4 mg</td>
<td>Medrone 4mg tablets</td>
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<tr>
<td>Methylprednisolone 16 mg</td>
<td>Medrone 16mg tablets</td>
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<tr>
<td>Methylprednisolone 100 mg</td>
<td>Medrone 100mg tablets</td>
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Powder and solvent for solution for injection
CAUTIONARY AND ADVISORY LABELS 10
- Methylprednisolone (Non-proprietary) Methylprednisolone (as Methylprednisolone sodium succinate) 1 gram | Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials | 1 vial £17.30 |
- Methylprednisolone (as Methylprednisolone sodium succinate) 500 mg | Methylprednisolone sodium succinate 500mg powder and solvent for solution for injection vials | 1 vial £9.60 |
- Methylprednisolone (as Methylprednisolone sodium succinate) 125 mg | Methylprednisolone sodium succinate 125mg powder and solvent for solution for injection vials | 1 vial £4.75 |

Suspension for injection
CAUTIONARY AND ADVISORY LABELS 10
- Depo-Medrone (Pfizer Ltd) Methylprednisolone acnate 40 mg per 1 ml | Depo-Medrone 40mg/1ml suspension for injection vials | 1 vial £3.44 DT price = £3.44 |
- Methylprednisolone 40 mg | Methylprednisolone 40mg/1ml suspension for injection vials | 1 vial £6.18 DT price = £6.18 |
- Methylprednisolone 125 mg | Methylprednisolone 125mg suspension for injection vials | 1 vial £8.96 DT price = £8.96 |

- Methylprednisolone 500 mg | Methylprednisolone 500mg suspension for injection vials | 1 vial £11.70 |

- Methylprednisolone (as Methylprednisolone sodium succinate) 2 gram | Methylprednisolone sodium succinate 2g powder and solvent for solution for injection vials | 1 vial £1.58 |
- Methylprednisolone (as Methylprednisolone sodium succinate) 125 mg | Methylprednisolone sodium succinate 125mg powder and solvent for solution for injection vials | 1 vial £4.75 |
- Methylprednisolone (as Methylprednisolone sodium succinate) 500 mg | Methylprednisolone sodium succinate 500mg powder and solvent for solution for injection vials | 1 vial £8.96 |

- Methylprednisolone (as Methylprednisolone sodium succinate) 1 gram | Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials | 1 vial £11.70 |

- Methylprednisolone (as Methylprednisolone sodium succinate) 2 gram | Methylprednisolone sodium succinate 2g powder and solvent for solution for injection vials | 1 vial £1.58 |
- Methylprednisolone (as Methylprednisolone sodium succinate) 125 mg | Methylprednisolone sodium succinate 125mg powder and solvent for solution for injection vials | 1 vial £4.75 |
- Methylprednisolone (as Methylprednisolone sodium succinate) 500 mg | Methylprednisolone sodium succinate 500mg powder and solvent for solution for injection vials | 1 vial £8.96 |

- Methylprednisolone (as Methylprednisolone sodium succinate) 1 gram | Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials | 1 vial £11.70 |
Prednisolone

**INDICATIONS AND DOSE**

**Acute exacerbation of chronic obstructive pulmonary disease (if increased breathlessness interferes with daily activities)**
- **BY MOUTH**
  - Adult: 30 mg daily for 7–14 days

**Severe croup (before transfer to hospital) | Mild croup that might cause complications (before transfer to hospital)**
- **BY MOUTH**
  - Child 1 month: 2 mg/kg
  - Child 12–17 years: 0.5 mg/kg daily for at least 7 days

**Mild to moderate acute asthma (when oral corticosteroid taken for more than a few days) | Severe or life-threatening acute asthma (when oral corticosteroid taken for more than a few days)**
- **BY MOUTH**
  - Adult: Initially 10–20 mg daily, dose preferably taken in the morning after breakfast, can often be reduced within a few days but may need to be continued for several weeks or months; maintenance 2.5–15 mg daily, higher doses may be needed; cushingoid side-effects increasingly likely with doses above 7.5 mg daily
  - **BY INTRAMUSCULAR INJECTION**
  - Adult: 40–50 mg daily for at least 5 days

**Suppression of inflammatory and allergic disorders (initial dose in severe disease)**
- **BY MOUTH**
  - Adult: Initially up to 60 mg daily, dose preferably taken in the morning after breakfast, can often be reduced within a few days but may need to be continued for several weeks or months

**Idiopathic thrombocytopenic purpura**
- **BY MOUTH**
  - Adult: 1 mg/kg daily, gradually reduce dose over several weeks

**Ulcerative colitis | Crohn’s disease**
- **BY MOUTH**
  - Adult: Initially 20–40 mg daily until remission occurs, followed by reducing doses, up to 60 mg daily, may be used in some cases, doses preferably taken in the morning after breakfast

**Neuritic pain or weakness heralding rapid onset of permanent nerve damage (during reversal reactions multibacillary leprosy)**
- **BY MOUTH**
  - Adult: Initially 40–60 mg daily, dose to be instituted at once

**Generalised myasthenia gravis (when given on alternate days)**
- **BY MOUTH**
  - Adult: Initially 10 mg once daily on alternate days, then increased in steps of 10 mg once daily on alternate days, increased to 1–1.5 mg/kg once daily on alternate days (max. per dose 100 mg)

**Generalised myasthenia gravis in ventilated patients (when given on alternate days)**
- **BY MOUTH**
  - Adult: Initially 1.5 mg/kg once daily on alternate days (max. per dose 100 mg)

**Generalised myasthenia gravis (when giving daily)**
- **BY MOUTH**
  - Adult: Initially 5 mg daily, increased in steps of 5 mg daily, maintenance 60–80 mg daily, alternatively maintenance 0.75–1 mg/kg daily, ventilated patients may be started on 1.5 mg/kg (max. 100 mg) on alternate days

**Ocular myasthenia**
- **BY MOUTH**
  - Adult: 7.5 mg daily

**Polymyalgia rheumatica**
- **BY MOUTH**
  - Adult: 10–15 mg daily until remission of disease activity; maintenance 7.5–10 mg daily, reduce gradually to maintenance dose. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long term low-dose corticosteroid treatment

**Giant cell (temporal) arteritis**
- **BY MOUTH**
  - Adult: 40–60 mg daily until remission of disease activity, the higher dose being used if visual symptoms occur; maintenance 7.5–10 mg daily, reduce gradually to maintenance dose. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long term low-dose corticosteroid treatment

**Polyarteritis nodosa | Polymyositis | Systemic lupus erythematosus**
- **BY MOUTH**
  - Adult: Initially 60 mg daily, to be reduced gradually; maintenance 10–15 mg daily

**Anorexia (symptom control in palliative care)**
- **BY MOUTH**
  - Adult: 15–30 mg daily

**Pneumocystis pneumonia in moderate to severe infections associated with HIV infection**
- **BY MOUTH**
  - Adult: 50–80 mg daily for 5 days, the dose is then reduced to complete 21 days of treatment, corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete

**Short-term prophylaxis of episodic cluster headache as monotherapy or in combination with verapamil during verapamil titration**
- **BY MOUTH**
  - Adult: 60–100 mg once daily for 2–5 days, then reduced in steps of 10 mg every 2–3 days until prednisolone is discontinued

**Proctitis**
- **BY RECTUM USING RECTAL FOAM**
  - Adult: 1 metered application 1–2 times a day for 2 weeks, continued for further 2 weeks if good response, to be inserted into the rectum, 1 metered application contains 20 mg prednisolone
BY RECTUM USING SUPPOSITORIES
Adult: 5 mg twice daily, to be inserted in to the rectum morning and night, after a bowel movement

Distal ulcerative colitis
BY RECTUM USING RECTAL FOAM
Adult: 1 metered application 1–2 times a day for 2 weeks, continued for further 2 weeks if good response, to be inserted into the rectum, 1 metered application contains 20 mg prednisolone

Rectal complications of Crohn’s disease
BY RECTUM USING SUPPOSITORIES
Adult: 5 mg twice daily, to be inserted in to the rectum morning and night, after a bowel movement

Rectal and rectosigmoidal ulcerative colitis | Rectal and rectosigmoidal Crohn’s disease
BY RECTUM USING ENEMA
Adult: 20 mg daily for 2–4 weeks, continued if response good, to be used at bedtime

CONTRA-INDICATIONS
• With rectal use Bowel perforation - extensive fistulas - intestinal obstruction - recent intestinal anastomoses

CAUTIONS
• With systemic use Duchenne’s muscular dystrophy (possible transient rhabdomyolysis and myoglobinuria following strenuous physical activity)

PREGNANCY
As it crosses the placenta 88% of prednisolone is inactivated.

With systemic use Pregnant women with fluid retention should be monitored closely.

BREAST FEEDING
Prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant.

With systemic use Infant should be monitored for adrenal suppression if mother is taking a dose higher than 40 mg.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Prednisolone for asthma www.medicinesforchildren.org.uk/prednisolone-for-asthma

Prednisolone tablets (steroid card).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution enema

Tablet
CAUTIONARY AND ADVISORY LABELS 10, 21
Prednisolone (Non-proprietary)
Prednisolone 1 mg Prednisolone 1mg tablets | 28 tablet £0.76 | 100 tablet £0.68
Prednisolone 2.5 mg Prednisolone 2.5mg tablets | 28 tablet £0.68
Prednisolone 5 mg Prednisolone 5mg tablets | 28 tablet £0.87
Prednisolone 10 mg Prednisolone 10mg tablets | 28 tablet £2.72
Prednisolone 20 mg Prednisolone 20mg tablets | 28 tablet £5.43
Prednisolone 25 mg Prednisolone 25mg tablets | 56 tablet £7.50
Prednisolone 30 mg Prednisolone 30mg tablets | 28 tablet £8.15

Pevanti (AMCo)
Prednisolone 2.5 mg Pevanti 2.5mg tablets | 30 tablet £1.42
Prednisolone 5 mg Pevanti 5mg tablets | 30 tablet £0.95
Prednisolone 10 mg Pevanti 10mg tablets | 30 tablet £1.90
Prednisolone 20 mg Pevanti 20mg tablets | 30 tablet £3.80
Prednisolone 25 mg Pevanti 25mg tablets | 56 tablet £4.00

Prednisone
INDICATIONS AND DOSE
Moderate to severe rheumatoid arthritis
• BY MOUTH USING MODIFIED-RELEASE MEDICINES
Adult: 10–20 mg daily, adjusted according to response, dose to be taken at bedtime

HEPATIC IMPAIRMENT
Monitor patient closely in hepatic impairment.

PATIENT AND CARER ADVICE
Patient counselling is advised for prednisone tablets (steroid card).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 10, 21
Lodotra (Napp Pharmaceuticals Ltd)
Prednisone 1 mg Lodotra 1mg modified-release tablets | 30 tablet £26.00
Prednisone 2 mg Lodotra 2mg modified-release tablets | 30 tablet £26.70
Prednisone 5 mg Lodotra 5mg modified-release tablets | 30 tablet £26.70

### Triamcinolone acetonide

#### INDICATIONS AND DOSE

**Suppression of inflammatory and allergic disorders**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 40 mg (max. per dose 100 mg), repeated if necessary, dose given for depot effect, to be administered into gluteal muscle; repeated at intervals according to patient’s response

#### CAUTIONS

- High dosage (may cause proximal myopathy), avoid in chronic therapy

#### PATIENT AND CARER ADVICE

Patient counselling is advised for triamcinolone acetonide injection (steroid card).

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**CAUTIONARY AND ADVISORY LABELS**

- **EXCIPIENTS:** May contain Benzyl alcohol

**Triamcinolone acetonide 40 mg per 1 ml**

- Kenalog (Bristol-Myers Squibb Pharmaceuticals Ltd)
- Intramuscular 40mg/1ml suspension for injection vials | 5 vial pack

**£7.45 DT price = £7.45**

### 2.1 Cushing’s syndrome and disease

#### Cushing’s Syndrome

**Management**

Most types of Cushing’s syndrome are treated surgically, that which occasionally accompanies carcinoma of the bronchus is not usually amenable to surgery. Metyrapone p. 625 has been found helpful in controlling the symptoms of the disease; it is also used in other forms of Cushing’s syndrome to prepare the patient for surgery.

The dosages of metyrapone used are either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed.

Ketoconazole below may have a direct effect on corticotrophic tumour cells in patients with Cushing’s disease. It is used under specialist supervision for treatment of endogenous Cushing’s syndrome.

Other drugs used for Cushing’s syndrome and disease; Pasireotide, p. 847

#### ENZYME INHIBITORS

**Ketoconazole**

- **DRUG ACTION** An imidazole derivative which acts as a potent inhibitor of cortisol and aldosterone synthesis by inhibiting the activity of 17α-hydroxylase, 11-hydroxylation steps and at higher doses the cholesterol side-chain cleavage enzyme. It also inhibits the activity of adrenal C17–20 lyase enzymes resulting in androgen synthesis inhibition, and may have a direct effect on corticotrophic tumour cells in patients with Cushing’s disease.

- **INDICATIONS AND DOSE**
  - **Endogenous Cushing’s syndrome (specialist use only)**
    - **BY MOUTH**
    - Adult: Initially 400–600 mg daily in 2–3 divided doses, increased to 800–1200 mg daily; maintenance

400–800 mg daily in 2–3 divided doses, for dose titrations in patients with established dose, adjustments in adrenal insufficiency, or concomitant corticosteroid replacement therapy, consult product literature; maximum 1200 mg per day

#### IMPORTANT SAFETY INFORMATION

**CHMP ADVICE: KETOCONAZOLE (JULY 2013)**

The CHMP has recommended that the marketing authorisation for oral ketoconazole to treat fungal infections should be suspended. The CHMP concluded that the risk of hepatotoxicity associated with oral ketoconazole is greater than the benefit in treating fungal infections. Doctors should review patients who are being treated with oral ketoconazole for fungal infections, with a view to stopping treatment or choosing an alternative treatment. Patients with a prescription of oral ketoconazole for fungal infections should be referred back to their doctors.

Oral ketoconazole for Cushing’s syndrome and topical products containing ketoconazole are not affected by this advice.

- **CONTRA-INDICATIONS** Acquired QTc prolongation • avoid concomitant use of hepatotoxic drugs • congenital QTc prolongation
- **CAUTIONS** Risk of adrenal insufficiency
- **INTERACTIONS** → Appendix 1 (antifungals, imidazole).
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain • adrenal insufficiency • diarrhoea • hepatic enzymes increased • nausea • pruritus • rash • vomiting
  - **Uncommon** Alopecia • dizziness • headache • malaise • somnolence • thrombocytopenia • urticaria
  - **Rare** Hepatic failure • hepatitis • jaundice • liver damage
  - **Very rare** Pyrexia
  - **Frequency not known** Alcohol intolerance • anorexia • arthralgia • azoospermia • dermatitis • dry mouth • dysgeusia • dyspepsia • epistaxis • erectile dysfunction • erythema • flatulence • gynaecomastia • hot flush • increased appetite • insomnia • menstrual disorder • myalgia • nervousness • paraesthesia • peripheral oedema • photophobia • photosensitivity • raised intracranial pressure • reduced testosterone concentrations • tongue discoloration • xeroderma

**SIDE-EFFECTS, FURTHER INFORMATION**

- Hepatotoxicity Potentially life-threatening hepatotoxicity reported rarely.
- **CONCEPTION AND CONTRACEPTION** Effective contraception must be used in women of child-bearing potential.
- **PREGNANCY** Manufacturer advises avoid—teratogenic in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—present in breast milk.
- **HEPATIC IMPAIRMENT** Avoid in acute or chronic impairment. Do not initiate treatment if liver enzymes greater than 2 times the normal upper limit.
- **MONITORING REQUIREMENTS**
  - Monitor ECG before and one week after initiation, and then as clinically indicated thereafter.
  - Adrenal insufficiency Monitor adrenal function within one week of initiation, then regularly thereafter. When cortisol levels are normalised or close to target and effective dose established, monitor every 3–6 months as there is a risk of autoimmune disease development or exacerbation after normalisation of cortisol levels. If symptoms suggestive of adrenal insufficiency such as fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia, hyperkalaemia, and/or hypoglycaemia occur, measure cortisol levels and...
discontinue treatment temporarily (can be resumed thereafter at lower dose) or reduce dose and if necessary, initiate corticosteroid substitution.

- Hepatotoxicity Monitor liver function before initiation of treatment, then weekly for 1 month after initiation, then monthly for 6 months—more frequently if dose adjusted or abnormal liver function detected. Reduce dose if liver enzymes increase less than 3 times the normal upper limit—consult product literature; if liver enzymes are raised to 3 times or greater the normal upper limit, discontinue treatment permanently.

- **PATIENT AND CARER ADVICE**
  - Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain, or dark urine develop.
  - Patients or their carers should also be told how to recognise signs of adrenal insufficiency.

- **Driving and skilled tasks**
  - Dizziness and somnolence may affect the performance of skilled tasks (e.g. driving).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 2, 5, 21
  - Ketoconazole (non-proprietary) ▼
  - Ketoconazole 200 mg
  - Ketonazole 200 mg tablets | 60
  - Tablet P oM £48.00

### Metyrapone

- **DRUG ACTION**
  - Metyrapone is a competitive inhibitor of 11β-hydroxylation in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. Metyrapone may be used as a test of anterior pituitary function.

- **INDICATIONS AND DOSE**
  - Differential diagnosis of ACTH-dependent Cushing’s syndrome (specialist supervision in hospital)
    - BY MOUTH
    - Adult: 750 mg every 4 hours for 6 doses
  - Management of Cushing’s syndrome (specialist supervision in hospital)
    - BY MOUTH
    - Adult: Usual dose 0.25–6 g daily, dose to be tailored to cortisol production, dose is either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed
  - Resistant oedema due to increased aldosterone secretion in cirrhosis, nephrotic syndrome, and congestive heart failure (with glucocorticoid replacement therapy) (specialist supervision in hospital)
    - BY MOUTH
    - Adult: 3 g daily in divided doses

- **CONTRA-INDICATIONS**
  - Adrenocortical insufficiency

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930 · gross hypopituitarism (risk of precipitating acute adrenal failure) · hypertension on long-term administration · hypothyroidism (delayed response)

- **INTERACTIONS**
  - Many drugs interfere with diagnostic estimation of steroids.

- **SIDE-EFFECTS**
  - Rare: Abdominal pain · allergic skin reactions · hirsutism · hypoadrenalism

  - **Frequency not known**
    - Dizziness · headache · hypotension · nausea · sedation · vomiting

  - **PREGNANCY**
    - Avoid (may impair biosynthesis of fetal-placental steroids).

  - **BREAST FEEDING**
    - Avoid—no information available.

  - **HEPATIC IMPAIRMENT**
    - Use with caution in hepatic impairment (delayed response).

  - **PATIENT AND CARER ADVICE**
    - Driving and skilled tasks
      - Drowsiness may affect the performance of skilled tasks (e.g. driving).

### 3 Diabetes mellitus and hypoglycaemia

#### 3.1 Diabetes mellitus

### Overview

Diabetes mellitus occurs because of a lack of insulin or resistance to its action. It is diagnosed by measuring fasting or random blood-glucose concentration (and occasionally by oral glucose tolerance test). Although there are many subtypes, the two principal classes of diabetes are type 1 diabetes and type 2 diabetes.

- **Type 1 diabetes** (formerly referred to as insulin-dependent diabetes mellitus (IDDM)), occurs as a result of a deficiency of insulin following autoimmune destruction of pancreatic beta cells. Patients with type 1 diabetes require administration of insulin.

- **Type 2 diabetes** (formerly referred to as non-insulin-dependent diabetes (NIDDM)), is due to reduced secretion of insulin or to peripheral resistance to the action of insulin or to a combination of both. Although patients may be controlled on diet alone, many also require oral antidiabetic drugs or insulin (or both) to maintain satisfactory control. In overweight individuals, type 2 diabetes may be prevented by losing weight and increasing physical activity; use of the anti-obesity drug orlistat p. 86 may be considered in obese patients.

### Treatment of diabetes

Treatment of all forms of diabetes should be aimed at alleviating symptoms and minimising the risk of long-term complications; tight control of diabetes is essential.

Diabetes is a strong risk factor for cardiovascular disease. Other risk factors for cardiovascular disease such as smoking, hypertension, obesity, and hyperlipidaemia should be addressed. Cardiovascular risk in patients with diabetes can be further reduced by the use of an ACE inhibitor, low-dose aspirin p. 114 and a lipid-regulating drug.

### Prevention of diabetic complications

Optimal glycaemic control in both type 1 diabetes and type 2 diabetes reduces, in the long term, the risk of microvascular complications including retinopathy, development of proteinuria and to some extent neuropathy. However, a temporary deterioration in established diabetic retinopathy
may occur when normalising blood-glucose concentration (ACE inhibitors and angiotensin-II receptor antagonists may also have a role in the management of diabetic nephropathy).

A measure of the total glycosylated (or glycated) haemoglobin (HbA1c) or a specific fraction (HbA1c) provides a good indication of glycaemic control over the previous 2–3 months. Overall it is ideal to aim for an HbA1c (glycosylated haemoglobin) concentration of 48–59 mmol/mol or less (reference range 20–42 mmol/mol) but this cannot always be achieved and for those using insulin there is a significantly increased risk of disabling hypoglycaemia; in those at risk of arterial disease, the aim should be to maintain the HbA1c concentration at 48 mmol/mol or less. HbA1c should be measured every 3–6 months.

**Measurement of HbA1c**

HbA1c values are expressed in mmol of glycated haemoglobin per mol of haemoglobin (mmol/mol), a standardised unit specific for HbA1c, created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). HbA1c values were previously aligned to the assay used in the Diabetes Control and Complications Trial (DCCT) and expressed as a percentage.

<table>
<thead>
<tr>
<th>Equivalent values</th>
<th>IFCC-HbA1c (mmol/mol)</th>
<th>DCCT-HbA1c(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>7.0</td>
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<td>59</td>
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<td>64</td>
<td>8.0</td>
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</tr>
<tr>
<td>75</td>
<td>9.0</td>
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</tr>
</tbody>
</table>

Laboratory measurement of serum-fructosamine concentration is technically simpler and cheaper than the measurement of HbA1c, and can be used to assess control over short periods of time, particularly when HbA1c monitoring is invalid (e.g. disturbed erythrocyte turnover or abnormal haemoglobin type).

Tight control of blood pressure in hypertensive patients with type 2 diabetes reduces mortality and protects visual acuity (by reducing considerably the risks of maculopathy and retinal photocoagulation).

**Driving**

Drivers with diabetes may be required to notify the Driver and Vehicle Licensing Agency (DVLA) of their condition depending on their treatment, the type of licence, and whether they have diabetic complications. Detailed guidance on eligibility to drive, and precautions required, is available from the DVLA ([www.gov.uk/government/publications/at-a-glance](https://www.gov.uk/government/publications/at-a-glance)).

Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems. Drivers treated with insulin should normally check their blood-glucose concentration before driving and, on long journeys, at 2-hour intervals as specified by DVLA guidance; depending on the type of licence, monitoring may also be necessary for drivers taking oral antidiabetic drugs which carry a risk of hypoglycaemia (e.g. sulfonylureas, nateglinide p. 640, repaglinide p. 640). Drivers treated with insulin should ensure that a supply of sugar is always available in the vehicle and they should avoid driving if their meal is delayed. If hypoglycaemia occurs, or warning signs develop, the driver should:

- stop the vehicle in a safe place;
- switch off the ignition and move from the driver’s seat;
- eat or drink a suitable source of sugar;
- wait until 45 minutes after blood glucose has returned to normal, before continuing journey.

**Diabetic nephropathy**

Regular review of diabetic patients should include an annual test for urinary protein (using *Albustix*®) and serum creatinine measurement. If the urinary protein test is negative, the urine should be tested for microalbuminuria (the earliest sign of nephropathy). If reagent strip tests (*Micral-Test II*® or *Microbumintest*®) are used and prove positive, the result should be confirmed by laboratory analysis of a urine sample. Provided there are no contra-indications, all diabetic patients with nephropathy causing proteinuria or with established microalbuminuria (at least 3 positive tests) should be treated with an ACE inhibitor or an angiotensin-II receptor antagonist even if the blood pressure is normal; in any case, to minimise the risk of renal deterioration, blood pressure should be carefully controlled. Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor together with an angiotensin-II receptor antagonist.

ACE inhibitors can potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs; this effect is more likely during the first weeks of combined treatment and in patients with renal impairment.

See also treatment of hypertension in diabetes.

**Diabetic neuropathy**

Optimal diabetic control is beneficial for the management of painful neuropathy in patients with type 1 diabetes. Paracetamol p. 414 or a non-steroidal anti-inflammatory drug such as ibuprofen p. 999 may relieve *mild to moderate pain*.

Duloxetine p. 345 is effective for the treatment of painful diabetic neuropathy; amitriptyline hydrochloride p. 349 [unlicensed use] can be used if duloxetine is ineffective or unsuitable. Nortriptyline p. 355 [unlicensed use] may be better tolerated than amitriptyline hydrochloride. If treatment with amitriptyline hydrochloride or duloxetine is inadequate, treatment with pregabalin p. 304 should be tried. Combination therapy of duloxetine or amitriptyline hydrochloride with pregabalin can be used if monotherapy at the maximum tolerated dose does not control symptoms.

Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for tramadol hydrochloride p. 435, morphine p. 429, and oxycodone hydrochloride p. 431; however treatment with morphine or oxycodone hydrochloride should be initiated only under specialist supervision. Tramadol hydrochloride can be prescribed while the patient is waiting for assessment by a specialist if other treatments have been unsuccessful.

Gabapentin p. 295 and carbamazepine p. 291 are sometimes used for the treatment of neuropathic pain. Capsaicin cream 0.075% p. 446 is licensed for painful diabetic neuropathy and may have some effect, but it produces an intense burning sensation during the initial treatment period.

In autonomic neuropathy diabetic diarrhoea can often be managed by tetracycline [unlicensed use], otherwise codeine phosphate p. 421 is the best drug, but other antidiarrhoeal preparations can be tried. Erythromycin p. 497 (especially when given intravenously) may be beneficial for gastroparesis [unlicensed use] but this needs confirmation. In neuropathic postural hypotension increased salt intake and the use of the mineralcorticoid fludrocortisone acetate p. 619 [unlicensed use] may help by increasing plasma volume, but uncomfortable oedema is a common side-effect. Fludrocortisone can also be combined with flurbiprofen p. 998 and ephedrine hydrochloride p. 254 [both unlicensed]. Midodrine [unlicensed], an alpha agonist, may also be useful in postural hypotension.
Include complex structure. There are differences in the amino-acid sequence of animal insulins, human insulins and the human insulin analogues. Insulin may be extracted from pork pancreas and purified by crystallisation; it may also be extracted from beef pancreas, but beef insulins are now rarely used. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin (emp) or biosynthetically by recombinant DNA technology using bacteria (crb, prb) or yeast (pyr).

All insulin preparations are to a greater or lesser extent immunogenic in man but immunological resistance to insulin action is uncommon. Preparations of human sequence insulin should theoretically be less immunogenic, but no real advantage has been shown in trials.

Insulin is inactivated by gastro-intestinal enzymes, and must therefore be given by injection; the subcutaneous route is ideal in most circumstances. Insulin is usually injected into the upper arms, thighs, buttocks, or abdomen; absorption from a limb site may be increased if the limb is used in strenuous exercise after the injection. Generally subcutaneous insulin injections cause few problems; lipodystrophy may occur but can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Insulin is needed by all patients with ketoacidosis, and it is likely to be needed by most patients with:
- rapid onset of symptoms;
- substantial loss of weight;
- weakness;
- ketonuria;
- a first-degree relative who has type 1 diabetes.

Insulin is also needed for type 2 diabetes when other methods have failed to achieve good control, and temporarily in the presence of intercurrent illness or peri-operatively. Pregnant women with type 2 diabetes may be treated with insulin when diet alone fails. Antidiabetic drugs have a role in the management of diabetes in pregnancy.

### Management of diabetes with insulin

The aim of treatment is to achieve the best possible control of blood-glucose concentration without making the patient obsessional and to avoid disabling hypoglycaemia; close cooperation is needed between the patient and the medical team because good control reduces the risk of complications. Insulin preparations can be divided into 3 types:
- those of short duration which have a relatively rapid onset of action, namely soluble insulin and the rapid-acting insulin analogues, insulin aspart p. 653, insulin lispro p. 655, and insulin glargine p. 654;
- those with an intermediate action, e.g. isophane insulin p. 649; and
- those whose action is slower in onset and lasts for long periods, e.g. protamine zinc insulin p. 652, insulin detemir p. 651, and insulin glargine p. 651.

The duration of action of a particular type of insulin varies considerably from one patient to another, and needs to be assessed individually.

Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual patient. Treatment should be started with a short-acting insulin (e.g. soluble insulin) or a rapid-acting insulin analogue (e.g. insulin aspart) given before meals with intermediate-acting or long-acting insulin once or twice daily. Alternatively, for those who have difficulty with, or prefer not to use, multiple injection regimens, a mixture of premixed short-acting insulin or rapid-acting insulin analogue with an intermediate-acting or long-acting insulin (most commonly in a proportion of 30% soluble insulin and 70% isophane insulin) can be given once or twice daily. The dose of short-acting or rapid-acting insulin (or the proportion of the short-acting soluble insulin component in premixed insulin) can be increased in those with excessive postprandial hyperglycaemia. The dose of insulin is

### Insulins and anti-diabetic drugs

#### Insulins

Insulin plays a key role in the regulation of carbohydrate, fat, and protein metabolism. It is a polypeptide hormone of complex structure. There are differences in the amino-acid postprandial hyperglycaemia. The dose of insulin is

#### Diabetic ketoacidosis

**Management**


- To restore circulating volume if systolic blood pressure is below 90 mmHg (adjusted for age, sex, and medication as appropriate), give 500 mL sodium chloride 0.9% by intravenous infusion over 10–15 minutes; repeat if blood pressure remains below 90 mmHg and seek senior medical advice.

- When blood pressure is over 90 mmHg, sodium chloride 0.9% should be given by intravenous infusion at a rate that replaces deficit and provides maintenance; see guideline or suggested regimen.

- Include potassium chloride in the fluids unless anuria is suspected; adjust according to plasma-potassium concentration (measure at 60 minutes, 2 hours, and 2 hourly thereafter; measure hourly if outside the normal range).

- Start an intravenous insulin infusion: soluble insulin should be diluted (and mixed thoroughly) with sodium chloride 0.9% intravenous infusion to a concentration of 1 unit/mL; infuse at a fixed rate of 0.1 units/kg/hour.

- Established subcutaneous therapy with long-acting insulin analogues (insulin detemir p. 651 or insulin glargine p. 651) should be continued during treatment of diabetic ketoacidosis.

- Monitor blood-ketone and blood-glucose concentrations hourly and adjust the insulin infusion rate accordingly. Blood-ketone concentration should fall by at least 0.5 mmol/litre/hour and blood-glucose concentration should fall by at least 3 mmol/litre/hour.

- Once blood-glucose concentration falls below 14 mmol/litre, glucose 10% should be given by intravenous infusion (into a large vein through a large-gauge needle) at a rate of 125 mL/hour, in addition to the sodium chloride 0.9% infusion.

- Continue insulin infusion until blood-ketone concentration is below 0.3 mmol/litre, blood pH is above 7.3 and the patient is able to eat and drink; ideally give subcutaneous fast-acting insulin and a meal, and stop the insulin infusion 1 hour later.

The management of hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma is similar to that of diabetic ketoacidosis, although lower rates of insulin infusion are usually necessary and slower rehydration may be required.
increased gradually according to the patient’s individual requirements, taking care to avoid troublesome hypoglycaemic reactions.

Insulin requirements may be increased by infection, stress, accidental or surgical trauma, and during puberty. Requirements may be decreased in those with certain endocrine disorders (e.g. Addison’s disease, hypopituitarism), or in coeliac disease.

**Examples of recommended insulin regimens**

- Multiple injection regimen: short-acting insulin or rapid-acting insulin analogue, before meals. With intermediate-acting or long-acting insulin, once or twice daily;
- Short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting or long-acting insulin, once or twice daily (before meals);
- Intermediate-acting or long-acting insulin, once or twice daily. With or without short-acting insulin or rapid-acting insulin before meals;
- Continuous subcutaneous insulin infusion.

**Hypoglycaemia**

Loss of warning of hypoglycaemia among insulin-treated patients can be a serious hazard, especially for drivers and those in dangerous occupations. Very tight control of diabetes lowers the blood-glucose concentration needed to trigger hypoglycaemic symptoms; an increase in the frequency of hypoglycaemic episodes may reduce the warning symptoms experienced by the patient. Beta-blockers can also blunt hypoglycaemic awareness (and also delay recovery).

To restore the warning signs, episodes of hypoglycaemia must be minimised; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

Some patients have reported loss of hypoglycaemia warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemia awareness. If a patient believes that human insulin is responsible for the loss of warning it is reasonable to revert to animal insulin and essential to educate the patient about responsible for the loss of warning it is reasonable to revert to animal insulin and essential to educate the patient about awareness. If a patient believes that human insulin is not con

**Intermediate-acting or long-acting insulin**

Intermediate- or long-acting insulin, once or twice daily. Examples of recommended insulin regimens include the patient’s volume depletion, cardiac function, and age.

Protocols should include specific instructions on how to manage resistant cases (such as patients who are in shock or severely ill or those receiving corticosteroids or sympathomimetics) and those with hypoglycaemia.

If a syringe pump is not available, soluble insulin should be added to the intravenous infusion of glucose p. 915 and potassium chloride p. 929 (provided the patient is not hyperkalaemic), and the infusion run at the rate appropriate to the patient’s fluid requirements (usually 125 mL per hour) with the insulin dose adjusted according to blood-glucose concentration in line with locally agreed protocols.

Once the patient starts to eat and drink, give subcutaneous insulin before breakfast and stop intravenous insulin 30 minutes later; the dose may need to be 10–20% more than usual if the patient is still in bed or unwell. If the patient was not previously receiving insulin, an appropriate initial dose is 30–40 units daily in four divided doses using soluble insulin before meals and intermediate-acting insulin at bedtime and the dose adjusted from day to day. Patients with hyperglycaemia often relapse after conversion back to subcutaneous insulin calling for one of the following approaches:

- additional doses of soluble insulin at any of the four injection times (before meals or bedtime) or
- temporary addition of intravenous insulin infusion (while continuing the subcutaneous regimen) until blood-glucose concentration is satisfactory or
- complete reversion to the intravenous regimen (especially if the patient is unwell).

**Short-acting insulins**

**Soluble insulin** is a short-acting form of insulin. For maintenance regimens it is usual to inject it 15 to 30 minutes before meals.

Soluble insulin is the most appropriate form of insulin for use in diabetic emergencies e.g. diabetic ketoacidosis (see Diabetic ketoacidosis p. 627) and at the time of surgery. It can be given intravenously and intramuscularly, as well as subcutaneously.

When injected subcutaneously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.

The rapid-acting human insulin analogues, insulin aspart p. 653, insulin glulisine p. 653, and insulin lispro p. 654 have a faster onset and shorter duration of action than soluble insulin; as a result, compared to soluble insulin, fasting and preprandial blood-glucose concentrations are a little higher, postprandial blood-glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently.

Subcutaneous injection of insulin analogues may be convenient for those who wish to inject shortly before or, when necessary, shortly after a meal. They can also help those susceptible to hypoglycaemia before lunch and those who eat late in the evening and are prone to nocturnal hypoglycaemia. They can also be administered by subcutaneous infusion. Insulin aspart and insulin lispro can be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

**Intermediate- and long-acting insulins**

When given by subcutaneous injection, intermediate- and long-acting insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours, and a duration of 16–42 hours. Some are given twice daily in conjunction with short-acting (soluble) insulin, and others are given once daily, particularly in elderly patients. Soluble insulin can be mixed with intermediate and long-acting
insulins (except insulin detemir p. 651, insulin glargine p. 651, and insulin degludec p. 650) in the syringe, essentially retaining the properties of the two components, although there may be some blunting of the initial effect of the soluble insulin component (especially on mixing with protamine zinc insulin p. 652).

Isophane insulin p. 649 is a suspension of insulin with protamine; it is of particular value for initiation of twice-daily insulin regimens. Patients usually mix isophane with soluble insulin but ready-mixed preparations may be appropriate (biphasic isophane insulin p. 649, biphasic insulin aspart p. 650, or biphasic insulin lispro p. 650).

Insulin zinc suspension p. 652 (30% amorphous, 70% crystalline) has a more prolonged duration of action. Protamine zinc insulin is usually given once daily with short-acting (soluble) insulin. It has the drawback of binding with the soluble insulin when mixed in the same syringe and is now rarely used.

Insulin glargine and insulin detemir are both long-acting human insulin analogues with a prolonged duration of action; insulin glargine is given once daily and insulin detemir is given once or twice daily. NICE (December 2002) has recommended that insulin glargine should be available as an option for patients with type 1 diabetes.

NICE (May 2009) has recommended that, if insulin is required in patients with type 2 diabetes, insulin detemir or insulin glargine may be considered for those:

- who require assistance with injecting insulin or
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia or
- who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs or
- who cannot use the device needed to inject isophane insulin.

Insulin detemir is also licensed as add-on therapy in patients receiving treatment with liraglutide p. 639.

Insulin degludec is a long-acting human insulin analogue for once daily subcutaneous administration.

**Hypodermic equipment**

Patients should be advised on the safe disposal of lancets, single-use syringes, and needles. Suitable arrangements for the safe disposal of contaminated waste must be made before these products are prescribed for patients who are carriers of infectious diseases.

Lancets, needles, syringes, and accessories are listed under Hypodermic Equipment in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 of the Scottish Drug Tariff). The drug Tariffs can be accessed online at:

- National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm
- Health and Personal Social Services for Northern Ireland Drug Tariff: www.hscbusiness.hscni.net/services/2034.htm
- Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

**Antidiabetic drugs**

Oral antidiabetic drugs are used for the treatment of type 2 diabetes mellitus. They should be prescribed only if the patient fails to respond adequately to at least 3 months’ restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them.

For patients not adequately controlled by diet and oral hypoglycaemic drugs, insulin may be added to the treatment regimen or substituted for oral therapy. When insulin is added to oral therapy, it is generally given at bedtime as isophane or long-acting insulin, and when insulin replaces an oral regimen it may be given as twice-daily injections of a biphasic insulin (or isophane insulin p. 649 mixed with soluble insulin), or a multiple injection regimen. Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain may be reduced if the insulin is given in combination with metformin hydrochloride p. 631.

**Pregnancy and breast-feeding**

During pregnancy, women with pre-existing diabetes can be treated with metformin hydrochloride [unlicensed use], either alone or in combination with insulin. Metformin hydrochloride can be continued, or glibenclamide p. 645 resumed, during breast-feeding for those with pre-existing diabetes. Women with gestational diabetes may be treated, with or without concomitant insulin, with glibenclamide from 11 weeks gestation (after organogenesis) [unlicensed use] or with metformin [unlicensed use]. Women with gestational diabetes should discontinue hypoglycaemic treatment after giving birth.

**Sulfonylureas**

The sulfonylureas act mainly by increasing insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.

Sulfonylureas are considered for patients who are not overweight, or in whom metformin hydrochloride is contra-indicated or not tolerated. Several sulfonylureas are available and choice is determined by side-effects and the duration of action as well as the patient’s age and renal function. Glibenclamide, a long-acting sulfonylurea, is associated with a greater risk of hypoglycaemia; for this reason it should be avoided in the elderly, and shorter-acting alternatives, such as gliquidone p. 645 or tolbutamide p. 647, should be used instead.

When the combination of strict diet and sulfonylurea treatment fails, other options include:

- combining with metformin;
- combining with pioglitazone;
- combining with alogliptin, linagliptin, saxagliptin, sitagliptin, or vildagliptin;
- combining with canagliflozin, dapagliflozin or empagliflozin;
- combining with exenatide, liraglutide, or lixisenatide;
- combining with acarbose, which may have a small beneficial effect, but flatulence can be a problem;
- combining with bedtime isophane insulin but weight gain and hypoglycaemia can occur.

Insulin therapy should be instituted temporarily during intercurrent illness (such as myocardial infarction, coma, infection, and trauma). Sulfonylureas should be omitted on the morning of surgery; insulin is required because of the ensuing hyperglycaemia in these circumstances.

**Biguanides**

Metformin hydrochloride, the only available biguanide, has a different mode of action from the sulfonylureas, and is not interchangeable with them.

Metformin hydrochloride is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes, if appropriate it may also be considered as an option in patients who are not overweight. It is also used when diabetes is inadequately controlled with sulfonylurea treatment. When the combination of strict diet and metformin hydrochloride treatment fails, other options include:

- combining with a sulfonylurea;
- combining with pioglitazone p. 647;
- combining with repaglinide p. 640 or nateglinide p. 640;
- combining with alogliptin p. 633, linagliptin p. 633, saxagliptin p. 634, sitagliptin p. 635, or vildagliptin p. 636;
Postprandial hyperglycaemia in type 2 hypoglycaemics are not tolerated or are contra-indicated. Use of acarbose is usually reserved for when other oral antidiabetic drugs are continued only if HbA1c concentration is reduced by at least 0.5 percentage points within 6 months of starting treatment.

Linaclotide is licensed for use in type 2 diabetes as monotherapy (if metformin hydrochloride inappropriate), or in combination with metformin hydrochloride (when treatment with metformin hydrochloride alone fails to achieve adequate glycaemic control), or both metformin hydrochloride and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control). Linaclotide may also be used in combination with insulin (with or without metformin hydrochloride) when a stable dose of insulin has not provided adequate glycaemic control.

Saxagliptin and vildagliptin are licensed for use in type 2 diabetes as monotherapy (if metformin hydrochloride inappropriate), or in combination with metformin hydrochloride or a sulfonylurea (if metformin hydrochloride inappropriate), or pioglitazone p. 647 (when treatment with either metformin hydrochloride p. 631 or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control), and also in combination with both metformin hydrochloride and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control). The combination of either saxagliptin p. 634 or vildagliptin p. 636, and insulin (with or without metformin hydrochloride) is also licensed for use when a stable dose of insulin has not provided adequate glycaemic control.

Alogliptin p. 633 is also licensed for use as triple therapy in combination with metformin hydrochloride and either pioglitazone or insulin.

NICE (May 2009) has recommended that, when glycaemic control is inadequate with existing treatment:
- sitagliptin or vildagliptin (instead of a sulfonylurea) can be added to metformin, if there is a significant risk of hypoglycaemia or if a sulfonylurea is contra-indicated or not tolerated;
- sitagliptin or vildagliptin can be added to a sulfonylurea, if metformin is contra-indicated or not tolerated;
- sitagliptin can be added to both metformin and a sulfonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese. NICE has recommended that treatment with sitagliptin p. 635 or vildagliptin is continued only if HbA1c concentration is reduced by at least 0.5 percentage points within 6 months of starting treatment.

Treatment with exenatide p. 638, liraglutide p. 639, and lixisenatide p. 639 is associated with the prevention of weight gain and possible promotion of weight loss which can be beneficial in overweight patients. They are given by subcutaneous injection for the treatment of type 2 diabetes mellitus.

Exenatide is licensed in combination with metformin hydrochloride or a sulfonylurea, or both, or with pioglitazone, or with both metformin hydrochloride and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination; standard-release exenatide is also licensed in combination with basal insulin alone or with metformin hydrochloride or pioglitazone (or both).

NICE (May 2009) has recommended that, when glycaemic control is inadequate with metformin hydrochloride and sulfonylurea treatment, the addition of standard-release exenatide may be considered if the patient has:
- a body mass index of 35 kg/m² or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems or
- a body mass index less than 35 kg/m², and insulin would be unacceptable for occupational reasons or weight loss would benefit other significant obesity-related comorbidities.

NICE has recommended that treatment with standard release exenatide is continued only if HbA1c concentration is
reduced by at least 1 percentage point and a weight loss of at least 3% is achieved within 6 months of starting treatment.

Acarbose p. 636 is licensed for the treatment of type 2 diabetes mellitus, either alone (if metformin hydrochloride inappropriate) or in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control).

Dulaglutide p. 637 is licensed for the treatment of type 2 diabetes mellitus alone (if metformin is inappropriate) or in combination with other antidiabetic drugs in patients who have not achieved adequate glycaemic control with these drugs.

Liraglutide is licensed for the treatment of type 2 diabetes mellitus in combination with metformin hydrochloride or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. Liraglutide is also licensed for use in combination with basal insulin or both metformin hydrochloride and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control. Liraglutide is licensed for use in combination with basal insulin or both metformin hydrochloride and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control.

Lixisenatide is licensed for the treatment of type 2 diabetes as monotherapy (if metformin hydrochloride inappropriate) or in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control). Dapagliflozin is not recommended in combination with pioglitazone.

BLOOD GLUCOSE LOWERING DRUGS ▶ ALPHA GLUCOSIDASE INHIBITORS

Acarbose

DRUG ACTION Acarbose, an inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose; it has a small but significant effect in lowering blood glucose.

INDICATIONS AND DOSE Diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs

- Adult: Initially 50 mg daily, then increased to 50 mg 3 times a day for 6–8 weeks, then increased if necessary to 100 mg 3 times a day (max. per dose 200 mg 3 times a day)

CONTRA-INDICATIONS Hernia - inflammatory bowel disease - predisposition to partial intestinal obstruction - previous abdominal surgery

CAUTIONS May enhance hypoglycaemic effects of insulin and sulfonylureas (hypoglycaemic episodes may be treated with oral glucose but not with sucrose)

INTERACTIONS ▶ Appendix 1 (antidiabetics).

SIDE-EFFECTS

- Common or very common Abdominal distention and pain - diarrhoea (may need to reduce dose or withdraw) - flatulence - soft stools

- Rare Abnormal liver function tests - nausea - skin reactions

- Very rare Hepatitis - ileus - jaundice - oedema

SIDE-EFFECTS, FURTHER INFORMATION Antacids Antacids unlikely to be beneficial for treating side effects.
Diabetes mellitus and hypoglycaemia

● UNLICENSED USE
In adults Doses in the BNF may differ from those in the product literature. Not licensed for polycystic ovary syndrome.
In children Not licensed for use in children under 10 years.

● CONTRA-INDICATIONS KETOACIDOSIS · use of general anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to baseline)
CONTRA-INDICATIONS, FURTHER INFORMATION
- Iodine-containing x-ray contrast media Intravascular administration of iodinated contrast agents can cause renal failure, which can increase the risk of lactic acidosis with metformin. Suspend metformin prior to the test; restart no earlier than 48 hours after the test if renal function has returned to baseline.

● CAUTIONS Can provoke lactic acidosis
● INTERACTIONS Appendix 1 (anti-diabetics)

● SIDE-EFFECTS
- Common or very common Abdominal pain · anorexia · diarrhoea (usually transient) · nausea · taste disturbance · vomiting
- Rare Decreased vitamin-B12 absorption · erythema · lactic acidosis (withdraw treatment) · pruritus · urticaria
- Frequency not known Hepatitis
SIDE-EFFECTS, FURTHER INFORMATION
- Gastro-intestinal side-effects Gastro-intestinal side-effects are initially common with metformin, and may persist in some patients, particularly when very high doses are given. A slow increase in dose may improve tolerability.

● PREGNANCY Can be used in pregnancy for both pre-existing and gestational diabetes. Women with gestational diabetes should discontinue treatment after giving birth.

● BREAST FEEDING May be used during breast-feeding in women with pre-existing diabetes.

● HEPATIC IMPAIRMENT Withdraw if tissue hypoxia likely.

● RENAL IMPAIRMENT Use with caution in renal impairment—increased risk of lactic acidosis. Lactic acidosis Withdraw or interrupt treatment in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or those who have recently had a myocardial infarction.
In adults NICE (clinical guideline 87 (May 2009): Type 2 diabetes: The management of type 2 diabetes) recommends that the dose should be reviewed if eGFR less than 45 mL/minute/1.73 m² and to avoid if eGFR less than 30 mL/minute/1.73 m².
In children Avoid in significant renal impairment.

● MONITORING REQUIREMENTS Determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected).

● PRESCRIBING AND DISPENSING INFORMATION
● in adults Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of metformin modified release; not suitable if dose of standard-release tablets more than 2 g daily.

● PATIENT AND CARER ADVICE
Medicines for Children leaflet: Metformin for diabetes www.medicinesforchildren.org.uk/metformin-diabetes

● NATIONAL FUNDING/ACCESS DECISIONS

GLUCOPHAGE® SR
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (September 2009) that Glucophage® SR is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in adult patients who are intolerant of standard-release metformin, and in whom the prolonged-release tablet allows the use of a dose of metformin not previously tolerated, or in patients for whom a once daily preparation offers a clinically significant benefit.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Tablet CAUTIONARY AND ADVISORY LABELS 21
- Metformin hydrochloride (Non-proprietary) Metformin hydrochloride 500 mg Metformin 500mg tablets | 28 tablet POM £1.55 DT price = £0.96 | 84 tablet POM £2.58 | 500 tablet POM £15.36
- Metformin hydrochloride 850 mg Metformin 850mg tablets | 56 tablet POM £2.48 DT price = £1.20 | 60 tablet POM no price available | 300 tablet POM £7.07
- Glucophage (Merck Serono Ltd) Metformin hydrochloride 500 mg Glucophage 500mg tablets | 84 tablet POM £2.88
- Metformin hydrochloride 850 mg Glucophage 850mg tablets | 56 tablet POM £3.20 DT price = £1.20

Modified-release tablet CAUTIONARY AND ADVISORY LABELS 21, 25
- Metformin hydrochloride (Non-proprietary) Metformin hydrochloride 500 mg Metformin 500mg modified-release tablets | 28 tablet POM £2.66 | 56 tablet POM £5.32 DT price = £5.32
- Metformin hydrochloride 750 mg Metformin 750mg modified-release tablets | 28 tablet POM £6.40
- Metformin hydrochloride 1 gram Metformin 1g modified-release tablets | 28 tablet POM £4.26 | 56 tablet POM £8.70 DT price = £8.52
- Bolamyn SR (Teva UK Ltd) Metformin hydrochloride 500 mg Bolamyn SR 500mg tablets | 28 tablet POM £3.20 | 56 tablet POM £6.40 DT price = £5.32
- Diagemet NR (Genus Pharmaceuticals Ltd) Metformin hydrochloride 500 mg Diagemet NR 500mg tablets | 28 tablet POM £1.49 | 56 tablet POM £2.97 DT price = £5.32
- Glucient SR (Consilient Health Ltd) Metformin hydrochloride 500 mg Glucient SR 500mg tablets | 28 tablet POM £2.51 | 56 tablet POM £5.03 DT price = £5.32
- Glucient SR (Consilient Health Ltd) Metformin hydrochloride 750 mg Glucient SR 750mg tablets | 28 tablet POM £3.20
- Glucophase SR (Metrom Serono Ltd) Metformin hydrochloride 750 mg Glucophage SR 750mg tablets | 28 tablet POM £2.66 | 56 tablet POM £5.32 DT price = £5.32

Oral solution CAUTIONARY AND ADVISORY LABELS 21
- Metformin hydrochloride (Non-proprietary) Metformin hydrochloride 100 mg per 1 ml Metformin 500mg/5ml oral solution sugar free sugar-free | 100 ml POM £15.00 sugar-free | 150 ml POM £60.00 DT price = £15.65
- Metformin hydrochloride 170 mg per 1 ml Metformin 850mg/5ml oral solution sugar free sugar-free | 150 ml POM £19.95
- Metformin hydrochloride 200 mg per 1 ml Metformin 1g/5ml oral solution sugar free sugar-free | 150 ml POM £23.48
Dipeptidylpeptidase-4 inhibitors (GLIPTINS)

Alogliptin

**DRUG ACTION** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus as dual therapy in combination with either metformin, pioglitazone, a sulfonylurea, or insulin (when treatment with these drugs alone fails to achieve adequate glycaemic control), or as triple therapy in combination with metformin and either pioglitazone or insulin

- **BY MOUTH**
  - Adult: 25 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant sulfonylurea or insulin may need to be reduced. Caution with use in combination with both metformin and pioglitazone—risk of hypoglycaemia (dose of metformin or pioglitazone may need to be reduced).

**CONTRA-INDICATIONS** Ketaendosis

**CAUTIONS** History of pancreatitis. Not recommended in moderate to severe heart failure (limited experience)

**INTERACTIONS** → Appendix 1 (antidiabetics).

**SIDE-EFFECTS**

- Common or very common Abdominal pain, gastro-oesophageal reflux, headache, nasopharyngitis, pruritus, rash, upper respiratory tract infection
- Frequency not known Angioedema, hepatic impairment, pancreatitis, Stevens-Johnson syndrome, urticaria

**SIDE-EFFECTS, FURTHER INFORMATION**

Pancreatitis: Discontinue if symptoms of acute pancreatitis (persistent, severe, abdominal pain).

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of serious hypersensitivity to dipeptidylpeptidase-4 inhibitors.

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.

**RENAL IMPAIRMENT** Reduce dose to 12.5 mg once daily if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 6.25 mg once daily if eGFR less than 30 mL/minute/1.73 m². Use with caution if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Determine renal function before treatment and periodically thereafter.

**MEDICINAL FORMS**

- **Tablet**
  - Alogliptin (as Alogliptin benzoate) 6.25 mg. Alogliptin 6.25mg tablets | 28 tablet pack | no price available DT price = £26.60

Alogliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, alogliptin above, metformin hydrochloride p. 631.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either pioglitazone or insulin

- **BY MOUTH**
  - Adult: 1 tablet twice daily, based on patient’s current metformin dose

**INTERACTIONS**

Dose of concomitant sulfonylurea or insulin may need to be reduced. Caution with use in combination with both metformin and pioglitazone—risk of hypoglycaemia (dose of metformin or pioglitazone may need to be reduced).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21

- Alogliptin with metformin (non-proprietary) ▼
  - Alogliptin (as Alogliptin benzoate) 12.5 mg, Metformin hydrochloride 1 gram. Alogliptin 12.5mg / Metformin 1g tablets | 28 tablet pack | no price available DT price = £26.60
  - Vipedia (Takeda UK Ltd) ▼
    - Alogliptin (as Alogliptin benzoate) 6.25 mg, Vipedia 6.25mg tablets | 28 tablet pack | £26.60 DT price = £26.60

Linagliptin

**DRUG ACTION** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with metformin (when treatment with metformin alone fails to achieve adequate glycaemic control), or both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control) or Type 2 diabetes mellitus in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control

- **BY MOUTH**
  - Adult: 5 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant sulfonylurea or insulin may need to be reduced.

**INTERACTIONS** → Appendix 1 (antidiabetics).

**SIDE-EFFECTS**

- Uncommon: Cough, nasopharyngitis
- Frequency not known: Pancreatitis
**SIDE-EFFECTS, FURTHER INFORMATION**

- **Pancreatitis** Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).
- **PREGNANCY** Avoid—no information available.
- **BREAST FEEDING** Avoid—present in milk in animal studies.
- **NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised that linagliptin (Trajenta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as monotherapy when both metformin and a sulfonylurea are inappropriate (January 2013), and in combination with metformin when addition of a sulfonylurea is inappropriate (December 2011).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Tradjenta** (Boehringer Ingelheim Ltd)
- Linagliptin 5 mg Tradjenta 5mg tablets | 28 tablet POM £33.26

**Linagliptin with metformin**
The properties listed below are those particular to the combination only. For the properties of the components please consider, linagliptin p. 633, metformin hydrochloride p. 631.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin

- **BY MOUTH**
- **Adult**: 1 tablet twice daily, based on patient’s current metformin dose

**INTERACTIONS**
Dose of concomitant sulfonylurea or insulin may need to be reduced.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (May 2015) that linagliptin plus metformin combination tablets (Jentadueto®) are accepted for restricted use within NHS Scotland for the treatment of adult patients with type 2 diabetes mellitus in combination with insulin, as an adjunct to diet and exercise to improve glycaemic control when a combination of insulin and metformin alone is inadequate. It is restricted to use in the treatment of patients for whom a combination of linagliptin and metformin is an appropriate choice of therapy and the fixed doses are considered appropriate.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Jentadueto** (Boehringer Ingelheim Ltd)
- Linagliptin 2.5 mg, Metformin hydrochloride 850 mg Jentadueto 2.5mg/850mg tablets | 56 tablet POM £33.26
- Linagliptin 2.5 mg, Metformin hydrochloride 1000 mg Jentadueto 2.5mg/1000mg tablets | 56 tablet POM £33.26

**Saxagliptin**

**DRUG ACTION**
Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with metformin or a sulfonylurea (if metformin inappropriate), or pioglitazone (when treatment with either metformin or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control), and also in combination with both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control) | Type 2 diabetes mellitus in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control

- **BY MOUTH**
- **Adult**: 5 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CAUTIONS**
Elderly

**INTERACTIONS**
→ Appendix 1 (antidiabetics).

**SIDE-EFFECTS**

- **Common or very common** Dizziness, dyspepsia, fatigue, gastritis, gastroenteritis, headache, hypoglycaemia, myalgia, nasopharyngitis, peripheral oedema, sinusitis, upper respiratory tract infection, urinary tract infection, vomiting
- **Uncommon** Anaphylaxis, arthralgia, dyslipidaemia, erectile dysfunction, hypersensitivity reactions, hypertriglyceridaemia, pancreatitis
- **Frequency not known** Rash

**SIDE-EFFECTS, FURTHER INFORMATION**
Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated if patient has a history of serious hypersensitivity to dipeptidylpeptidase-4 inhibitors.

**PREGNANCY**
Avoid unless essential—toxicity in animal studies.

**BREAST FEEDING**
Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Use with caution in moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
Reduce dose to 2.5 mg once daily in moderate to severe impairment. Use with caution in severe impairment.

**MONITORING REQUIREMENTS**
Determine renal function before treatment and periodically thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised that saxagliptin (Onglyza®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as triple therapy in combination with metformin and a sulfonylurea, as an alternative to existing dipeptidyl peptidase-4 inhibitors, when treatment with metformin and a sulfonylurea is inadequate (November 2013).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Onglyza** (AstraZeneca UK Ltd)
- Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg Onglyza 2.5mg tablets | 28 tablet POM £31.60
- Saxagliptin (as Saxagliptin hydrochloride) 5 mg Onglyza 5mg tablets | 28 tablet POM £31.60

**DISPENSING INSTRUCTIONS**

- **CAUTIONARY AND ADVISORY LABELS**

- **Tablet**

- **Jentadueto** (Boehringer Ingelheim Ltd)
- Linagliptin 2.5 mg, Metformin hydrochloride 850 mg Jentadueto 2.5mg/850mg tablets | 56 tablet POM £33.26
- Linagliptin 2.5 mg, Metformin hydrochloride 1000 mg Jentadueto 2.5mg/1000mg tablets | 56 tablet POM £33.26

- **Onglyza** (AstraZeneca UK Ltd)
- Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg Onglyza 2.5mg tablets | 28 tablet POM £31.60
- Saxagliptin (as Saxagliptin hydrochloride) 5 mg Onglyza 5mg tablets | 28 tablet POM £31.60

**DOSAGE ADJUSTMENTS DUE TO INTERACTIONS**
Dose of concomitant sulfonylurea or insulin may need to be reduced.
Saxagliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, saxagliptin p. 634, metformin hydrochloride p. 631.

- **INDICATIONS AND DOSE**
  - Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin
    - **BY MOUTH**
    - Adult: 1 tablet twice daily, based on patient’s current metformin dose

- **INTERACTIONS** Dose of concomitant sulfonylurea or insulin may need to be reduced.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (May 2013) that Komboglyze® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone and when the addition of a sulfonylurea is inappropriate.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - **CAUTIONARY AND ADVISORY LABELS 21**
      - Komboglyze (AstraZeneca UK Ltd)
        - Metformin hydrochloride 1 gram, Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg, Metformin hydrochloride 850 mg. For the properties of the components containing the same drug.
      - Sitagliptin with metformin (as Sitagliptin phosphate) 25 mg
        - Januvia 25mg tablets 56 tablet £31.60 DT price = £31.60
      - Sitagliptin with metformin (as Sitagliptin phosphate) 50 mg
        - Januvia 50mg tablets 56 tablet £33.26 DT price = £33.26
      - Sitagliptin with metformin (as Sitagliptin phosphate) 100 mg
        - Januvia 100mg tablets 28 tablet £33.26 DT price = £33.26

  - **Table**
    - Januvia (Merck Sharp & Dohme Ltd)
      - Sitagliptin (as Sitagliptin phosphate) 25 mg Januvia 25mg tablets 28 tablet (POM) £33.26 DT price = £33.26
      - Sitagliptin (as Sitagliptin phosphate) 50 mg Januvia 50mg tablets 28 tablet (POM) £33.26 DT price = £33.26
      - Sitagliptin (as Sitagliptin phosphate) 100 mg Januvia 100mg tablets 28 tablet (POM) £33.26 DT price = £33.26

Sitagliptin

- **INDICATIONS AND DOSE**
  - Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with metformin or a sulfonylurea (if metformin inappropriate), or pioglitazone (when treatment with either metformin or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control), and also in combination with both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control) | Type 2 diabetes mellitus in combination with both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control, and may also be used in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control
  - **BY MOUTH**
  - Adult: 100 mg once daily

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Dose of concomitant sulfonylurea or insulin may need to be reduced.

- **CONTRA-INDICATIONS**
  - Ketoacidosis

- **INTERACTIONS** ➔ Appendix 1 (antidiabetics).

- **SIDE-EFFECTS**
  - Common or very common ➔ Gastro-intestinal disturbances ➔ nasopharyngitis ➔ pain ➔ peripheral oedema ➔ upper respiratory tract infection
  - Uncommon ➔ Anorexia ➔ dizziness ➔ drowsiness ➔ dry mouth ➔ headache ➔ hypoglycaemia ➔ osteoarthritis

- **FREQUENCY NOT KNOWN**
  - Cutaneous vasculitis ➔ pancreatitis ➔ rash ➔ Stevens-Johnson syndrome

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

- **PREGNANCY**
  - Avoid ➔ toxicity in animal studies.

- **BREAST FEEDING**
  - Avoid ➔ present in milk in animal studies.

- **RENAL IMPAIRMENT**
  - Reduce dose to 50 mg once daily if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 25 mg once daily if eGFR less than 30 mL/minute/1.73 m².

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (June 2010) that Januvia® is accepted for restricted use within NHS Scotland as monotherapy, to improve glycaemic control in patients with type 2 diabetes mellitus, for whom both metformin and sulfonylureas are not appropriate.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - Januvia (Merck Sharp & Dohme Ltd)
      - Sitagliptin (as Sitagliptin phosphate) 25 mg Januvia 25mg tablets 56 tablet (POM) £31.60 DT price = £31.60
      - Sitagliptin (as Sitagliptin phosphate) 50 mg Januvia 50mg tablets 56 tablet (POM) £33.26 DT price = £33.26
      - Sitagliptin (as Sitagliptin phosphate) 100 mg Januvia 100mg tablets 28 tablet (POM) £33.26 DT price = £33.26

Sitagliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, sitagliptin above, metformin hydrochloride p. 631.

- **INDICATIONS AND DOSE**
  - Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or pioglitazone or insulin
  - **BY MOUTH**
  - Adult: 1 tablet twice daily

- **INTERACTIONS** Dose of concomitant sulfonylurea or insulin may need to be reduced.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (July 2008) that Janumet® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus when the addition of a sulfonylurea to metformin is not appropriate; it is also accepted for use in NHS Scotland in combination with a sulfonylurea in patients inadequately controlled on maximum tolerated doses of metformin and a sulfonylurea.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - Janumet (Merck Sharp & Dohme Ltd)
      - Metformin hydrochloride 1 gram, Sitagliptin (as Sitagliptin phosphate) 25 mg Janumet 25mg tablets 56 tablet (POM) £33.26 DT price = £33.26
      - Metformin hydrochloride 1 gram, Sitagliptin (as Sitagliptin phosphate) 50 mg Janumet 50mg tablets 56 tablet (POM) £33.26 DT price = £33.26
Vildagliptin

- **DRUG ACTION** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

- **INDICATIONS AND DOSE**
  Type 2 diabetes mellitus as monotherapy (if metformin inappropriate) | Type 2 diabetes mellitus in combination with metformin or pioglitazone (when treatment with either metformin or pioglitazone fails to achieve adequate glycaemic control) | Type 2 diabetes mellitus in combination with both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control) | Type 2 diabetes mellitus in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control
  
  ▶ **BY MOUTH**
  
  Adult: 50 mg twice daily

  Type 2 diabetes mellitus in combination with sulfonylurea (if metformin inappropriate)
  
  ▶ **BY MOUTH**
  
  Adult: 50 mg daily, dose to be taken in the morning

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  Dose of concomitant sulfonylurea or insulin may need to be reduced.

- **CONTRA-INDICATIONS** KETOACIDOSIS

- **CAUTIONS** Manufacturer advises avoid in severe heart failure—no information available

- **INTERACTIONS** → Appendix 1 (antidiabetics).

- **SIDE-EFFECTS**
  ▶ **Common or very common** Asthenia · dizziness · headache · nausea · peripheral oedema · tremor
  ▶ **Uncommon** Arthralgia · constipation · hypoglycaemia
  ▶ **Rare** Hepatic dysfunction
  ▶ **Very rare** Nasopharyngitis · upper respiratory tract infection
  ▶ **Frequency not known** Bullous skin reactions · exfoliative skin reactions · pancreatitis

- **SIDE-EFFECTS, FURTHER INFORMATION**
  ▶ Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).
  ▶ Liver toxicity Rare reports of liver dysfunction; discontinue if jaundice or other signs of liver dysfunction occur.

- **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Avoid.

- **RENAL IMPAIRMENT** Reduce dose to 50 mg once daily if eGFR less than 50 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS** Monitor liver function before treatment and every 3 months for first year and periodically thereafter.

- **PATIENT AND CARER ADVICE**
  Liver toxicity Patients should be advised to seek prompt medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue, and dark urine develop.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  **Scottish Medicines Consortium (SMC) Decisions**
  The Scottish Medicines Consortium has advised that vildagliptin (Galvus®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as monotherapy when treatment with metformin or a sulfonylurea is inappropriate (December 2012), and in combination with metformin when addition of a sulfonylurea is inappropriate (March 2008), and in combination with a sulfonylurea if metformin is inappropriate (September 2009), and also as triple therapy in combination with metformin and a sulfonylurea, as an alternative to existing dipeptidyl peptidase-4 inhibitors, when treatment with metformin and a sulfonylurea is inadequate (November 2013).

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  ▶ **Galvus** (Novartis Pharmaceuticals UK Ltd)
  Vildagliptin 50 mg | 56 tablet [POT] £33.35 DT price = £33.35

Vildagliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, vildagliptin above, metformin hydrochloride p. 631.

- **INDICATIONS AND DOSE**
  Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin
  
  ▶ **BY MOUTH**
  
  Adult: 1 tablet twice daily, based on patient’s current metformin dose

- **INTERACTIONS** Dose of concomitant sulfonylurea or insulin may need to be reduced.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  **Scottish Medicines Consortium (SMC) Decisions**
  The Scottish Medicines Consortium has advised (June 2008) that Eucreas® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone or those already treated with vildagliptin and metformin as separate tablets.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 21
  ▶ **Eucreas** (Novartis Pharmaceuticals UK Ltd)
  Metformin hydrochloride 1 gram, Vildagliptin 50 mg | 60 tablet [POT] £35.68 DT price = £35.68
  Vildagliptin 50 mg, Metformin hydrochloride 850 mg | 60 tablet [POT] £35.68 DT price = £35.68

**BLOOD GLUCOSE LOWERING DRUGS**

**GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS**

**Albiglutide**

- **DRUG ACTION** Albiglutide is a GLP-1 (glucagon-like peptide-1) receptor agonist that augments glucose-dependent insulin secretion, and slows gastric emptying.

- **INDICATIONS AND DOSE**
  Type 2 diabetes mellitus as monotherapy when treatment with metformin is considered inappropriate | Type 2 diabetes mellitus in combination with basal insulin and other oral glucose lowering agents
  
  ▶ **BY SUBCUTANEOUS INJECTION**
  
  Adult: 30 mg once weekly, increased if necessary up to 50 mg once weekly, to be administered on the same day each week

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

- **CONTRA-INDICATIONS** Severe gastrointestinal disease—no information available
Dulaglutide

**Drug Action**
Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist that augments glucose-dependent insulin secretion, and slows gastric emptying.

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - Eperzan (GlaxoSmithKline UK Ltd) ▼
    - Dulaglutide 30 mg Eperzan 30mg powder and solvent for solution for injection pre-filled pen | 4 pre-filled disposable injection £71.00
    - Dulaglutide 50 mg Eperzan 50mg powder and solvent for solution for injection pre-filled pen | 4 pre-filled disposable injection £71.00

**Dose for injection**
- **Adult:** 1.5 mg once weekly

**Indications and dose**
Type 2 diabetes mellitus as monotherapy if metformin inappropriate
- By subcutaneous injection
- Adult: 0.75 mg once weekly

**Dose Adjustments due to Interactions**
Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**Contra-indications**
Severe gastro-intestinal disease—no information available

**Side-effects**
- Common or very common
  - Abdominal distention, constipation, decreased appetite, diarrhoea, dyspepsia, fatigue, headache, weight loss
  - Nausea, vomiting, dyspepsia

**Conception and Contraception**
Manufacturer advises avoid—no information available.

**Pregnancy**
Manufacturer advises avoid—no information available.

**Breast Feeding**
Manufacturer advises avoid—no information available.

**Renal Impairment**
Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m².

**Handling and Storage**
Store at 2–8°C. May be stored at temperatures up to 30°C for up to 4 weeks.

**Patient and Carer Advice**
Patients or carers should be given advice on how to administer albiglutide injection.
Acute pancreatitis
Patients should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek medical attention if symptoms such as persistent, severe abdominal pain develop.

**Missed Doses**
If a dose is missed it should be administered as soon as possible within 3 days; if more than 3 days have passed, the missed dose should not be taken and the next dose should be taken at the normal time.

**National Funding/Access Decisions**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2016) that albiglutide (Eperzan®) is accepted for restricted use for treating adults with type 2 diabetes to improve glycaemic control in combination with other glucose-lowering medicines when these, together with diet and exercise, do not provide adequate glycaemic control. It is restricted to use as an alternative once weekly GLP-1 mimetic for use in combination with oral anti-diabetic agents as a third-line pre-insulin treatment option.

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - Eperzan (GlaxoSmithKline UK Ltd) ▼
    - Albiglutide 30 mg Eperzan 30mg powder and solvent for solution for injection pre-filled pen | 4 pre-filled disposable injection £71.00
    - Albiglutide 50 mg Eperzan 50mg powder and solvent for solution for injection pre-filled pen | 4 pre-filled disposable injection £71.00

Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)

- By subcutaneous injection
- Adult: 1.5 mg once weekly

**Indications and dose**
Type 2 diabetes mellitus as monotherapy if metformin inappropriate
- By subcutaneous injection
- Adult: 0.75 mg once weekly

**Contra-indications**
Severe gastro-intestinal disease—no information available

**Side-effects**
- Common or very common
  - Abdominal distention, constipation, decreased appetite, diarrhoea, dyspepsia, fatigue, headache, weight loss
  - Nausea, vomiting, dyspepsia

**Conception and Contraception**
Manufacturer advises avoid—no information available.

**Pregnancy**
Manufacturer advises avoid—no information available.

**Breast Feeding**
Manufacturer advises avoid—no information available.

**Renal Impairment**
Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m².

**Handling and Storage**
Store at 2–8°C. May be stored at temperatures up to 30°C for up to 4 weeks.

**Patient and Carer Advice**
Patients or carers should be given advice on how to administer dulaglutide injection.
Acute pancreatitis
Patients should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek medical attention if symptoms such as persistent, severe abdominal pain develop.

**Missed Doses**
If a dose is missed, it should be administered as soon as possible. If less than 3 days have passed, the missed dose should not be taken and the next dose should be taken at the normal time.

**National Funding/Access Decisions**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2016) that dulaglutide (Trulicity®) is accepted for restricted use for treating adults with type 2 diabetes to improve glycaemic control as add-on therapy in combination with other glucose-lowering medicines when these, together with diet and exercise, do not provide adequate glycaemic control. It is restricted to use as part of a triple therapy in people with inadequate glycaemic control on 2 oral anti-diabetic medicines, as an alternative GLP-1 mimetic option.

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Trulicity (Eli Lilly and Company Ltd) ▼
  - Dulaglutide 1.5 mg per 1 ml Trulicity 0.75mg/0.5ml solution for injection pre-filled pen | 4 pre-filled disposable injection £73.25
  - Dulaglutide 3 mg per 1 ml Trulicity 1.5mg/0.5ml solution for injection pre-filled pen | 4 pre-filled disposable injection £73.25
Exenatide

- **DRUG ACTION** Binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

- **INDICATIONS AND DOSE**
  Type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, or with pioglitazone, or with both metformin and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination
  - By subcutaneous injection using immediate-release medicines
    - Adult: Initially 5 micrograms twice daily for at least 1 month, then increased if necessary up to 10 micrograms twice daily, dose to be taken within 1 hour before 2 main meals (at least 6 hours apart)
  - By subcutaneous injection using modified-release medicines
    - Adult: 2 mg once weekly

- **INTERACTIONS**
- **CONTRA-INDICATIONS**
- **CAUTIONS**
- **INTERACTIONS** → Appendix 1 (antidiabetics)
  Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when exenatide is not administered, to minimise possible interference with absorption.

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain and distension - agitation - appetite increase - breathlessness - constipation - decreased appetite - diarrhoea - dizziness - dyspepsia - gastro-intestinal disturbances - gastro-oesophageal reflux disease - headache - hypoglycaemia - increased sweating - injection-site reactions - nausea - vomiting - weight loss
  - Uncommon Pancreatitis
  - Rare Alopecia
  - Very rare Anaphylactic reactions
  - Frequency not known Angioedema - constipation - dehydration - drowsiness - eructation - flatulence - pruritus - rash - renal impairment - taste disturbance - urticaria

- **SIDE-EFFECTS, FURTHER INFORMATION**
  Severe pancreatitis (sometimes fatal), including haemorrhagic or necrotising pancreatitis, has been reported rarely; discontinue permanently if pancreatitis is diagnosed.

- **CONCEPTION AND CONTRACEPTION**
  Women of child-bearing age should use effective contraception during treatment with modified-release exenatide and for 12 weeks after discontinuation.

- **PREGNANCY**
  Avoid — toxicity in animal studies.

- **BREAST FEEDING**
  Avoid — no information available.

- **RENAI IMPAIRMENT**
  For standard-release injection, use with caution if eGFR 30–50 mL/minute/1.73 m². For standard-release injection, avoid if eGFR less than 30 mL/minute/1.73 m². For modified-release injection, avoid if eGFR less than 50 mL/minute/1.73 m².

- **PATIENT AND CARER ADVICE**
  Patients changing from standard-release to modified-release exenatide formulation may experience initial transient increase in blood glucose.
  Some oral medications should be taken at least 1 hour before or 4 hours after exenatide injection — consult product literature for details.
  Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek prompt medical attention if symptoms such as abdominal pain, nausea, and vomiting develop.

- **Missed doses**
  If a dose of the immediate-release medicine is missed, continue with the next scheduled dose — do not administer after a meal.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  Scottish Medicines Consortium (SMC) Decisions
  The Scottish Medicines Consortium has advised (June 2007) that standard-release exenatide (Byetta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with metformin or sulfonylurea (or both), as an alternative to treatment with insulin in patients where treatment with metformin or sulfonylurea (or both) at maximally tolerated doses has been inadequate, and treatment with insulin would be the next option.
  The Scottish Medicines Consortium has also advised (February 2011) that standard-release exenatide (Byetta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with metformin and pioglitazone as a third-line pre-insulin treatment option.
  The Scottish Medicines Consortium has advised (December 2011) that modified-release exenatide (Bydureon®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes as a third-line treatment option.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  **CAUTIONARY AND ADVISORY LABELS**
  - **Byetta** (Astrazeneca UK Ltd)
    - Exenatide 250 microgram per 1 ml Byetta 10 micrograms/0.04 ml solution for injection 2.4ml pre-filled disposable devices | 1 pre-filled disposable injection (P02) £68.24 DT price = £68.24
    - Byetta 5 micrograms/0.02 ml solution for injection 1.2 ml pre-filled disposable devices | 1 pre-filled disposable injection (P02) £68.24 DT price = £68.24

- **Powder and solvent for suspension for injection**
  **CAUTIONARY AND ADVISORY LABELS**
  - **Bydureon** (Astrazeneca UK Ltd)
    - Exenatide 2 mg Bydureon 2 mg powder and solvent for prolonged-release suspension for injection pre-filled pen | 4 pre-filled disposable injection (P02) £73.36
    - Bydureon 2 mg powder and solvent for suspension for prolonged-release injection vials | 4 vials (P02) £73.36
Liraglutide

01-Jun-2016

**DRUG ACTION** Liraglutide binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination

- **Type 2 diabetes mellitus in combination with basal insulin or both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control**
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 0.6 mg once daily for at least 1 week, then increased to 1.2 mg once daily for at least 1 week, then increased if necessary up to 1.8 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
Dose of concomitant insulin or sulfonylurea may need to be reduced.

**CONTRA-INDICATIONS** Diabetic gastroparesis, inflammatory bowel disease, ketoadiposis, moderate to severe congestive heart failure—no information available

**CAUTIONS** History of pancreatitis, mild congestive heart failure—limited experience, thyroid disease

**INTERACTIONS** → Appendix 1 (antidiabetics).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain and distension, bronchitis, constipation, decreased appetite, diarrhoea, dizziness, dyspepsia, flatulence, gastritis, gastrointestinal disturbances, gastro-oesophageal reflux disease, headache, hypoglycaemia, injection site reactions, malaise, nasopharyngitis, nausea, tachycardia, vomiting
- **Uncommon** Acute renal failure, dehydration, renal impairment
- **Very rare** Acute pancreatitis
- **Frequency not known** Goitre, increased blood calcitonin, thyroid neoplasm

**SIDE-EFFECTS, FURTHER INFORMATION**
- Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).
- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies (recommendation also supported by primary literature).
- **BREAST FEEDING** Avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid—limited experience.
- **RENAL IMPAIRMENT** Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m²—limited experience.
- **HANDLING AND STORAGE** Store in a refrigerator (2°C–8°C); after first use can be stored below 30°C, discard 1 month after first use.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer liraglutide injection. Acute pancreatitis Patients should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek immediate medical attention if symptoms such as persistent, severe abdominal pain develop.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Liraglutide (Non-proprietary)**
  - Liraglutide 6 mg per 1 ml Liraglutide 6 mg/ml solution for injection 3 ml pre-filled disposable devices 2 pre-filled disposable injection £78.48 3 pre-filled disposable injection £117.72

**CONTRA-INDICATIONS** Ketoacidosis, severe gastrointestinal disease

**INTERACTIONS** → Appendix 1 (antidiabetics).

Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after liraglutide injection, or taken with a meal when lixisenatide is not administered, to minimise possible interference with absorption.

**SIDE-EFFECTS**
- **Common or very common** Diarrhoea, dizziness, drowsiness, dyspepsia, headache, hypoglycaemia, nausea, palpitation, vomiting
- **Uncommon** Tachycardia, urticaria

**SIDE-EFFECTS, FURTHER INFORMATION**
- Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).
- **CONCEPTION AND CONTRACEPTION** Women of child-bearing age should use effective contraception.
- **PREGNANCY** Avoid—toxicity in animal studies.
- **BREAST FEEDING** Avoid—no information available.
- **RENAL IMPAIRMENT** Use with caution if eGFR 30–50 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m²—no information available.
- **PATIENT AND CARER ADVICE** Some oral medications should be taken at least 1 hour before or 4 hours after lixisenatide injection—consult product literature for details.

**Missed doses**
If a dose is missed, inject within 1 hour before the next meal—do not administer after a meal.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (August 2013) that lixisenatide (Lyxumia®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with oral antidiabetic drugs or basal insulin (or both), when adequate glycaemic control has not been achieved with these drugs; use is restricted to patients in whom a GLP-1 agonist is appropriate, as an alternative to an existing GLP-1 agonist (exenatide or liraglutide).
Repaglinide

**DRUG ACTION** Repaglinide stimulates insulin secretion.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate)

- **BY MOUTH**
  - Adult 18–74 years: Initially 500 micrograms (max. per dose 4 mg), adjusted according to response, dose to be taken within 30 minutes before main meals and adjusted at intervals of 1–2 weeks; maximum 16 mg per day
  - Adult 75 years and over: Not recommended

Type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate), if transferring from another oral antidiabetic drug

- **BY MOUTH**
  - Adult 18–74 years: Initially 1 mg (max. per dose 4 mg), adjusted according to response, dose to be taken within 30 minutes before main meals and adjusted at intervals of 1–2 weeks; maximum 16 mg per day
  - Adult 75 years and over: Not recommended

**CONTRA-INDICATIONS** Ketoacidosis

**CAUTIONS** Debilitated patients, malnourished patients

**CAUTIONS, FURTHER INFORMATION** Substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit repaglinide on morning of surgery and recommence when eating and drinking normally).

**INTERACTIONS** Appendix 1 (antidiabetics).

**SIDE-EFFECTS**

- Common or very common Abdominal pain, constipation, diarrhoea, nausea, vomiting
- Rare Hypersensitivity reactions, hypoglycaemia, pruritus, rashes, urticaria, vasculitis, visual disturbances

**PREGNANCY** Avoid.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Avoid in severe impairment—no information available.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Repaglinide (Non-proprietary)
  - Repaglinide 1 mg Repaglinide 1mg tablets | 30 tablet [Pom] £3.92 | 90 tablet [Pom] £11.76 DT price = £10.58
  - Repaglinide 500 microgram Repaglinide 500microgram tablets | 30 tablet [Pom] £3.92 | 90 tablet [Pom] £11.76 DT price = £9.03
  - Repaglinide 2 mg Repaglinide 2mg tablets | 90 tablet [Pom] £28.00 DT price = £5.88

- Enyglid (Consilient Health Ltd)
  - Repaglinide 1 mg Enyglid 1mg tablets | 30 tablet [Pom] £3.33 | 90 tablet [Pom] £9.99 DT price = £10.58
  - Repaglinide 500 microgram Enyglid 0.5mg tablets | 30 tablet [Pom] £3.33 | 90 tablet [Pom] £9.99 DT price = £9.03
  - Repaglinide 2 mg Enyglid 2mg tablets | 90 tablet [Pom] £9.99 DT price = £5.88

- Prandin (Novo Nordisk Ltd)
  - Repaglinide 1 mg Prandin 1mg tablets | 30 tablet [Pom] £3.92
  - Repaglinide 500 microgram Prandin 0.5mg tablets | 30 tablet [Pom] £3.92
  - Repaglinide 2 mg Prandin 2mg tablets | 90 tablet [Pom] £11.76 DT price = £5.88
BLOOD GLUCOSE LOWERING DRUGS > SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS

**Canagliflozin**

**DRUG ACTION** Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus as monotherapy (if metformin inappropriate)**

- **Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)**
  - **BY MOUTH**
    - Adult: 100 mg once daily; increased if tolerated to 300 mg once daily if required, dose to be taken preferably before breakfast

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (JUNE 2016): SIGNAL OF INCREASED RISK OF LOWER EXTREMITY AMPUTATIONS OBSERVED IN TRIAL IN HIGH CARDIOVASCULAR RISK PATIENTS**

A signal of increased lower limb amputation (mostly affecting toes) has been reported in an ongoing clinical trial in high cardiovascular risk patients. The MHRA has issued the following advice while this report is under investigation:

- Consider stopping canagliflozin if a patient develops a significant lower limb complication (e.g. skin ulcer, osteomyelitis, or gangrene), at least until the condition has resolved, and continue to monitor the patient closely
- Carefully monitor patients who have risk factors for amputation (e.g. previous amputations, existing peripheral vascular disease, or neuropathy)
- Monitor all patients for signs and symptoms of water or salt loss; ensure patients stay sufficiently hydrated to prevent volume depletion in line with the manufacturer’s recommendations
- Advise patients to stay well hydrated, carry out routine preventive foot care, and seek medical advice promptly if they develop skin ulceration, discolouration, or new pain or tenderness
- Start treatment for foot problems (e.g. ulceration, infection, or new pain or tenderness) as early as possible
- Continue to follow standard treatment guidelines for routine preventive foot care for people with diabetes.

**MHRA/CHM ADVICE (JUNE 2015): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS (CANAGLIFLOZIN, DAPAGLIFLOZIN OR EMPIAGLIFLOZIN)**

Serious and potentially life-threatening cases of diabetic ketoacidosis (DKA) have been reported in patients taking the SGLT2 inhibitor canagliflozin for type 2 diabetes. To minimise the risk of such effects when treating patients with a SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

- Test for raised ketones in patients presenting with symptoms of DKA, even if plasma glucose levels are near-normal; omitting this test could delay diagnosis of DKA.
- Discontinue treatment if DKA is suspected.
- If DKA is confirmed, take appropriate measures to correct the DKA and monitor glucose levels.
- Patients should be advised on how to recognise the signs and symptoms of DKA such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness, and to seek prompt medical attention if symptoms of DKA develop.

**CONTRA-INDICATIONS**

- Ketoacidosis
- **CAUTIOUS** Cardiovascular disease (risk of hypotension) - elderly (risk of hypotension) - elevated haematocrit - history of hypotension

**CAUTIONS, FURTHER INFORMATION**

- Volume depletion: Correct hypovolaemia before starting treatment.
- **INTERACTIONS**
  - Appendix 1 (antidiabetics).
- **SIDE-EFFECTS**
  - Common or very common
    - Constipation
    - Dyslipidaemia
    - Genital infection
    - Hypoglycaemia (in combination with insulin or sulfonylurea)
    - Nausea
    - Polyuria
    - Raised haematocrit
    - Thirst
    - Urinary frequency
    - Urinary-tract infection
  - Uncommon
    - Dehydration
    - Dizziness
    - Hypovolaemia
    - Postural hypotension
    - Raised serum creatinine
    - Raised serum urea
    - Rash
    - Syncope

**SIDE-EFFECTS, FURTHER INFORMATION**

- Volume depletion: Consider interrupting treatment if volume depletion occurs.
- PREGNANCY: Avoid—toxicity in animal studies.
- BREAST FEEDING: Avoid—present in milk in animal studies.
- HEPATIC IMPAIRMENT: Manufacturer advises avoid in severe impairment—no information available.

**RENAL IMPAIRMENT**

Reduce dose to 100 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m² and existing canagliflozin treatment tolerated. Avoid initiation if eGFR less than 60 mL/minute/1.73 m². Avoid if eGFR less than 45 mL/minute/1.73 m². Monitor renal function at least twice a year in moderate impairment.

**MONITORING REQUIREMENTS**

Determine renal function before treatment and at least annually thereafter, and before initiation of concomitant drugs that reduce renal function and periodically thereafter.

**PATIENT AND CARER ADVICE**

Patients should be advised to report symptoms of volume depletion including postural hypotension and dizziness. Patients should be informed of the signs and symptoms of diabetic ketoacidosis, see MHRA advice.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016) NICE TA390

Canagliflozin as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contra-indicated or not tolerated, only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

Patients currently receiving canagliflozin whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA390

- Canagliflozin in combination therapy for treating type 2 diabetes (June 2014) NICE TA315

Canagliflozin in a dual therapy regimen in combination with metformin is recommended for the treatment of type 2 diabetes, only if a sulfonylurea is contra-indicated or not tolerated or the patient has a significant risk of hypoglycaemia.

Canagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with
metformin and a sulfonylurea or metformin and a thiazolidinedione.

Canagliflozin in combination with insulin (alone or with other antidiabetic drugs) is an option for the treatment of type 2 diabetes.

Patients currently receiving canagliflozin in a dual or triple therapy regimen that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA315

Canagliflozin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, canagliflozin p. 641, metformin hydrochloride p. 631.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs

- **BY MOUTH**
  - Adult: 1 tablet twice daily, dose based on patient’s current metformin dose, daily dose of metformin should not exceed 2 g

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 60 mL/minute/1.73 m².

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (December 2014) that Vokanamet is accepted for restricted use within NHS Scotland in patients with type 2 diabetes mellitus for whom a combination of canagliflozin and metformin is an appropriate choice of therapy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Invokana** (Janssen-Cilag Ltd ▼)
  - Canagliflozin (as Canagliflozin hemihydrate) 100 mg Invokana 100mg tablets | 30 tablet POM £39.20 DT price = £39.20
  - Canagliflozin (as Canagliflozin hemihydrate) 300 mg Invokana 300mg tablets | 30 tablet POM £39.20 DT price = £39.20

**Dapagliflozin**

- **DRUG ACTION**
  - Reversibly inhibits sodium–glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

- **INDICATIONS AND DOSE**
  - Type 2 diabetes mellitus as monotherapy (if metformin inappropriate)
  - Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)
    - **BY MOUTH**
      - Adult 18–74 years: 10 mg once daily
      - Adult 75 years and over: Initiation not recommended

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**IMPORANT SAFETY INFORMATION**

MHRA/CHM ADVICE (JUNE 2015): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM–GLUCOSE CO-TRANSPORTER 2 INHIBITORS (CANAGLIFLOZIN, DAPAGLIFLOZIN OR EMPAGLIFLOZIN)

Serious and potentially life-threatening cases of diabetic ketoacidosis (DKA) have been reported in patients taking the SGLT2 inhibitor dapagliflozin for type 2 diabetes. To minimise the risk of such effects when treating patients with a SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

- Test for raised ketones in patients presenting with symptoms of DKA, even if plasma glucose levels are near-normal; omitting this test could delay diagnosis of DKA.
- Discontinue treatment if DKA is suspected.
- If DKA is confirmed, take appropriate measures to correct the DKA and monitor glucose levels.
- Patients should be advised on how to recognise the signs and symptoms of DKA such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness, and to seek prompt medical attention if symptoms of DKA develop.

- **CONTRA-INDICATIONS**
  - Ketoacidosis
- **CAUTIONS**
  - Cardiovascular disease (risk of hypotension) • elderly (risk of hypotension) • electrolyte disturbances • hypotension • raised haematocrit

CAUTIONS, FURTHER INFORMATION

- Volume depletion Correct hypovolaemia before starting treatment.

**INTERACTIONS**

- Appendix 1 (antidiabetics).

**SIDE-EFFECTS**

- Common or very common
  - Back pain • constipation • dyslipidaemia • dysuria • genital infection • hypoglycaemia (in combination with insulin or sulphonylurea) • polyuria • sweating • thirst • urinary-tract infection
- Uncommon
  - Dehydration • dizziness • hypotension • hypovolaemia • nausea • nocturia • raised serum creatinine • raised serum urea • rash

SIDE-EFFECTS, FURTHER INFORMATION

- Volume depletion Consider interrupting treatment if volume depletion occurs.

**PREGNANCY**

Avoid—toxicity in animal studies.

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Initial dose 5 mg daily in severe impairment, increased according to response.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 60 mL/minute/1.73 m² (ineffective).
Dapagliflozin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dapagliflozin p. 642, metformin hydrochloride p. 631.

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs**

- **BY MOUTH**
  - Adult 18-74 years: 1 tablet twice daily, based on patient’s current metformin dose
  - Adult 75 years and over: Initiation not recommended

**INTERACTIONS** Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**HEPATIC IMPAIRMENT** Avoid.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (July 2014) that dapagliflozin plus metformin (Xigduo®) is accepted for restricted use within NHS Scotland in patients for whom a combination of dapagliflozin and metformin is an appropriate choice of therapy i.e when metformin alone does not provide adequate glycaemic control and a sulfonylurea is inappropriate, or in combination with insulin, when insulin and metformin does not provide adequate control, or in combination with a sulphonylurea, when a sulfonylurea and metformin does not provide adequate control.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Xigduo (AstraZeneca UK Ltd)**
  - Dapagliflozin 5 mg, Metformin hydrochloride 1 gram
  - Dapagliflozin 5 mg | 56 tablet pack | £36.59 DT price = £36.59
  - Dapagliflozin 5 mg | 850mg tablets | 56 tablet pack | £36.59 DT price = £36.59

**Empagliflozin**

**DRUG ACTION** Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus as monotherapy (if metformin inappropriate)** / **Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)**

- **BY MOUTH**
  - Adult 18-84 years: 10 mg once daily, increased to 25 mg once daily if necessary and if tolerated
  - Adult 85 years and over: Initiation not recommended

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (JUNE 2015): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS (CANAGLIFLOZIN, DAPAGLIFLOZIN OR EMPAGLIFLOZIN)

Serious and potentially life-threatening cases of diabetic ketoacidosis (DKA) have been reported in patients taking the SGLT2 inhibitor empagliflozin for type 2 diabetes. To
minimise the risk of such effects when treating patients with a SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

- Test for raised ketones in patients presenting with symptoms of DKA, even if plasma glucose levels are near-normal; omitting this test could delay diagnosis of DKA.
- Discontinue treatment if DKA is suspected.
- If DKA is confirmed, take appropriate measures to correct the DKA and monitor glucose levels.
- Patients should be advised on how to recognise the signs and symptoms of DKA such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness, and to seek prompt medical attention if symptoms of DKA develop.

- CONTRA-INDICATIONS Diabetic ketoacidosis
- CAUTIONS Cardiovascular disease (increased risk of volume depletion) - complicated urinary tract infections - consider temporarily interrupting treatment - concomitant antihypertensive therapy (increased risk of volume depletion) - elderly patients aged over 75 years (increased risk of volume depletion) - heart failure - history of hypotension (increased risk of volume depletion) - patients at increased risk of volume depletion - predisposition to fluid disturbances e.g. gastro-intestinal illness, concomitant use of diuretics (increased risk of volume depletion)

CAUTIONS, FURTHER INFORMATION
- Volume depletion: Correct hypovolaemia before starting treatment. Consider interrupting treatment if volume depletion occurs.

- INTERACTIONS Appendix 1 (antidiabetics).
- SIDE-EFFECTS
  - Common or very common: Genital infection - hypoglycaemia (in combination with insulin or sulfonylurea) - polyuria - pruritus - urinary tract infection
  - Uncommon: Dysuria - volume depletion
- PREGNANCY: Manufacturer advises avoid—toxicity in animal studies.
- BREAST FEEDING: Manufacturer advises avoid—present in milk in animal studies.
- HEPATIC IMPAIRMENT: Manufacturer advises avoid in severe impairment—no information available.
- RENAL IMPAIRMENT: Reduce dose to 10 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m². Avoid initiation if eGFR below 60 mL/minute/1.73 m². Avoid if eGFR is persistently below 45 mL/minute/1.73 m².
- MONITORING REQUIREMENTS: Determine renal function before treatment and before initiation of concomitant drugs that may reduce renal function, then at least annually thereafter.
- PATIENT AND CARER ADVICE: Patients should be informed of the signs and symptoms of diabetic ketoacidosis, see MHRA advice.

- NATIONAL FUNDING/ACCESS DECISIONS
  - NICE technology appraisals (TAs)
    - Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016) NICE TA390
      Empagliflozin as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contra-indicated or not tolerated, only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

      Patients currently receiving empagliflozin whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

      www.nice.org.uk/TA390
    - Empagliflozin in combination therapy for treating type 2 diabetes (March 2015) NICE TA336
      Empagliflozin in a dual therapy regimen in combination with metformin is an option for the treatment of type 2 diabetes, only if:
      - a sulfonylurea is contra-indicated or not tolerated, or
      - the patient is at significant risk of hypoglycaemia or its consequences.

      Empagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with:
      - metformin and a sulfonylurea or
      - metformin and a thiazolidinedione.

      Empagliflozin in combination with insulin with or without other antidiabetic drugs is an option for the treatment of type 2 diabetes.

      Patients currently receiving empagliflozin whose disease does not meet the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.

      www.nice.org.uk/TA336

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - Jardiance (Boehringer Ingelheim Ltd)
      - Empagliflozin 10 mg Jardiance 10mg tablets 28 tablet Pack £36.59 OT price = £36.59
      - Empagliflozin 25 mg Jardiance 25mg tablets 28 tablet Pack £36.59 OT price = £36.59

Empagliflozin with metformin
25-Apr-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, empagliflozin p. 643, metformin hydrochloride p. 631.

- INDICATIONS AND DOSE
  - Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with other antidiabetic drugs or insulin
    - BY MOUTH
      - Adult 18–84 years: 5/850–5/1000 mg twice daily, based on patient’s current metformin dose, increased if necessary to 12.5/850–12.5/1000 mg twice daily
    - BY MOUTH
      - Adult 85 years and over: Initiation not recommended

DOSE ADJUSTMENTS DUE TO INTERACTIONS
- Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

DOSE EQUIVALENCE AND CONVERSION
- The proportions are expressed in the form ‘x’/‘y’ where ‘x’ and ‘y’ are the strengths in milligrams of empagliflozin and metformin respectively.

- NATIONAL FUNDING/ACCESS DECISIONS
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (October 2015) that Synjardy® (empagliflozin with metformin) is accepted for restricted use within NHS Scotland in patients for whom a fixed dose combination of empagliflozin and metformin is an appropriate choice of therapy or when use of a sulfonylurea is considered inappropriate.
Goldwhite

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  
  **CAUTIONARY AND ADVISORY LABELS 21**
  
  ▶ **Glibenclamide** (Boehringer Ingelheim Ltd)

  **Empagliflozin 12.5 mg, Metformin hydrochloride 1 gram** Synjardy 12.5mg/1000mg tablets | 56 tablet (Post) £36.59
  
  **Empagliflozin 12.5 mg, Metformin hydrochloride 850 mg** Synjardy 12.5mg/850mg tablets | 56 tablet (Post) £36.59
  
  **Empagliflozin 5 mg, Metformin hydrochloride 1 gram** Synjardy 5mg/1000mg tablets | 56 tablet (Post) £36.59
  
  **Empagliflozin 5 mg, Metformin hydrochloride 850 mg** Synjardy 5mg/850mg tablets | 56 tablet (Post) £36.59

- **BLOOD GLUCOSE LOWERING DRUGS › SULFONYLUREAS**

  **Sulfonylureas**

  - **DRUG ACTION** The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action.
  
  - **CONTRA-INDICATIONS** Presence of ketoadiabetes
  
  - **CAUTIONS** Can encourage weight gain (should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting) • elderly • G6PD deficiency
  
  - **SIDE-EFFECTS**
    
  ▶ **Uncommon** Hypoglycaemia
  
  ▶ **Rare** Agranulocytosis • aplastic anaemia • blood disorders • cholestatic jaundice • haemolytic anaemia • hepatic failure • hepatitis • leucopenia • pancytopenia • thrombocytopenia
  
  ▶ **Frequency not known** Allergic skin reactions (usually in the first 6–8 weeks of therapy) • constipation • diarrhoea • disturbance in liver function • erythema multiforme (usually in the first 6–8 weeks of therapy) • exfoliative dermatitis (usually in the first 6–8 weeks of therapy) • fever (usually in the first 6–8 weeks of therapy) • gastrointestinal disturbances • hypersensitivity reactions (usually in the first 6–8 weeks of therapy) • jaundice (usually in the first 6–8 weeks of therapy) • nausea • vomiting
  
  **SIDE-EFFECTS, FURTHER INFORMATION**

  ▶ **Hypoglycaemia** This is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.
  
  ▶ **HEPATIC IMPAIRMENT** Sulfonylureas should be avoided or a reduced dose should be used in severe hepatic impairment, because there is an increased risk of hypoglycaemia. Jaundice may occur.
  
  ▶ **RENAL IMPAIRMENT** Sulfonylureas should be used with care in those with mild to moderate renal impairment, because of the hazard of hypoglycaemia. Care is required to use the lowest dose that adequately controls blood glucose. Avoid where possible in severe renal impairment.
  
  ▶ **PATIENT AND CARER ADVICE**

  The risk of hypoglycaemia associated with sulfonylureas should be discussed with the patient, especially when concomitant glucose-lowering drugs are prescribed.

  **Driving and skilled tasks**

  Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.

- **Glibenclamide**

  - **INDICATIONS AND DOSE**

    **Type 2 diabetes mellitus**

    ▶ **BY MOUTH**

    ▶ **Adult** Initially 5 mg daily, adjusted according to response, dose to be taken with or immediately after breakfast; maximum 15 mg per day


    - **CONTRA-INDICATIONS** Avoid where possible in acute porphyrias p. 930

    - **INTERACTIONS** → Appendix 1 (antidiabetics).

    - **PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia; however, glibenclamide can be used during the second and third trimesters of pregnancy in women with gestational diabetes.

    - **BREAST FEEDING** Glibenclamide can be used during breast-feeding in women with pre-existing diabetes.

  - **MEDICINAL FORMS**

    There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

    **Tablet**

    ▶ **Glibenclamide (Non-proprietary)**

    **Glibenclamide 2.5 mg** Glibenclamide 2.5mg tablets | 28 tablet (Post) £1.46 DT price = £7.13

    **Glibenclamide 5 mg** Glibenclamide 5mg tablets | 28 tablet (Post) £1.40 DT price = £0.82

- **Gliclazide**

  - **INDICATIONS AND DOSE**

    **Type 2 diabetes mellitus**

    ▶ **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

    ▶ **Adult** Initially 40–80 mg daily, adjusted according to response, increased if necessary up to 160 mg once daily, dose to be taken with breakfast, doses higher than 160 mg to be given in divided doses; maximum 320 mg per day

    ▶ **BY MOUTH USING MODIFIED-RELEASE MEDICINES**

    ▶ **Adult** Initially 30 mg daily, dose to be taken with breakfast, adjust dose according to response every 4 weeks (after 2 weeks if no decrease in blood glucose); maximum 120 mg per day

  **DOSE EQUIVALENT AND CONVERSION**

  ▶ Gliclazide modified release 30 mg may be considered to be approximately equivalent in therapeutic effect to standard formulation gliclazide 80 mg.

    - **CONTRA-INDICATIONS** Avoid where possible in acute porphyrias p. 930

    - **INTERACTIONS** → Appendix 1 (antidiabetics).

    - **PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

    - **BREAST FEEDING** Avoid— theoretical possibility of hypoglycaemia in the infant.

    - **RENAL IMPAIRMENT** If necessary, gliclazide which is principally metabolised in the liver, can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.
Glimepiride

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus**
    - **BY MOUTH**
    - Adult: Initially 1 mg daily, adjusted according to response, doses may be increased in steps of 1 mg every 1–2 weeks, increased to 4 mg daily, dose to be taken shortly before or with first main meal, the daily dose may be increased further, in exceptional circumstances; maximum 6 mg per day

- **CAUTIONS**
  - **CAUTIONS, FURTHER INFORMATION**
    - Porphyria Sulphonylureas should be avoided where possible in acute porphyrias p. 930 but glimepiride is thought to be safe.
  - **INTERACTIONS** → Appendix 1 (antidiabetics).
  - **SIDE-EFFECTS**
    - Hyponatraemia
  - **PREGNANCY**
    - The use of sulphonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.
  - **BREAST FEEDING**
    - Avoid— theoretical possibility of hypoglycaemia in the infant.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Glimepiride (Non-proprietary)
  - Glimepiride 1 mg Glimepiride 1mg tablets | 20 tablet Pom £4.33 DT price = £0.22
  - Glimepiride 2 mg Glimepiride 2mg tablets | 30 tablet Pom £7.13 DT price = £0.24
  - Glimepiride 3 mg Glimepiride 3mg tablets | 30 tablet Pom £10.75 DT price = £0.36
- Amaryl (Zentiva)
  - Glimepiride 3 mg Amaryl 3mg tablets | 30 tablet Pom £10.75 DT price = £0.36

**MONITORING REQUIREMENTS**
Manufacturer recommends regular hepatic and haematological monitoring but limited evidence of clinical value.

**Diabetes mellitus and hypoglycaemia**

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Glimepiride (Non-proprietary)
  - Glimepiride 1 mg Glimepiride 1mg tablets | 30 tablet Pom £4.33 DT price = £0.22
  - Glimepiride 2 mg Glimepiride 2mg tablets | 30 tablet Pom £7.13 DT price = £0.24
  - Glimepiride 3 mg Glimepiride 3mg tablets | 30 tablet Pom £10.75 DT price = £0.36
- Amaryl (Zentiva)
  - Glimepiride 3 mg Amaryl 3mg tablets | 30 tablet Pom £10.75 DT price = £0.36

**Glipizide**

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus**
    - **BY MOUTH**
    - Adult: Initially 2.5–5 mg daily, adjusted according to response, dose to be taken shortly before breakfast or lunch, doses up to 15 mg may be given as a single dose, higher doses to be given in divided doses; maximum 20 mg per day

- **CAUTIONS**
  - **CAUTIONS, FURTHER INFORMATION**
    - Porphyra Sulphonylureas should be avoided where possible in acute porphyrias p. 930 but glipizide is thought to be safe.
  - **INTERACTIONS** → Appendix 1 (antidiabetics).
  - **SIDE-EFFECTS**
    - Rare Photosensitivity
    - Frequency not known Dizziness, drowsiness, hyponatraemia
  - **PREGNANCY**
    - The use of sulphonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.
  - **BREAST FEEDING** Avoid— theoretical possibility of hypoglycaemia in the infant.
  - **HEPATIC IMPAIRMENT** Avoid if the patient has both renal and hepatic impairment.
  - **RENAL IMPAIRMENT** Avoid if the patient has both renal and hepatic impairment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Glipizide (Non-proprietary)
  - Glipizide 5 mg Glipizide 5mg tablets | 28 tablet Pom £2.48 DT price = £0.22
  - Minodiab (Pfizer Ltd)
    - Glipizide 5 mg Minodiab 5mg tablets | 28 tablet Pom £1.26 DT price = £0.22
### Tolbutamide

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

- **BY MOUTH**
  - Adult: 0.5–1.5 g daily in divided doses, dose to be taken with or immediately after meals, alternatively 0.5–1.5 g once daily, dose to be taken with or immediately after breakfast; maximum 2 g per day

- **CONTRA-INDICATIONS** Avoid where possible in acute porphyrias p. 930

- **INTERACTIONS** → Appendix 1 (antidiabetics).

- **SIDE-EFFECTS** Headache; tinnitus

- **PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

- **BREAST FEEDING** The use of sulfonylureas in breast-feeding should be avoided because there is a theoretical possibility of hypoglycaemia in the infant.

- **RENAL IMPAIRMENT** If necessary, the short-acting drug tolbutamide can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
  - **Tablet**
    - Tolbutamide (Non-proprietary)
      - Tolbutamide 500 mg Tolbutamide 500mg tablets | 28 tablet [PoM] £34.88 DT price = £8.14 | 112 tablet [PoM] £39.44

### Blood Glucose Lowering Drugs

#### Thiazolidinediones

### Pioglitazone

**DRUG ACTION** The thiazolidinedione, pioglitazone, reduces peripheral insulin resistance, leading to a reduction of blood-glucose concentration.

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus (alone or combined with metformin or a sulfonylurea, or with both, or with insulin)**

- **BY MOUTH**
  - Adult: Initially 15–30 mg once daily, adjusted according to response to 45 mg once daily, in elderly patients, initiate with lowest possible dose and increase gradually; review treatment after 3–6 months and regularly thereafter

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Dose of concomitant sulfonylurea or insulin may need to be reduced.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: PIOGLITAZONE CARDIOVASCULAR SAFETY (DECEMBER 2007 AND JANUARY 2011)

Incidence of heart failure is increased when pioglitazone is combined with insulin especially in patients with predisposing factors e.g. previous myocardial infarction. Patients who take pioglitazone should be closely monitored for signs of heart failure; treatment should be discontinued if any deterioration in cardiac status occurs.

Pioglitazone should not be used in patients with heart failure or a history of heart failure.

POIGLITAZONE: RISK OF BLADDER CANCER (JULY 2011)

The European Medicines Agency has advised that there is a small increased risk of bladder cancer associated with pioglitazone use. However, in patients who respond adequately to treatment, the benefits of pioglitazone continue to outweigh the risks.

Pioglitazone should not be used in patients with active bladder cancer or a past history of bladder cancer, or in those who have uninvestigated macroscopic haematuria. Pioglitazone should be used with caution in elderly patients as the risk of bladder cancer increases with age.

Before initiating treatment with pioglitazone, patients should be assessed for risk factors of bladder cancer (including age, smoking status, exposure to certain occupational or chemotherapy agents, or previous radiation therapy to the pelvic region) and any macroscopic haematuria should be investigated. The safety and efficacy of pioglitazone should be reviewed after 3–6 months and pioglitazone should be stopped in patients who do not respond adequately to treatment.

Patients already receiving treatment with pioglitazone should be assessed for risk factors of bladder cancer and treatment should be reviewed after 3–6 months, as above.

Patients should be advised to report promptly any haematuria, dysuria, or urinary urgency during treatment.

**CONTRA-INDICATIONS** History of heart failure; previous or active bladder cancer; uninvestigated macroscopic haematuria

**CAUTIONS** Avoid in acute porphyrias p. 930; cardiovascular disease or in combination with insulin (risk of heart failure); elderly (increased risk of heart failure, fractures, and bladder cancer); increased risk of bone fractures, particularly in women; risk factors for bladder cancer

**CAUTIONS, FURTHER INFORMATION**

Substitute insulin during peri-operative period (omit pioglitazone on morning of surgery and recommence when eating and drinking normally).

**SIDE-EFFECTS, FURTHER INFORMATION**

- Liver toxicity Rare reports of liver dysfunction; discontinue if jaundice occurs.
- **PREGNANCY** Avoid—tumour in animal studies.
- **BREAST FEEDING** Avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Avoid.
- **MONITORING REQUIREMENTS** Monitor liver function before treatment and periodically thereafter.
- **PATIENT AND CARER ADVICE**
  - Liver toxicity Patients should be advised to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium accepts use of pioglitazone (February 2007) with metformin and a sulfonylurea, for patients (especially if overweight) whose glycaemic control is inadequate despite the use of 2 oral hypoglycaemic drugs and who are unable or unwilling to
take insulin; treatment should be initiated and monitored by an experienced diabetes physician.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Tablet**
  - Pioglitazone (Non-proprietary)
    - Pioglitazone (as Pioglitazone hydrochloride) 15 mg
      - Pioglitazone 15 mg tablets | 28 tablet (Pat) $25.83 DT price = $8.23
    - Pioglitazone (as Pioglitazone hydrochloride) 30 mg
      - Pioglitazone 30 mg tablets | 28 tablet (Pat) $35.89 DT price = $10.89
    - Pioglitazone (as Pioglitazone hydrochloride) 45 mg
      - Pioglitazone 45 mg tablets | 28 tablet (Pat) $39.55 DT price = $11.71

- **Actos** (Takeda UK Ltd)
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg
    - Actos 15 mg tablets | 28 tablet (Pat) $25.83 DT price = $8.23
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg
    - Actos 30 mg tablets | 28 tablet (Pat) $35.89 DT price = $10.89
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg
    - Actos 45 mg tablets | 28 tablet (Pat) $39.55 DT price = $11.71

- **Diabion** (Tillomed Laboratories Ltd)
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg
    - Diabion 15 mg tablets | 28 tablet (Pat) $26.00 DT price = $8.23
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg
    - Diabion 30 mg tablets | 28 tablet (Pat) $36.00 DT price = $10.89
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg
    - Diabion 45 mg tablets | 28 tablet (Pat) $40.00 DT price = $11.71

- **Glipidion** (Actavis UK Ltd)
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg
    - Glipidion 15 mg tablets | 28 tablet (Pat) $25.83 DT price = $8.23
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg
    - Glipidion 30 mg tablets | 28 tablet (Pat) $35.89 DT price = $10.89
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg
    - Glipidion 45 mg tablets | 28 tablet (Pat) $39.55 DT price = $11.71

**Insulins**

**INSULINS**

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg
    - Pioglitazone hydrochloride 15 mg tablets | 28 tablet (Pat) $25.83 DT price = $8.23
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg
    - Pioglitazone hydrochloride 30 mg tablets | 28 tablet (Pat) $35.89 DT price = $10.89
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg
    - Pioglitazone hydrochloride 45 mg tablets | 28 tablet (Pat) $39.55 DT price = $11.71

**Insulins**

**IMPORANT SAFETY INFORMATION**

**NHS IMPROVEMENT PATIENT SAFETY ALERT: RISK OF SEVERE HARM AND DEATH DUE TO WITHDRAWING INSULIN FROM PEN DEVICES (NOVEMBER 2016)**

Insulin should not be extracted from insulin pen devices. The strength of insulin in pen devices can vary by multiples of 100 units/mL. Insulin syringes have graduations only suitable for calculating doses of standard 100 units/mL. If insulin extracted from a pen or cartridge is of a higher strength, and that is not considered in determining the volume required, it can lead to a significant and potentially fatal overdose.

**SIDE-EFFECTS**

- **Common or very common** Fat hypertrophy at injection site - local reactions at injection site - transient oedema
- **Rare** Hypersensitivity reactions - rash - urticaria
  - **Overdose**

**BNF 73**
Insulin Passport Insulin Passports and patient information booklets should be offered to patients receiving insulin. The Insulin Passport provides a record of the patient’s current insulin preparations and contains a section for emergency information. The patient information booklet provides advice on the safe use of insulin. They are available for purchase from:
3M Security Print and Systems Limited
Gorse Street, Chadderton
Oldham
OL9 9QH
Tel: 0845 610 1112
GP practices can obtain supplies through their Local Area Team stores.
NHS Trusts can order supplies from www.nhsforms.co.uk/or by emailing nhsforms@mmm.com. Further information is available at www.npsa.nhs.uk.

Hypoglycaemia Hypoglycaemia is a potential problem with insulin therapy. All patients must be carefully instructed on how to avoid it; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

INSULINS INTERMEDIATE-ACTING

Biphasic isophane insulin (Biphasic Isophase Insulin Injection—intermediate acting)

- INDICATIONS AND DOSE
  Diabetes mellitus
  - BY SUBCUTANEOUS INJECTION
  - Child: According to requirements
  - Adult: According to requirements

- INTERACTIONS Appendix 1 (antidiabetics).
- SIDE-EFFECTS Protamine may cause allergic reactions
- PRESCRIBING AND DISPENSING INFORMATION A sterile buffered suspension of either porcine or human insulin complexed with protamine sulfate (or another suitable protamine) in a solution of insulin of the same species. Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Suspension for injection
  - Humulin M3 (Eli Lilly and Company Ltd)
    Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Humulin M3 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £19.08 DT price = £19.08
    Humulin M3 cartridges for injection 10ml vials | 1 vial (Pdp) £15.68
  - Humulin M3 KwikPen (Eli Lilly and Company Ltd)
    Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Humulin M3 KwikPen 100units/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection (Pdp) £21.70 DT price = £21.70
  - Hypurin Porcine 30/70 Mix (Wockhardt UK Ltd)
    Insulin porcine (as Insulin soluble porcine) 30 unit per 1 ml, Insulin porcine (as Insulin isophane porcine) 70 unit per 1 ml Hypurin Porcine 30/70 Mix 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £37.80
    Hypurin Porcine 30/70 Mix 100units/ml suspension for injection 10ml vials | 1 vial (Pdp) £22.20
  - Insulatard (Novo Nordisk Ltd)
    Insulin human (as Insulin isophane human) 100 unit per 1 ml Insulatard 100units/ml suspension for injection 10ml vials | 1 vial (Pdp) £7.48

- INSUMAN Comb 15 (Sanofi)
  Insulin human (as Insulin soluble human) 15 unit per 1 ml, Insulin human (as Insulin isophane human) 85 unit per 1 ml Insumen Comb 15 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £17.50

- INSUMAN Comb 25 (Sanofi)
  Insulin human (as Insulin soluble human) 25 unit per 1 ml, Insulin human (as Insulin isophane human) 75 unit per 1 ml Insumen Comb 25 100units/ml suspension for injection 5ml vials | 1 vial (Pdp) £5.61
  Insumen Comb 25 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £17.50

- INSUMAN Comb 25 SoloStar (Sanofi)
  Insulin human (as Insulin soluble human) 25 unit per 1 ml, Insulin human (as Insulin isophane human) 75 unit per 1 ml Insumen Comb 25 100units/ml suspension for injection 3ml pre-filled SoloStar pen | 5 pre-filled disposable injection (Pdp) £19.80

- INSUMAN Comb 50 (Sanofi)
  Insulin human (as Insulin isophane human) 50 unit per 1 ml, Insulin human (as Insulin soluble human) 50 unit per 1 ml Insumen Comb 50 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £17.50

Isophane insulin (Insophane Insulin Injection; Isophane Protamine Insulin Injection; Isophane Insulin (NPH)—intermediate acting)

- INDICATIONS AND DOSE
  Diabetes mellitus
  - BY SUBCUTANEOUS INJECTION
  - Child: According to requirements
  - Adult: According to requirements

- INTERACTIONS Appendix 1 (antidiabetics).
- SIDE-EFFECTS Protamine may cause allergic reactions
- PREGNANCY Recommended where longer-acting insulins are needed.
- PRESCRIBING AND DISPENSING INFORMATION A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulfate or another suitable protamine.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Suspension for injection
  - Humulin I (Eli Lilly and Company Ltd)
    Insulin human (as Insulin isophane human) 100 unit per 1 ml Humulin I 100units/ml suspension for injection 10ml vials | 1 vial (Pdp) £15.68
    Humulin I 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £19.08 DT price = £19.08
  - Humulin I KwikPen (Eli Lilly and Company Ltd)
    Insulin human (as Insulin isophane human) 100 unit per 1 ml Humulin I KwikPen 100units/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection (Pdp) £21.70 DT price = £21.70
  - Hyprurin Bovine Isophane (Wockhardt UK Ltd)
    Insulin bovine (as Insulin isophane bovine) 100 unit per 1 ml Hyprurin Bovine Isophane 100units/ml suspension for injection 10ml vials | 1 vial (Pdp) £27.72
    Hyprurin Bovine Isophane 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £41.58
  - Hyprurin Porcine Isophane (Wockhardt UK Ltd)
    Insulin porcine (as Insulin isophane porcine) 100 unit per 1 ml Hyprurin Porcine Isophane 100units/ml suspension for injection 3ml cartridges | 5 cartridge (Pdp) £37.80
    Hyprurin Porcine Isophane 100units/ml suspension for injection 10ml vials | 1 vial (Pdp) £25.20
  - Insulatard (Novo Nordisk Ltd)
    Insulin human (as Insulin isophane human) 100 unit per 1 ml Insulatard 100units/ml suspension for injection 10ml vials | 1 vial (Pdp) £7.48
Insulatard InnoLet (Novo Nordisk Ltd)
Insulin human (as Insulin isophane human) 100 unit per 1 ml Insulatard InnoLet 100 units/ml suspension for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (POD) £20.40 DT price = £21.70

Insulatard Penfill (Novo Nordisk Ltd)
Insulin human (as Insulin isophane human) 100 unit per 1 ml Insulatard Penfill 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (POD) £22.90 DT price = £19.08

Insumin Basal (Sanofi)
Insulin human (as Insulin isophane human) 100 unit per 1 ml Insumin Basal 100 units/ml suspension for injection 5 ml vials | 1 vial (POD) £5.61
Insumin Basal 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (POD) £17.50 DT price = £19.08

Insumin Basal SoloStar (Sanofi)
Insulin human (as Insulin isophane human) 100 unit per 1 ml Insumin Basal 100 units/ml suspension for injection 3 ml pre-filled SoloStar pen | 5 pre-filled disposable injection (POD) £19.80 DT price = £21.70

INSULINS › INTERMEDIATE-ACTING COMBINED WITH RAPID-ACTING

Biphasic insulin aspart (Intermediate-acting insulin)

- INDICATIONS AND DOSE
  Diabetes mellitus
  - BY SUBCUTANEOUS INJECTION
  - Child: Administer up to 10 minutes before or soon after a meal, according to requirements
  - Adult: Administer up to 10 minutes before or soon after a meal, according to requirements

- INTERACTIONS ➔ Appendix 1 (antidiabetics).

- SIDE-EFFECTS
  Protamine may cause allergic reactions

- PRESCRIBING AND DISPENSING INFORMATION
  Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Suspension for injection
  - Humalog Mix52 (Eli Lilly and Company Ltd)
    Insulin lispro 25 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 75 unit per 1 ml Humalog Mix52 100 units/ml suspension for injection 10 ml vials | 1 vial (POD) £16.61
    Humalog Mix52 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (POD) £29.46 DT price = £29.46
  - Humalog Mix25 KwikPen (Eli Lilly and Company Ltd)
    Insulin lispro 25 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 75 unit per 1 ml Humalog Mix25 KwikPen 100 units/ml suspension for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (POD) £30.98 DT price = £30.98
  - Humalog Mix50 (Eli Lilly and Company Ltd)
    Insulin lispro 50 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 100 unit per 1 ml Humalog Mix50 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (POD) £29.46
  - Humalog Mix50 KwikPen (Eli Lilly and Company Ltd)
    Insulin lispro 50 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 100 unit per 1 ml Humalog Mix50 KwikPen 100 units/ml suspension for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (POD) £30.98 DT price = £30.98

INSULINS › LONG-ACTING

Insulin degludec (Recombinant human insulin analogue—long acting)

- INDICATIONS AND DOSE
  Diabetes mellitus
  - BY SUBCUTANEOUS INJECTION
  - Child 1-17 years: Dose to be given according to requirements
  - Adult: Dose to be given according to requirements

- INTERACTIONS ➔ Appendix 1 (antidiabetics).

- PREGNANCY
  Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

- PRESCRIBING AND DISPENSING INFORMATION
  Insulin degludec (Tresiba®) is available in strengths of 100 units/ml (allows 1-unit dose adjustment) and 200 units/ml (allows 2-unit dose adjustment)—ensure correct strength prescribed.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Solution for injection
  - Tresiba FlexTouch (Novo Nordisk Ltd)
    Insulin human (as Insulin degludec) 100 unit per 1 ml Tresiba FlexTouch 100 units/ml solution for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (POD) £46.60
    Insulin human (as Insulin degludec) 200 unit per 1 ml Tresiba FlexTouch 200 units/ml solution for injection 3 ml pre-filled pen | 3 pre-filled disposable injection (POD) £55.92
  - Tresiba Penfill (Novo Nordisk Ltd)
    Insulin human (as Insulin degludec) 100 unit per 1 ml Tresiba Penfill 100 units/ml solution for injection 3 ml cartridges | 5 cartridge (POD) £46.60

Biphasic insulin lispro (Intermediate-acting insulin)

- INDICATIONS AND DOSE
  Diabetes mellitus
  - BY SUBCUTANEOUS INJECTION
  - Child: Administer up to 15 minutes before or soon after a meal, according to requirements
  - Adult: Administer up to 15 minutes before or soon after a meal, according to requirements

- CAUTIONS
  Children under 12 years (use only if benefit likely compared to soluble insulin)
  - INTERACTIONS ➔ Appendix 1 (antidiabetics).

- SIDE-EFFECTS
  Protamine may cause allergic reactions

- PRESCRIBING AND DISPENSING INFORMATION
  Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).
Insulin degludec with liraglutide

The properties listed below are those particular to the combination only. For the properties of the components please consider, insulin degludec p. 650, liraglutide p. 639.

- **INDICATIONS AND DOSE**
  - As add-on to oral antidiabetics in type 2 diabetes mellitus not controlled by oral antidiabetics alone
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: Initially 10 dose-steps once daily, adjusted according to response; maximum 50 dose-steps per day
  - When transferring from basal insulin in type 2 diabetes mellitus not controlled by oral antidiabetics in combination with basal insulin
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: Initially 16 dose-steps once daily, adjusted according to response; maximum 50 dose-steps per day

- **INTERACTIONS**
  - Dose of concomitant sulfonylurea may need to be reduced.

- **PATIENT AND CARER ADVICE**
  - Counselling advised on administration. Show container to patient and confirm that patient is expecting the version dispensed.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (October 2015) that insulin degludec with liraglutide (Xultophy®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or with basal insulin do not provide adequate glycaemic control.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - Xultophy (Novo Nordisk Ltd)
      - Insulin human (as Insulin degludec) 100 unit per 1 ml, Liraglutide 3.6 mg per 1 ml Xultophy 100units/ml / 3.6mg/ml solution for injection 3ml pre-filled pen | 3 pre-filled disposable injection £95.53

Insulin detemir

*(Recombinant human insulin analogue—long acting)*

- **INDICATIONS AND DOSE**
  - **Diabetes mellitus**
    - **BY SUBCUTANEOUS INJECTION**
    - Child 2-17 years: According to requirements
    - Adult: According to requirements

- **INTERACTIONS**
  - Appendix 1 (antidiabetics).

- **PREGNANCY**
  - Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Insulin glargine is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.
  - Dose adjustments and close metabolic monitoring is recommended if switching between insulin glargine preparations.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised that Lantus® preparations (April 2013) and Toujeo® (August 2015) are accepted for restricted use within NHS Scotland for the treatment of type 1 diabetes:
      - In those who are at risk of or experience unacceptable frequency or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with other insulins
      - As a once daily insulin therapy for patients who require a carer to administer their insulin
    - It is not recommended for routine use in patients with type 2 diabetes unless they suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - Levemir FlexPen (Novo Nordisk Ltd)
      - Insulin human (as Insulin detemir) 100 unit per 1 ml Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection £42.00
    - Levemir InnoLet (Novo Nordisk Ltd)
      - Insulin human (as Insulin detemir) 100 unit per 1 ml Levemir InnoLet 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection £44.85
    - Levemir Penfill (Novo Nordisk Ltd)
      - Insulin human (as Insulin detemir) 100 unit per 1 ml Levemir Penfill 100units/ml solution for injection 3ml cartridges | 5 cartridge £42.00 DT price = £42.00

- **Diabetes mellitus**
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: According to requirements

- **TOUJEO®**
  - **Diabetes mellitus**
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: According to requirements

- **INTERACTIONS**
  - Appendix 1 (antidiabetics).

- **PREGNANCY**
  - Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Insulin glargine is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.
  - Dose adjustments and close metabolic monitoring is recommended if switching between insulin glargine preparations.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised that Lantus® preparations (April 2013) and Toujeo® (August 2015) are accepted for restricted use within NHS Scotland for the treatment of type 1 diabetes:
      - In those who are at risk of or experience unacceptable frequency or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with other insulins
      - As a once daily insulin therapy for patients who require a carer to administer their insulin
    - It is not recommended for routine use in patients with type 2 diabetes unless they suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - Abasaglar (Eli Lilly and Company Ltd)
      - Insulin human (as Insulin glargine) 100 unit per 1 ml Abasaglar 100units/ml solution for injection 3ml cartridges | 5 cartridge £35.28 DT price = £41.50
    - Abasaglar KwikPen (Eli Lilly and Company Ltd)
      - Insulin human (as Insulin glargine) 100 unit per 1 ml Abasaglar KwikPen 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection £35.28 DT price = £41.50
    - Lantus (Sanofi)
      - Insulin human (as Insulin glargine) 100 unit per 1 ml Lantus 100units/ml solution for injection 3ml cartridges | 5 cartridge £41.50 DT price = £41.50
      - Lantus 100units/ml solution for injection 10ml vials | 1 vial £30.68
Insulin zinc suspension
(Insulin zinc suspension (mixed)—long acting)

**INDICATIONS AND DOSE**

**Diabetes mellitus**
- **Adult:** According to requirements
- **Child:** According to requirements

**INTERACTIONS** 
- Appendix 1 (antidiabetics).

**PREGNANCY**
Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin p. 649 is recommended where longer-acting insulins are needed; insulin detemir p. 651 may also be considered.

**PRESCRIBING AND DISPENSING INFORMATION**
A sterile neutral suspension of bovine and/or porcine insulin or of human insulin in the form of a complex obtained by the addition of a suitable zinc salt; consists of rhombohedral crystals (10–40 microns) and of particles of no uniform shape (not exceeding 2 microns).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **Hypurin Bovine Lente** (Wockhardt UK Ltd)
  - Insulin bovine (as Insulin zinc suspension mixed bovine) 100 unit per 1 ml Hypurin Bovine Lente 100 units/ml suspension for injection 10ml vials | 1 vial (GB) £27.72

Protamine zinc insulin
(Protamine zinc insulin injection—long acting)

**INDICATIONS AND DOSE**

**Diabetes mellitus**
- **Adult:** According to requirements
- **Child:** According to requirements

**INTERACTIONS** 
- Appendix 1 (antidiabetics).

**SIDE-EFFECTS**
Protamine may cause allergic reactions

**PREGNANCY**
Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin p. 649 is recommended where longer-acting insulins are needed; insulin detemir p. 651 may also be considered.

**PRESCRIBING AND DISPENSING INFORMATION**
A sterile suspension of insulin in the form of a complex obtained by the addition of a suitable protamine and zinc chloride; this preparation was included in BP 1980 but is not included in BP 1988.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **Hypurin Bovine Protamine Zinc** (Wockhardt UK Ltd)
  - Insulin bovine (as Insulin protamine zinc bovine) 100 unit per 1 ml Hypurin Bovine Protamine Zinc 100 units/ml suspension for injection 10ml vials | 1 vial (GB) £27.72

**INSULINS > RAPID-ACTING**

**Insulin**
(Insulin Injection; Neutral Insulin; Soluble Insulin—short acting)

**INDICATIONS AND DOSE**

**Diabetes mellitus**
- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - **Adult:** According to requirements
  - **Diabetic ketoacidosis / Diabetes during surgery**
    - **BY INTRAVENOUS INFUSION**
    - **Adult:** (consult local protocol)

**INTERACTIONS** 
- Appendix 1 (antidiabetics).

**DIRECTIONS FOR ADMINISTRATION**
Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team. Some insulin preparations are not recommended for use in subcutaneous insulin infusion pumps—may precipitate in catheter or needle—consult product literature.

For **intravenous infusion** give continuously in Sodium chloride 0.9%. Adsorbed to some extent by plastic infusion set; ensure insulin is not injected into ‘dead space’ of injection port of the infusion bag.

**PRESCRIBING AND DISPENSING INFORMATION**
A sterile solution of insulin (i.e. bovine or porcine) or of human insulin; pH 6.6–8.0.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151
Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:
- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or
- whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol] despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).
Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

www.nice.org.uk/TA151

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

**Solution for injection**
- **Insulin (Non-proprietary)**
  - Insulin human 100 unit per 1 ml Humulin R 100 units/ml solution for injection 10ml vials | 1 vial (GB) no price available
Insulin human 500 unit per 1 ml Humulin R 500 units/ml solution for injection 20ml vials | 1 vial (Pom) no price available

- Actrapid (Novo Nordisk Ltd)
- Humulin S 100 units/ml solution for injection 10ml vials | 1 vial (Pom) £15.68
- Humulin S 100 units/ml solution for injection 3ml cartridges | 5 cartridges (Pom) £19.08
- Hypurin Bovine Neutral (Wockhardt UK Ltd)
- Insulin bovine (as Insulin soluble bovine) 100 unit per 1 ml Hypurin Bovine Neutral 100units/ml solution for injection 10ml vials | 1 vial (Pom) £27.72
- Hypurin Bovine Neutral 100units/ml solution for injection 3ml cartridges | 5 cartridge (Pom) £41.58
- Hypurin Porcine Neutral (Wockhardt UK Ltd)
- Insulin porcine (as Insulin soluble porcine) 100 unit per 1 ml Hypurin Porcine Neutral 100units/ml solution for injection 10ml vials | 1 vial (Pom) £25.20

- Insulin Infusat (Sanofi)
- Insulin human 100 unit per 1 ml Insulin Infusat 100units/ml solution for injection 3ml cartridges | 5 cartridge (Pom) £37.80
- Insulin Rapid (Sanofi)
- Insulin human (as Insulin soluble human) 100 unit per 1 ml Insulin human 100 unit per ml solution for injection 3ml cartridges | 5 cartridge (Pom) £17.50

**Insulin aspart**
*(Recombinant human insulin analogue—short acting)*

- **INDICATIONS AND DOSE**
  - **Diabetes mellitus**
    - **BY SUBCUTANEOUS INJECTION**
    - Child 2-17 years: Administer immediately before meals or when necessary shortly after meals, according to requirements
    - Adult: Administer immediately before meals or when necessary shortly after meals, according to requirements
  - **BY SUBCUTANEOUS INFUSION, OR BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
    - Child 2-17 years: According to requirements
    - Adult: According to requirements

- **UNLICENSED USE**
  - Not licensed for use in children under 2 years.
- **INTERACTIONS** → Appendix 1 (antidiabetics).
- **PREGNANCY**
  - Not known to be harmful—may be used during pregnancy.
- **BREAST FEEDING**
  - Not known to be harmful—may be used during lactation.
- **DIRECTIONS FOR ADMINISTRATION**
  - Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.
  - With intravenous use in adults: For *intravenous infusion*, give continuously in Glucose 5% or Sodium chloride 0.9%; dilute to 0.05-1 unit/ml with infusion fluid; adsorbed to some extent by plastics of infusion set.
  - With intravenous use in children: For *intravenous infusion*, dilute to a concentration of 0.05–1 unit/ml with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 ml of infusion fluid containing insulin.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - **Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151**
      - Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:
        - Who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or
        - Whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).
      - Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.
      - [www.nice.org.uk/TA151](http://www.nice.org.uk/TA151)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **NovoRapid (Novo Nordisk Ltd)**
      - Insulin aspart 100 unit per 1 ml NovoRapid 100units/ml solution for injection 10ml vials | 1 vial (Pom) £14.08 DT price = £14.08
      - NovoRapid FlexPen (Novo Nordisk Ltd)
        - Insulin aspart 100 unit per 1 ml NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection (Pom) £30.60 DT price = £30.60
        - NovoRapid FlexTouch (Novo Nordisk Ltd)
          - Insulin aspart 100 unit per 1 ml NovoRapid FlexTouch 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection (Pom) £22.13 DT price = £30.60
        - NovoRapid Penfill (Novo Nordisk Ltd)
          - Insulin aspart 100 unit per 1 ml NovoRapid Penfill 100units/ml solution for injection 3ml cartridges | 5 cartridge (Pom) £28.31 DT price = £28.31
        - NovoRapid PumpCart (Novo Nordisk Ltd)
          - Insulin aspart 100 unit per 1 ml NovoRapid PumpCart 100units/ml solution for injection 1.6ml cartridges | 5 cartridge (Pom) £15.10

**Insulin glulisine**
*(Recombinant human insulin analogue—short acting)*

- **INDICATIONS AND DOSE**
  - **Diabetes mellitus**
    - **BY SUBCUTANEOUS INJECTION**
      - Child: Administer immediately before meals or when necessary shortly after meals, according to requirements
      - Adult: Administer immediately before meals or when necessary shortly after meals, according to requirements
    - **BY SUBCUTANEOUS INFUSION, OR BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
      - Child: According to requirements
      - Adult: According to requirements

- **UNLICENSED USE**
  - Not licensed for children under 6 years.
- **INTERACTIONS** → Appendix 1 (antidiabetics).
**DIRECTIONS FOR ADMINISTRATION** Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

- With intravenous use in adults: For intravenous infusion (Apidra®), give continuously in Sodium chloride 0.9%; dilute to 1 unit/mL with infusion fluid; use a co-extruded polyolefin/polyamide plastic infusion bag with a dedicated infusion line.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or

- whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

www.nice.org.uk/TA151

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (October 2008) that Apidra® is accepted for restricted use within NHS Scotland for the treatment of adults and children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Apidra®** (Sanofi)
  - Insulin lispro 100 unit per 1 ml Apidra 100 units/ml solution for injection 10 ml vials | 1 vial (PSt) £16.00
  - Apidra 100 units/ml solution for injection 3 ml cartridges | 5 cartridge (PSt) £28.30

- **Apidra SoloStar®** (Sanofi)
  - Insulin lispro 100 unit per 1 ml Apidra 100 units/ml solution for injection 3 ml pre-filled SoloStar pen | 5 pre-filled disposable injection (PSt) £28.30 DT price = £28.30

**Insulin lispro**

*(Recombinant human insulin analogue—short acting)*

**INDICATIONS AND DOSE**

- **Diabetes mellitus**
  - **BY SUBCUTANEOUS INJECTION**
    - Child 2-17 years: Administer shortly before meals or when necessary shortly after meals, according to requirements
  - Adult: Administer shortly before meals or when necessary shortly after meals, according to requirements
  - **BY SUBCUTANEOUS INFUSION, OR BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
    - Child 2-17 years: According to requirements
    - Adult: According to requirements

**UNLICENSED USE** Not licensed for use in children under 2 years.

**CAUTIONS** Children under 12 years (use only if benefit likely compared to soluble insulin)

**INTERACTIONS** → Appendix 1 (antidiabetics).

**PREGNANCY** Not known to be harmful—may be used during pregnancy.

**BREAST FEEDING** Not known to be harmful—may be used during lactation.

**DIRECTIONS FOR ADMINISTRATION** Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens (see also NICE guidance, below). Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

- With intravenous use in adults: For intravenous infusion give continuously in Glucose 5% or Sodium chloride 0.9%. Adsorbed to some extent by plastics of infusion set.

- With intravenous use in children: For intravenous infusion, dilute to a concentration of 0.1–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or

- whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

www.nice.org.uk/TA151

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Humalog®** (Eli Lilly and Company Ltd)
  - Insulin lispro 100 unit per 1 ml Humalog 100 units/ml solution for injection 10 ml vials | 1 vial (PSt) £16.61 DT price = £16.61
  - Humalog 100 units/ml solution for injection 3 ml cartridges | 5 cartridge (PSt) £28.31 DT price = £28.31
The oral glucose tolerance test generally involves giving anhydrous glucose by mouth to the fasting patient, and measuring blood-glucose concentrations at intervals. The appropriate amount of glucose should be given with 200–300 mL fluid. Anhydrous glucose may alternatively be given as 113 mL Polycal® with extra fluid to administer a total volume of 200–300 mL, or as Rapilose® OGTT oral solution.
### Meters and test strips

<table>
<thead>
<tr>
<th>Meter (all NHS)</th>
<th>Type of monitoring</th>
<th>Compatible test strips</th>
<th>Test strip net price</th>
<th>Sensitivity range (mmol/litre)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu-Chek® Active</td>
<td>Blood glucose</td>
<td>Active®</td>
<td>50 strip = £9.95</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>Accu-Chek® Advantage Meter no longer available</td>
<td>Blood glucose</td>
<td>Advantage Plus®</td>
<td>50 strip = £0.00</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>Accu-Chek® Aviva</td>
<td>Blood glucose</td>
<td>Aviva®</td>
<td>50 strip = £15.96</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>Accu-Chek® Aviva Expert</td>
<td>Blood glucose</td>
<td>Aviva®</td>
<td>50 strip = £15.96</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>Accu-Chek® Compact Plus Meter no longer available</td>
<td>Blood glucose</td>
<td>Compact®</td>
<td>3 × 17 strips = £16.39</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>Accu-Chek® Mobile</td>
<td>Blood glucose</td>
<td>Mobile®</td>
<td>100 device = £32.48</td>
<td>0.3–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>Accu-Chek® Aviva Nano</td>
<td>Blood glucose</td>
<td>Aviva®</td>
<td>50 strip = £15.96</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>BGStar® Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>BGStar®</td>
<td>50 strip = £14.73</td>
<td>1.1–33.3 mmol/litre</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Breeze 2®</td>
<td>Blood glucose</td>
<td>Breeze 2®</td>
<td>50 strip = £15.00</td>
<td>0.6–33.3 mmol/litre</td>
<td>Bayer Plc</td>
</tr>
<tr>
<td>CareSens N® Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>CareSens N®</td>
<td>50 strip = £12.75</td>
<td>1.1–33.3 mmol/litre</td>
<td>Spirit Healthcare Ltd</td>
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<tr>
<td>Contour®</td>
<td>Blood glucose</td>
<td>Contour®</td>
<td>50 strip = £9.95</td>
<td>0.6–33.3 mmol/litre</td>
<td>Bayer Diagnostics Manufacturing Ltd</td>
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<tr>
<td>Contour® XT</td>
<td>Blood glucose</td>
<td>Contour® Next</td>
<td>50 strip = £15.04</td>
<td>0.6–33.3 mmol/litre</td>
<td>Bayer Diagnostics Manufacturing Ltd</td>
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<tr>
<td>Element®</td>
<td>Blood glucose</td>
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<td>50 strip = £9.89</td>
<td>0.55–33.3 mmol/litre</td>
<td>Neon Diagnostics Ltd</td>
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<tr>
<td>FreeStyle® Meter no longer available</td>
<td>Blood glucose</td>
<td>FreeStyle®</td>
<td>50 strip = £15.97</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td>FreeStyle Freedom® Meter no longer available</td>
<td>Blood glucose</td>
<td>FreeStyle®</td>
<td>50 strip = £15.97</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<tr>
<td>FreeStyle Freedom Lite®</td>
<td>Blood glucose</td>
<td>FreeStyle Lite®</td>
<td>50 strip = £15.97</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<tr>
<td>FreeStyle InsuLinx®</td>
<td>Blood glucose</td>
<td>FreeStyle Lite®</td>
<td>50 strip = £15.97</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<td>FreeStyle Lite®</td>
<td>Blood glucose</td>
<td>FreeStyle Lite®</td>
<td>50 strip = £15.97</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<td>FreeStyle Mini® Meter no longer available</td>
<td>Blood glucose</td>
<td>FreeStyle®</td>
<td>50 strip = £15.97</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<td>FreeStyle Optium®</td>
<td>Blood glucose</td>
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<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<td>FreeStyle Optium®</td>
<td>Blood ketones</td>
<td>FreeStyle Optium®/β-ketone</td>
<td>10 strip = £21.36</td>
<td>0–8.0 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<tr>
<td>FreeStyle Optium Neo®</td>
<td>Blood glucose</td>
<td>FreeStyle Optium®</td>
<td>50 strip = £15.87</td>
<td>1.1–27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td>FreeStyle Optium Neo®</td>
<td>Blood ketones</td>
<td>FreeStyle Optium®/β-ketone</td>
<td>10 strip = £21.36</td>
<td>0–8.0 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
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<tr>
<td>GlucoDock® module</td>
<td>Blood glucose</td>
<td>GlucoDock®</td>
<td>50 strip = £14.90</td>
<td>1.1–33.3 mmol/litre For use with iPhone®, iPod touch®, and iPad®</td>
<td>Medisana Healthcare (UK) Ltd</td>
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<tr>
<td>GlucoLab®</td>
<td>Blood glucose</td>
<td>GlucoLab®</td>
<td>50 strip = £9.89</td>
<td>0.55–33.3 mmol/litre</td>
<td>Neon Diagnostics Ltd</td>
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<tr>
<td>GlucoMen® GM</td>
<td>Blood glucose</td>
<td>GlucoMen® GM</td>
<td>50 strip = £9.95</td>
<td>0.6–33.3 mmol/litre</td>
<td>Neon Diagnostics Ltd</td>
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<tr>
<td>Meter (all)</td>
<td>Type of monitoring</td>
<td>Compatible test strips</td>
<td>Test strip net price</td>
<td>Sensitivity range (mmol/litre)</td>
<td>Manufacturer</td>
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<td>GlucoMen® LX</td>
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<td>GlucoMen® LX Sensor</td>
<td>50 strip = £15.76</td>
<td>1.1-33.3 mmol/litre</td>
<td>A Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoMen® LX Plus</td>
<td>Blood glucose</td>
<td>GlucoMen® LX Sensor</td>
<td>50 strip = £15.76</td>
<td>1.1-33.3 mmol/litre</td>
<td>A Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoMen® LX Plus</td>
<td>Blood ketones</td>
<td>GlucoMen® LX Ketone</td>
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<td>0-0.8 mmol/litre</td>
<td>A Menarini Diagnostics Ltd</td>
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<tr>
<td>GlucoMen® Visio</td>
<td>Blood glucose</td>
<td>GlucoMen® Visio Sensor</td>
<td>50 strip = £15.75</td>
<td>1.1-33.3 mmol/litre</td>
<td>A Menarini Diagnostics Ltd</td>
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<tr>
<td>GlucoRx®</td>
<td>Blood glucose</td>
<td>GlucoRx®</td>
<td>50 strip = £9.45</td>
<td>1.1-33.3 mmol/litre</td>
<td>GlucoRx Ltd</td>
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<tr>
<td>GlucoRx Nexus®</td>
<td>Blood glucose</td>
<td>GlucoRx Nexus®</td>
<td>50 strip = £9.95</td>
<td>1.1-33.3 mmol/litre</td>
<td>GlucoRx Ltd</td>
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<tr>
<td>Glucotrend®</td>
<td>Blood glucose</td>
<td>Active®</td>
<td>50 strip = £9.95</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
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<tr>
<td>iBGStar®</td>
<td>Blood glucose</td>
<td>BGStar®</td>
<td>50 strip = £14.73</td>
<td>1.1-33.3 mmol/litre</td>
<td>Sanofi</td>
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<tr>
<td>IME-DC®</td>
<td>Blood glucose</td>
<td>IME-DC®</td>
<td>50 strip = £14.10</td>
<td>1.1-33.3 mmol/litre</td>
<td>Arctic Medical Ltd</td>
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<td>Mendor Discreet®</td>
<td>Blood glucose</td>
<td>Mendor Discreet®</td>
<td>50 strip = £14.75</td>
<td>1.1-33.3 mmol/litre</td>
<td>SpringMed Solutions Ltd</td>
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<tr>
<td>Microdot®</td>
<td>Blood glucose</td>
<td>Microdot®</td>
<td>50 strip = £9.49</td>
<td>1.1-29.2 mmol/litre</td>
<td>Cambridge Sensors Ltd</td>
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<td>MyGlucoHealth®</td>
<td>Blood glucose</td>
<td>MyGlucoHealth®</td>
<td>50 strip = £15.50</td>
<td>0.6-33.3 mmol/litre</td>
<td>Entra Health Systems Ltd</td>
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<tr>
<td>Omnitest® 3</td>
<td>Blood glucose</td>
<td>Omnitest® 3</td>
<td>50 strip = £9.89</td>
<td>0.6-33.3 mmol/litre</td>
<td>B.Braun Medical Ltd</td>
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<tr>
<td>One Touch Ultra®</td>
<td>Blood glucose</td>
<td>One Touch Ultra®</td>
<td>50 strip = £9.99</td>
<td>1.1-33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch Ultra 2®</td>
<td>Blood glucose</td>
<td>One Touch Ultra®</td>
<td>50 strip = £9.99</td>
<td>1.1-33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch UltraEasy®</td>
<td>Blood glucose</td>
<td>One Touch Ultra®</td>
<td>50 strip = £9.99</td>
<td>1.1-33.3 mmol/litre</td>
<td>LifeScan</td>
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<tr>
<td>One Touch UltraSmart®</td>
<td>Blood glucose</td>
<td>One Touch Ultra®</td>
<td>50 strip = £9.99</td>
<td>1.1-33.3 mmol/litre</td>
<td>LifeScan</td>
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<tr>
<td>One Touch VerioPro®</td>
<td>Blood glucose</td>
<td>One Touch® Verio</td>
<td>50 strip = £15.12</td>
<td>1.1-33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch Vita®</td>
<td>Blood glucose</td>
<td>One Touch® Vita</td>
<td>50 strip = £15.07</td>
<td>1.1-33.3 mmol/litre</td>
<td>LifeScan</td>
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<tr>
<td>SD CodeFree®</td>
<td>Blood glucose</td>
<td>SD CodeFree®</td>
<td>50 strip = £6.99</td>
<td>0.6-33.3 mmol/litre</td>
<td>SD Biosensor Inc</td>
</tr>
<tr>
<td>Sensocard Plus®</td>
<td>Blood glucose</td>
<td>Sensocard®</td>
<td>50 strip = £16.30</td>
<td>1.1-33.3 mmol/litre</td>
<td>BBI Healthcare Ltd</td>
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<tr>
<td>Meter (all)</td>
<td>Type of monitoring</td>
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<td>Test strip net price</td>
<td>Sensitivity range (mmol/litre)</td>
<td>Manufacturer</td>
</tr>
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<tr>
<td>GlucoMen Visio testing strips (A Menarini Diagnostics Ltd)</td>
<td>Blood glucose</td>
<td>GlucoMen Visio testing strips (A Menarini Diagnostics Ltd)</td>
<td>50 strip - NHS indicative price = £15.75 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
</tr>
<tr>
<td>GlucoMen areo Sensor testing strips (A Menarini Diagnostics Ltd)</td>
<td>Blood glucose</td>
<td>GlucoMen areo Sensor testing strips (A Menarini Diagnostics Ltd)</td>
<td>50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<tr>
<td>GlucoNavii testing strips (Neon Diagnostics Ltd)</td>
<td>Blood glucose</td>
<td>GlucoNavii testing strips (Neon Diagnostics Ltd)</td>
<td>50 strip - NHS indicative price = £8.95 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>GlucoRx GO testing strips (GlucoRx Ltd)</td>
<td>Blood glucose</td>
<td>GlucoRx GO testing strips</td>
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<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>GlucoRx HCT Glucose testing strips (GlucoRx Ltd)</td>
<td>Blood glucose</td>
<td>GlucoRx HCT Glucose testing strips</td>
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<td>GlucoRx Nexus testing strips (GlucoRx Ltd)</td>
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<td>GlucoRx Original testing strips (GlucoRx Ltd)</td>
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<td>Apollo Medical Technologies Ltd</td>
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<td>GlucoFlex-R testing strips (Bio-Diagnostics Ltd)</td>
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<td>IME-DC testing strips (Arctic Medical Ltd)</td>
<td>Blood glucose</td>
<td>IME-DC testing strips</td>
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<td>MODZ testing strips (Modz Oy)</td>
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<td>Medi-Test Glucose testing strips (BHR Pharmaceuticals Ltd)</td>
<td>Blood glucose</td>
<td>Medi-Test Glucose testing strips</td>
<td>50 strip - NHS indicative price = £2.33 - Drug Tariff (Part IXr)</td>
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<td>Apollo Medical Technologies Ltd</td>
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<tr>
<td>MediSense SoftSense testing strips (Abbott Laboratories Ltd)</td>
<td>Blood glucose</td>
<td>MediSense SoftSense testing strips</td>
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<tr>
<td>MediTouch 2 testing strips (Medisana Healthcare (UK) Ltd)</td>
<td>Blood glucose</td>
<td>MediTouch 2 testing strips</td>
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<td>Apollo Medical Technologies Ltd</td>
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<td>Mendor Discreet testing strips (SpringMed Solutions Ltd)</td>
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<td>Mission Glucose testing strips</td>
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<td>Mobile cassette (Roche Diabetes Care Ltd)</td>
<td>Blood glucose</td>
<td>Mobile cassette</td>
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<tr>
<td>Myglucohealth testing strips (Entra Health Systems Ltd)</td>
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<td>Myglucohealth testing strips</td>
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<td>1.1–33.3 mmol/litre</td>
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<tr>
<td>Mylife Pura testing strips (Ypsomed Ltd)</td>
<td>Blood glucose</td>
<td>Mylife Pura testing strips</td>
<td>50 strip - NHS indicative price = £9.50 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>Mylife Unio testing strips (Ypsomed Ltd)</td>
<td>Blood glucose</td>
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<td>50 strip - NHS indicative price = £9.50 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>Ommitest 3 testing strips (B Braun Medical Ltd)</td>
<td>Blood glucose</td>
<td>Ommitest 3 testing strips</td>
<td>50 strip - NHS indicative price = £9.99 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<tr>
<td>On-Call Advanced testing strips (Point Of Care Testing Ltd)</td>
<td>Blood glucose</td>
<td>On-Call Advanced testing strips</td>
<td>50 strip - NHS indicative price = £13.65 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<tr>
<td>OneTouch Select Plus testing strips (LifeScan)</td>
<td>Blood glucose</td>
<td>OneTouch Select Plus testing strips</td>
<td>50 strip - NHS indicative price = £9.99 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
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<td>OneTouch Ultra testing strips (LifeScan)</td>
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<td>OneTouch Ultra testing strips</td>
<td>50 strip - NHS indicative price = £9.99 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>1.1–33.3 mmol/litre</td>
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<td>OneTouch Vita testing strips (LifeScan)</td>
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<td>OneTouch Vita testing strips</td>
<td>50 strip - NHS indicative price = £15.07 - Drug Tariff (Part IXr)</td>
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<td>Apollo Medical Technologies Ltd</td>
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<td>Performa testing strips (Roche Diabetes Care Ltd)</td>
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<td>Performa testing strips</td>
<td>50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>SD CodeFree testing strips (SD Biosensor Inc)</td>
<td>Blood glucose</td>
<td>SD CodeFree testing strips</td>
<td>50 strip - NHS indicative price = £6.99 - Drug Tariff (Part IXr)</td>
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<td>SUREREIGN Resure testing strips (Ciga Healthcare Ltd)</td>
<td>Blood glucose</td>
<td>SUREREIGN Resure testing strips</td>
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<td>Sensocard testing strips (ABI Healthcare Ltd)</td>
<td>Blood glucose</td>
<td>Sensocard testing strips</td>
<td>50 strip - NHS indicative price = £16.30 - Drug Tariff (Part IXr)</td>
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<td>SuperCheck 2D testing strips (Apollo Medical Technologies Ltd)</td>
<td>Blood glucose</td>
<td>SuperCheck 2D testing strips</td>
<td>50 strip - NHS indicative price = £9.45 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
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<td>SuperCheck Plus testing strips (Apollo Medical Technologies Ltd)</td>
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<td>SuperCheck Plus testing strips</td>
<td>50 strip - NHS indicative price = £9.45 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
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<td>TEE2 testing strips (Spiritt Healthcare Ltd)</td>
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<td>TEE2 testing strips</td>
<td>50 strip - NHS indicative price = £7.75 - Drug Tariff (Part IXr)</td>
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<td>Apollo Medical Technologies Ltd</td>
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<td>TRUEResult testing strips (Nipro Diagnostics (UK) Ltd)</td>
<td>Blood glucose</td>
<td>TRUEResult testing strips</td>
<td>50 strip - NHS indicative price = £14.99 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>TRUEyou testing strips (Nipro Diagnostics (UK) Ltd)</td>
<td>Blood glucose</td>
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<td>50 strip - NHS indicative price = £9.99 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
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<td>VivaChek Ino testing strips (IR Biomedical Ltd)</td>
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<td>VivaChek Ino testing strips</td>
<td>50 strip - NHS indicative price = £8.99 - Drug Tariff (Part IXr)</td>
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<tr>
<td>WaveSense JAZZ Duo testing strips (Agamatrix Europe Ltd)</td>
<td>Blood glucose</td>
<td>WaveSense JAZZ Duo testing strips</td>
<td>50 strip - NHS indicative price = £9.99 - Drug Tariff (Part IXr)</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
</tr>
</tbody>
</table>
Hypoglycaemia

### Needle free Insulin delivery systems

**INSUJET**

For use with any 10-mL vial or 3-mL cartridge of insulin, allowing 1-unit dosage adjustment, max 40 units. Available as starter set (InsuJet® device, nozzle cap, nozzle and piston, 1 × 10-mL adaptor, 1 × 3-mL adaptor, 1 cartridge cap removal key), nozzle pack (15 nozzles), cartridge adapter pack (15 adaptors), or vial adaptor pack (15 adaptors).

**InsuJet starter set** (Spirit Healthcare Ltd)

1 pack - NHS indicative price = £90.00 - Drug Tariff (Part Ixa)

### Urinanalysis reagent strips

**PRESCRIBING AND DISPENSING INFORMATION**

Other reagent strips available for urinanalysis

Include: *Combur-3 Test®* (glucose and protein—Roche Diagnostics); *Clinitek Microalbumin®* (albumin and creatinine—Siemens); *Ketodixast®* (glucose and ketones—Bayer Diagnostics); *Medi-Test Combi 2®* (glucose and protein—BHR); *Mical-Test II®*, used to detect microaluminuria but this should be followed by confirmation in the laboratory—false positive results are common (albumin—Roche Diagnostics); *Microalbumin®* (albumin and creatinine—Siemens); *Uristix®* (glucose and protein—Siemens).

These reagent strips are not prescribable under National Health Service (NHS).

**URINE GLUCOSE TESTING STRIPS**

**Diastix testing strips** (Bayer Diagnostics Manufacturing Ltd)

50 strip - NHS indicative price = £2.89 - Drug Tariff (Part Ix)

**Medi-Test Glucose testing strips** (BHR Pharmaceuticals Ltd)

50 strip - NHS indicative price = £2.33 - Drug Tariff (Part Ix)

**Mission Glucose testing strips** (Spirit Healthcare Ltd)

50 strip - NHS indicative price = £2.29 - Drug Tariff (Part Ix)

**URINE PROTEIN TESTING STRIPS**

**Albustix testing strips** (Siemens Medical Solutions Diagnostics Ltd)

50 strip - NHS indicative price = £4.10 - Drug Tariff (Part Ix)

**Medi-Test Protein 2 testing strips** (BHR Pharmaceuticals Ltd)

50 strip - NHS indicative price = £3.27 - Drug Tariff (Part Ix)

**URINE KETONES TESTING STRIPS**

**GlucoRx KetoRx Sticks 2GK testing strips** (GlucoRx Ltd)

50 strip - NHS indicative price = £2.25 - Drug Tariff (Part Ix)

**Ketostix testing strips** (Bayer Diagnostics Manufacturing Ltd)

50 strip - NHS indicative price = £3.06 - Drug Tariff (Part Ix)

**Mission Ketone testing strips** (Spirit Healthcare Ltd)

50 strip - NHS indicative price = £2.50 - Drug Tariff (Part Ix)

### 3.2 Hypoglycaemia

**Hypoglycaemia**

**Treatment of hypoglycaemia**

Initially glucose 10–20 g p. 915 is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of *Lucozade® Energy Original* 55 mL, *Coca-Cola®* 100 mL, *Ribena®* Blackcurrant 19 mL (to be diluted), 2 teaspoons of sugar, and also from 3 sugar lumps.
Proprietary products of quick-acting carbohydrate (e.g. GlucoGel®, Dextrogel®, GSF-Syrup®, Rapilose® gel) are available on prescription for the patient to keep to hand in case of hypoglycaemia. If necessary this may be repeated in 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, or biscuits) or the next meal, if it is due, can prevent blood-glucose concentration from falling again.

Hypoglycaemia which causes unconsciousness is an emergency. Glucagon below, a polypeptide hormone produced by the alpha cells of the islets of Langerhans, is for saving life in emergency. Glucagon below, a polypeptide hormone increases plasma-glucose concentration by mobilising glycogen stored in the liver. In hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection. Carbohydrates should be given as soon as possible to restore liver glycogen; glucagon is not appropriate for chronic hypoglycaemia. Glucagon may be issued to close relatives of insulin-treated patients for emergency use in hypoglycaemic attacks. It is often advisable to prescribe on an ‘if necessary’ basis to hospitalised insulin-treated patients, so that it may be given rapidly by the nurses during an hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, glucose intravenous infusion 20% may be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Glucose intravenous infusion 10% may also be used but larger volumes are needed. Glucose intravenous infusion 50% is not recommended because of the higher risk of extravasation injury and because administration is difficult. Close monitoring is necessary in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Patients whose hypoglycaemia is caused by an oral antidiabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs may persist for many hours.

See also, emergency management of hypoglycaemia in dental practice for further advice.

**Chronic hypoglycaemia**

Diazoxide below, administered by mouth, is useful in the management of patients with chronic hypoglycaemia from excess endogenous insulin secretion, either from an islet cell tumour or islet cell hyperplasia. It has no place in the management of acute hypoglycaemia.

**GLYCOGENOLYTIC HORMONES**

**Glucagon**

- **INDICATIONS AND DOSE**
  - **Insulin-induced hypoglycaemia**
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Child 1 month–1 year: 500 micrograms
    - Child 2–7 years (body-weight up to 25 kg): 500 micrograms, if no response within 10 minutes intravenous glucose must be given
    - Child 2–7 years (body-weight 25 kg and above): 1 mg, if no response within 10 minutes intravenous glucose must be given
    - Adult: 1 mg, if no response within 10 minutes intravenous glucose must be given
  - **Beta-blocker poisoning (cardiogenic shock unresponsive to atropine)**
    - **INITIALLY BY INTRAVENOUS INJECTION**
    - Child: 50–150 micrograms/kg (max. per dose 10 mg), to be administered in glucose 5% (with precautions to protect the airway in case of vomiting), followed by (by intravenous infusion) 50 micrograms/kg/hour

- **Adult: 2–10 mg, to be administered in glucose 5% (with precautions to protect the airway in case of vomiting), followed by (by intravenous infusion)**
  - 50 micrograms/kg/hour

**DIAGNOSTIC AID**

- **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: (consult product literature)

**DOSE EQUIVALENCE AND CONVERSION**

- 1 unit of glucagon = 1 mg of glucagon.

**UNLICENSED USE**

Dose and indication for cardiogenic shock unresponsive to atropine in beta-blocker overdose not licensed.

**CONTRA-INDICATIONS**

- Phaeochromocytoma

**CAUTIONS**

- Glucagonoma: ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency.
- Insulinoma: when used in the diagnosis of growth hormone secretion, delayed hypoglycaemia may result—deaths reported (ensure a meal is eaten before discharge) (in children)

**SIDE-EFFECTS**

- Rare: Hypersensitivity reactions
- **Frequency not known**
  - Abdominal pain (in adults)
  - Diarrhoea (in children)
  - Hypokalaemia
  - Hypotension (in adults)
  - Nausea
  - Vomiting

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children: When administered by continuous intravenous infusion, do not add to infusion fluids containing calcium—precipitation may occur.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Glucagon for hypoglycaemia

www.medicinesforchildren.org.uk/glucagon-for-hypoglycaemia

**EXCEPTIONS TO LEGAL CATEGORY**

Prescription-only medicine restriction does not apply where administration is for saving life in emergency.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- **Glucagen Hypokit** (Novo Nordisk Ltd)
  - Glucagen hydrochloride 1 mg
  - Glucagen Hypokit 1mg powder and solvent for solution for injection
  - 1 vial £9.52

**SIDE-EFFECTS**

- Taste disturbance
- Headache
- Abdominal pain
- Nausea
- Vomiting

**Hypersensitivity reactions**

- **INJECTION**
  - Glucagon

**DOSE EQUIVALENCE AND CONVERSION**

- 1 unit of glucagon = 1 mg of glucagon.

**3.2a Chronic hypoglycaemia**

**THIAZIDE DERIVATIVES**

**Diazoxide**

- **INDICATIONS AND DOSE**
  - **Chronic intractable hypoglycaemia**
    - **BY MOUTH**
    - Adult: Initially 5 mg/kg daily in 2–3 divided doses, adjusted according to response; maintenance 3–8 mg/kg daily in 2–3 divided doses

**CAUTIONS**

- Aortic coarctation
- Aortic stenosis
- Arteriovenous shunt
- Heart failure
- Hyperuricaemia
- Impaired cardiac circulation
- Impaired cerebral circulation

**INTERACTIONS**

- Appendix 1 (diazoxide).

**SIDE-EFFECTS**

- Taste disturbance
- Abdominal pain
- Anaemia
- Anorexia (prolonged use)
- Bleeding
- Constipation
- Decreased libido
- Dermatitis
- Diarrhoea
- Dizziness
- Dyspnoea
- Eosinophilia
- Extrapyramidal effects
- Galactorrhoea
- Headache
- Heart failure
- Hyperglycaemia
- Hyperosmolar non-ketotic coma
- Hypertrichosis
- Hyperuricaemia (prolonged use)
- Hypotension
- Ileus
Bone metabolism

Osteoporosis

Osteoporosis occurs most commonly in postmenopausal women and in those taking long-term oral corticosteroids (glucocorticoids). Other risk factors for osteoporosis include low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis, and early menopause.

Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and any deficiency should be corrected by increasing dietary intake or taking supplements.

Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements. Reversible secondary causes of osteoporosis such as hyperthyroidism, hyperparathyroidism, osteomalacia or hypogonadism should be excluded, in both men and women, before treatment for osteoporosis is initiated.

Also see: calcium, phosphorus, vitamin D and oestrogens in postmenopausal osteoporosis.

Postmenopausal osteoporosis

The bisphosphonates (alendronic acid and risedronate) are effective for preventing postmenopausal osteoporosis.

Hormone replacement therapy (HRT) is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. The CSM has advised that HRT should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT. Women of Afro-Caribbean origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

Postmenopausal osteoporosis may be treated with a bisphosphonate. The bisphosphonates (such as alendronate and risedronate) decrease the risk of vertebral fracture; alendronate and risedronate have also been shown to reduce non-vertebral fractures. If bisphosphonates are unsuitable calcitriol p. 953 or strontium ranelate may be considered. Calcitonin (salmon) p. 668 is no longer recommended for the treatment of postmenopausal osteoporosis as the benefits are outweighed by the risk of malignancy associated with long-term use. Calcitonin (salmon) [unlicensed indication] has been used for pain relief for up to 3 months after a vertebral fracture when other analgesics were ineffective, but the benefits of treatment should be balanced against the risks. Teriparatide has been introduced for the treatment of postmenopausal osteoporosis.

Raloxifene hydrochloride p. 689 is licensed for the prophylaxis and treatment of vertebral fractures in postmenopausal women.

Corticosteroid-induced osteoporosis

To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible. The risk of osteoporosis may be related to cumulative dose of corticosteroids; even intermittent courses can therefore increase the risk. The greatest rate of bone loss occurs during the first 6–12 months of corticosteroid use and so early steps to prevent the development of osteoporosis are important. Long-term use of high-dose inhaled corticosteroids may also contribute to corticosteroid-induced osteoporosis.

Patients taking (or who are likely to take) an oral corticosteroid for 3 months or longer should be assessed and where necessary given prophylactic treatment; those aged over 65 years are at greater risk. Patients taking oral corticosteroids who have sustained a low trauma fracture should receive treatment for osteoporosis. The therapeutic options for prophylaxis and treatment of corticosteroid-induced osteoporosis are the same:

- a bisphosphonate;
- Calcitriol [unlicensed indication];
- hormone replacement (HRT) in women, testosterone in men [unlicensed indication].

Calcitonin and parathyroid hormone

Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homoeostasis. Calcitonin (salmon) (synthetic or recombinant salmon calcitonin) is used to lower the plasma-calcium concentration in patients with hypercalcaemia associated with malignancy.

Calcitonin (salmon) is also licensed for treatment of Paget’s disease of bone when other treatments are ineffective or inappropriate; it is also licensed for the prevention of acute bone loss due to sudden immobility. Calcitonin (salmon) is no longer recommended for the prevention or treatment of postmenopausal osteoporosis because the benefits are outweighed by the risk of malignancy associated with long-term use.

Teriparatide p. 670 (a recombinant fragment of parathyroid hormone) is used for the treatment of postmenopausal osteoporosis, osteoporosis in men at increased risk of fracture, and corticosteroid-induced osteoporosis.

Cinacalcet p. 918 is licensed for the treatment of hypercalcaemia in parathyroid carcinoma.
Bisphosphonates

Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; alendronate p. 663 or risedronate sodium p. 666 are considered the drugs of choice for these conditions.

Bisphosphonates are also used in the treatment of Paget’s disease, hypercalcaemia of malignancy, and in bone metastases in breast cancer.

Strontium ranelate

Strontium ranelate treatment has been associated with an increased risk of serious cardiovascular disease, including myocardial infarction, and the risk should be assessed before treatment and regularly during treatment. Strontium ranelate should be initiated only by specialists for the treatment of severe osteoporosis in postmenopausal women or men at high risk of fracture for whom other treatments are contra-indicated or not tolerated.

ANABOLIC STEROIDS

Nandrolone

- **INDICATIONS AND DOSE**
  - Osteoporosis in postmenopausal women (but not recommended)
  - Adult (female): 50 mg every 3 weeks.

- **CONTRA-INDICATIONS** Acute porphyria p. 930 - male breast cancer - prostate cancer

- **CAUTIONS**
  - Cardiac impairment - diabetes mellitus - epilepsy - hypertension - migraine - skeletal metastases (risk of hypercalcaemia)

- **INTERACTIONS** → Appendix 1 (anabolic steroids).

- **SIDE-EFFECTS** Abnormal liver-function tests (with high doses) - acnæ - amenorrhoea - inhibition of spermatogenesis - liver tumours (with prolonged treatment with anabolic steroids) - premature epiphyseal closure - sodium retention with oedema - virilisation (with high doses including voice changes—sometimes irreversible)

- **HEPATIC IMPAIRMENT** Use in severe hepatic impairment only if benefit outweighs risk.

- **RENAL IMPAIRMENT** Use with caution—may cause sodium and water retention.

- **MONITORING REQUIREMENTS** Monitor skeletal maturation in young patients.

- **LESS SUITABLE FOR PRESCRIBING** Nandrolone injection is less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - Excipients: May contain Arachis (peanut) oil, benzyl alcohol
  - Deca-Durabolin (Aspen Pharma Trading Ltd)
  - Nandrolone decanoate 50 mg per 1 ml

BISPHOSPHONATES

**Drug action**

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.

**Monitoring requirements**

- Renal impairment
- Hepatic impairment

**Contraindications**

- Pregnancy
- Breastfeeding
- Children

**Common side effects**

- Nausea
- Vomiting
- Stomach pain
- Bone pain

**Other side effects**

- Painful muscles
- Headache
- Swelling

**Interactions**

- With other medications
- With alcohol

**Precautions**

- Patients should avoid excessive consumption of alcohol.

**Monitoring**

- Regular monitoring of blood tests
- Regular monitoring of bone density

**Special populations**

- Elderly patients
- Children
- Pregnant or breastfeeding women

**Special considerations**

- Bone density may not improve in some patients
- Long-term use may increase the risk of osteonecrosis of the jaw

**Dental care**

- Patients should inform their doctor and dentist of any planned dental treatment
- Adequate dental hygiene should be maintained

**Other considerations**

- Bisphosphonates are not recommended for the treatment of Paget’s disease

**BNF**

- Bisphosphonates: Dental Clinical Guidance

**MHRA/CHM Advice**

- Bisphosphonates: Osteonecrosis of the Jaw
- Bisphosphonates: Atypical Femoral Fractures

**Further measures to minimise risk**

- Patients should be counselled about the risks and benefits of bisphosphonate treatment
- Patients should be informed about the need for regular dental checks
- Patients should be advised to avoid non-essential dental procedures

**Important safety information**

- Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis.
- The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.

- Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.
- Discontinuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

**Additional information**

- Bisphosphonates are used in the treatment of Paget’s disease, hypercalcaemia of malignancy, and in bone metastases in breast cancer.

**References**

- Scottish Dental Clinical Effectiveness Programme, April 2011
- www.sdcep.org.uk

**Important safety information**

- Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis.
- The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.
- Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.
- Discontinuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

**MHRA/CHM Advice**


- The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget’s disease.
- Risk factors for developing osteonecrosis of the jaw that should be considered are: potency of bisphosphonate (highest for zoledronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease.
- All patients should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment. Patients should also maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling, non-healing sores or discharge to a doctor and dentist during treatment.
- Before prescribing an intravenous bisphosphonate, patients should be given a patient reminder card and informed of the risk of osteonecrosis of the jaw. Advise patients to tell their doctor if they have any problems with their mouth or teeth before starting treatment, and if the patient wears dentures, they should make sure their dentures fit properly. Patients should tell their doctor and dentist that they are receiving an intravenous bisphosphonate if they need dental treatment or dental surgery.
- MHRA/CHM Advice: Bisphosphonates: Osteonecrosis of the External Auditory Canal (December 2015)
- Benign idiopathic osteonecrosis of the external auditory canal has been reported very rarely with bisphosphonate treatment, mainly in patients receiving long-term therapy (2 years or longer).
- The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or suspected cholesteatoma.
- Risk factors for developing osteonecrosis of the external auditory canal include: steroid use, chemotherapy, infection, an ear operation, or cotton-bud use.
- Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment with a bisphosphonate.
**INDICATIONS AND DOSE**

**Treatment of postmenopausal osteoporosis**
- **BY MOUTH**
  - Adult (female): 10 mg daily, alternatively 70 mg once weekly.

**Treatment of osteoporosis in men**
- **BY MOUTH**
  - Adult (male): 10 mg daily.

**Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy**
- **BY MOUTH**
  - Adult (female): 10 mg daily.

**CONTRA-INDICATIONS** Abnormalities of oesophagus - hypocalcaemia - other factors which delay emptying (e.g. stricture or achalasia)

**CAUTIONS** Active gastro-intestinal bleeding - atypical femoral fractures - duodenitis - dysphagia - exclude other causes of osteoporosis - gastritis - history (within 1 year) of ulcers - surgery of the upper gastro-intestinal tract - symptomatic oesophageal disease - ulcers - upper gastro-intestinal disorders

**INTERACTIONS** → Appendix 1 (bisphosphonates).

**SIDE-EFFECTS**
- Common or very common Abdominal distension - abdominal pain - constipation - diarrhea - dyspepsia - flatulence - headache - oesophageal reactions - regurgitation
- Uncommon Episcleritis - erythema - gastritis - nausea - rash - scleritis - uveitis - vomiting
- Rare Atypical femoral fractures with long-term use - hypocalcaemia - oesteonecrosis of the jaw - photosensitivity - severe skin reactions - Stevens-Johnson syndrome - toxic epidermal necrolysis - upper gastro-intestinal ulcers
- Very rare Osteonecrosis of the external auditory canal
- Frequency not known Musculoskeletal pain

**SIDE-EFFECTS, FURTHER INFORMATION**
Severe oesophageal reactions (oesophagitis, oesophageal strictures and oesophageal erosions) have been reported; patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

**PREGNANCY** Avoid.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT** Avoid if eGFR less than 35 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Correct disturbances of calcium and mineral metabolism (e.g. vitamin-D deficiency, hypocalcaemia) before starting treatment. Monitor serum-calcium concentration during treatment.

**DIRECTIONS FOR ADMINISTRATION** Tablets should be swallowed whole and oral solution should be swallowed as a single 100 mL dose. Doses should be taken with plenty of water while sitting or standing, on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after administration.

**PATIENT AND CARER ADVICE** Patients or their carers should be given advice on how to administer alendronic acid tablets and oral solution.

**INTERACTIONS**
Patients (or their carers) should be advised to stop taking alendronic acid and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160

**Alendronate** is recommended as a treatment option for the primary prevention of osteoporotic fractures in the following susceptible postmenopausal women:
- Women over 70 years who have an independent risk factor for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis) or an indicator of low bone mineral density (body mass index under 22 kg/m², ankylosing spondylitis, Crohn’s disease, prolonged immobility, untreated premature menopause, or rheumatoid arthritis) and confirmed osteoporosis.
- Women aged 65–69 years who have an independent risk factor for fracture and confirmed osteoporosis.
- Women under 65 years who have an independent risk factor for fracture and at least one additional indicator of low bone mineral density and confirmed osteoporosis.

www.nice.org.uk/TA160

- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161

This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.

**Alendronate** is recommended as a treatment option for the secondary prevention of osteoporotic fractures in susceptible postmenopausal women.

www.nice.org.uk/TA161

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (April 2016) that alendronic acid (Binosto®) is accepted for restricted use within NHS Scotland for the treatment of postmenopausal osteoporosis where alendronic acid is the appropriate treatment choice, but the patient is unable to swallow tablets.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**
- **Alendronic acid (Non-proprietary)**
  - Alendronic acid (as Alendronate sodium) 10 mg
  - Alendronic acid 10 mg tablets | 28 tablet (PO) £3.25 DT price = £1.76
  - Alendronic acid (as Alendronate sodium) 70 mg
  - Alendronic acid 70 mg tablets | 4 tablet (PO) £22.80 DT price = £5.78
- **Fosamax** (Merck Sharp & Dohme Ltd)
  - Alendronic acid (as Alendronate sodium) 10 mg
  - Fosamax 10 mg tablets | 28 tablet (PO) £23.12 DT price = £1.76
**Alendronic acid with colecalciferol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, alendronic acid p. 663, colecalciferol p. 953.

### Indications and dose

**Treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency**
- **By mouth**
  - Adult (female): 1 tablet once weekly.

### Directions for administration

The directions for administration are contingent on the specific dosing regimen. For example, tablets should be swallowed whole with plenty of water while sitting or standing. For intravenous use, a specific rate is recommended, typically 1 mg per minute. Special considerations, such as renal function, are noted. For oral use, the patient should stand or sit upright for at least 30 minutes after taking the tablet.

### Patient and Carer Advice

Patients or carers should be given advice on how to administer alendronic acid with colecalciferol tablets.

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Fosavance** (Merck Sharp & Dohme Ltd)
  - Alendronic acid (as Alendronate sodium) 70 mg, Colecalciferol 70 microgram
  - Fosavance tablets | 4 tablet [POM] £22.80 DT price = £22.80

### Ibandronic acid

**Indications and dose**

**Reduction of bone damage in bone metastases in breast cancer**
- **Initially by mouth**
  - Adult: 50 mg daily, alternatively (by intravenous infusion) 6 mg every 3–4 weeks

**Hypercalcaemia of malignancy**
- **By intravenous infusion**
  - Adult: 2–4 mg as a single infusion, dose to be adjusted according to serum calcium concentration

**Treatment of postmenopausal osteoporosis**
- **Initially by mouth**
  - Adult (female): 150 mg once a month, alternatively (by intravenous injection) 3 mg every 3 months, to be administered over 15–30 seconds.

### Contra-Indications

**General Contra-Indications**

- Hypocalcaemia

**Specific Contra-Indications**
- With oral use: Abnormalities of the oesophagus - other factors which delay emptying (e.g. stricture or achalasia)
- **Caution**: Atypical femoral fractures - cardiac disease (avoid fluid overload)
- **Interactions**: → Appendix 1 (bisphosphonates).

### Side-effects

**General Side-effects**

- **Common or very common**: Abdominal pain - asthma - bone pain - chills - diarhoea - dyspepsia - fever - gastritis - headache - hypocalcaemia - hypophosphataemia - influenza-like symptoms - muscle pain - nausea - pharyngitis - rash - vomiting
- **Rare**: Anaemia - angioedema - atypical femoral fractures - bronchospasm - hypersensitivity reactions - injection-site reactions - pruritus - urticaria
- **Very rare**: Osteonecrosis of the external auditory canal - osteonecrosis of the jaw.

**Specific SIDE-EFFECTS**

- **Common or very common**: With oral use - Severe oesophageal reactions (discontinue)
- **Pregnancy**: Avoid.
- **Breast Feeding**: Avoid—present in milk in animal studies.

**Renal Impairment**

- With intravenous use: When used for bone metastases, if eGFR 30–50 mL/minute/1.73 m² reduce dose to 4 mg and infuse over 1 hour; if eGFR less than 30 mL/minute/1.73 m² reduce dose to 2 mg and infuse over 1 hour.
- With oral use: When used for bone metastases, if eGFR 30–50 mL/minute/1.73 m² reduce dose to 50 mg on alternative days; if eGFR less than 30 mL/minute/1.73 m² reduce dose to 50 mg once weekly. When used for postmenopausal osteoporosis, avoid if eGFR less than 30 mL/minute/1.73 m².

**Monitoring Requirements**

Monitor renal function and serum calcium, phosphate and magnesium.

**Directions for Administration**

Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet.

**Patient and Carer Advice**

A patient reminder card should be provided to patients receiving intravenous ibandronic acid (risk of osteonecrosis of the jaw). Patients or carers should be given advice on how to administer ibandronic acid tablets. Oesophageal reactions Patients and carers should be advised to stop tablets and seek medical attention for symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Ibandronic acid (Non-proprietary)**
  - Ibandronic acid (as Ibandronic sodium monohydrate) 50 mg
    - Ibandronic acid 50mg tablets | 28 tablet [POM] £174.51 DT price = £6.27
  - Ibandronic acid (as Ibandronic sodium monohydrate) 150 mg
    - Ibandronic acid 150mg tablets | 1 tablet [POM] £174.48 DT price = £1.10
  - **Bonviva** (Roche Products Ltd)
    - Ibandronic acid (as Ibandronic sodium monohydrate) 50 mg
      - Bonviva 50mg tablets | 28 tablet [POM] £183.69 DT price = £6.27
    - **Bonviva** (Roche Products Ltd)
      - Ibandronic acid (as Ibandronic sodium monohydrate) 150 mg
        - Bonviva 150mg tablets | 1 tablet [POM] £18.40 DT price = £1.10
Pamidronate disodium
(Formerly called aminohydroxypropylidenediphosphonate disodium (APD))

**INDICATIONS AND DOSE**

**Hypercalcaemia of malignancy**

- **BY INTRAVENOUS INFUSION**
  - Adult: 15–60 mg, to be given (via cannula in a relatively large vein) as a single infusion or in divided doses over 2–4 days, dose adjusted according to serum calcium concentration; maximum 90 mg per course

**Osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma**

- **BY INTRAVENOUS INFUSION**
  - Adult: 90 mg every 4 weeks, to be administered via cannula in a relatively large vein, dose may alternatively be administered every 3 weeks, to coincide with chemotherapy in breast cancer

**Paget’s disease of bone**

- **BY INTRAVENOUS INFUSION**
  - Adult: 30 mg every week for a 6 week course (total dose 180 mg), alternatively initially 30 mg once weekly for 1 week, then increased to 60 mg every 2 weeks (max. per dose 60 mg) for a 6 week course (total dose 210 mg), to be administered via cannula in a relatively large vein, course may be repeated every 6 months; maximum 360 mg per course

**CAUTIONS** Atypical femoral fractures - cardiac disease (especially in elderly) - ensure adequate hydration - previous thyroid surgery (risk of hypocalcaemia)

**INTERACTIONS** Appendix 1 (bisphosphonates). Avoid concurrent use with other bisphosphonates.

**SIDE-EFFECTS**

- Common or very common Abdominal pain - anaemia - anorexia - arthralgia - bone pain - constipation - diarrhoea - drowsiness - fever - headache - hypertension - hypomagnesaemia - hypophosphataemia - influenza-like symptoms (sometimes accompanied by malaise, rigors, fatigue and flushed) - insomnia - lymphocytopenia - myalgia - nausea - paraesthesia - rash - symptomatic hypocalcaemia - tetany - thrombocytopenia - vomiting

- Rare Acute renal failure - agitation - atypical femoral fractures - confusion - conjunctivitis - deterioration of renal disease - dizziness - dyspepsia - haematuria - hallucinations - hyperkalaemia - hypertension - isolated cases of seizures - lethargy - leucopenia - muscle cramps - osteonecrosis of the jaw - other ocular symptoms - pruritus

- Very rare Osteonecrosis of the external auditory canal

- **Frequency not known** Atrial fibrillation - injection-site reactions - reactivation of herpes simplex - reactivation of herpes zoster

**SIDE-EFFECTS, FURTHER INFORMATION**

- Calcium and vitamin D supplements Oral supplements are advised to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases or multiple myeloma at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) and in those with Paget’s disease.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Avoid.

**HEPATIC IMPAIRMENT** Caution in severe hepatic impairment—no information available.

**RENAL IMPAIRMENT** Max. infusion rate 20 mg/hour. Avoid if eGFR less than 30 ml/minute/1.73 m², except in life-threatening hypercalcaemia if benefit outweighs risk. If renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value.

**MONITORING REQUIREMENTS**

- Monitor serum electrolytes, calcium and phosphate possibility of convulsions due to electrolyte changes.

- Assess renal function before each dose.

**DIRECTIONS FOR ADMINISTRATION** For slow intravenous infusion (Arelia®; Pamidronate disodium, Hospira, Medac, Wockhardt), give intermittently in Glucose 5% or Sodium Chloride 0.9%; give at a rate not exceeding 1 mg/minute; not to be given with infusion fluids containing calcium. For Arelia®, reconstitute initially with water for injections (15 mg in 5 ml, 30 mg or 90 mg in 10 ml), then dilute with infusion fluid to a concentration of not more than 90 mg in 250 ml. For Pamidronate disodium (Medac, Hospira, Wockhardt) dilute with infusion fluid to a concentration of not more than 90 mg in 250 ml.

**PATIENT AND CARER ADVICE**

A patient reminder card should be provided (risk of osteonecrosis of the jaw).

Driving and skilled tasks

Patients should be warned against performing skilled tasks (e.g. cycling, driving or operating machinery) immediately after treatment (somnolence or dizziness can occur).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Pamidronate disodium 3 mg per 1 ml
- Pamidronate disodium 15mg/5ml solution for infusion vials | 1 vial £27.50 (Hospital only) | 5 vial £149.15
- Pamidronate disodium 30mg/10ml solution for infusion vials | 1 vial £55.00 (Hospital only) | 1 vial £59.66
- Pamidronate disodium 60mg/20ml solution for infusion vials | 1 vial £110.00 (Hospital only) | 1 vial £165.00 (Hospital only)
- Pamidronate disodium 9 mg per 1 ml
- Pamidronate disodium 90mg/10ml solution for infusion vials | 1 vial £170.45
- Pamidronate disodium 15 mg per 1 ml
- Pamidronate disodium 60mg/4ml solution for infusion ampoules | 1 ampoule £119.32
- Pamidronate disodium 15mg/1ml solution for infusion ampoules | 4 ampoule £119.32
Risedronate sodium

- **INDICATIONS AND DOSE**

  **Paget's disease of bone**
  - **BY MOUTH**
  - Adult: 30 mg daily for 2 months, course may be repeated if necessary after at least 2 months

  **Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures**
  - **BY MOUTH**
  - Adult (female): 5 mg daily, alternatively 35 mg once weekly.

  **Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women**
  - **BY MOUTH**
  - Adult (female): 5 mg daily.

  **Treatment of osteoporosis in men at high risk of fractures**
  - **BY MOUTH**
  - Adult (male): 35 mg once weekly.

- **CONTRA-INDICATIONS**
  - Hypocalcaemia

- **CAUTIONS**
  - Atypical femoral fractures • oesophageal abnormalities • other factors which delay transit or emptying (e.g. stricture or achalasia)

- **INTERACTIONS**
  - Appendix 1 (bisphosphonates).

- **SIDE-EFFECTS**
  - Abdominal pain • constipation • diarrhoea • dyspepsia • headache • musculoskeletal pain • nausia
  - Duodenitis • dysphagia • gastritis • oesophageal ulcer • oesophagitis • uveitis
  - Atypical femoral fractures • glossitis • oesophageal stricture
  - Osteonecrosis of the external auditory canal
  - Frequency not known

  - Cutaneous vasculitis • gastroduodenal ulceration • hair loss • hepatic disorders • osteonecrosis of the jaw • Stevens-Johnson syndrome • toxic epidermal necrolysis

- **PREGNANCY**
  - Avoid

- **BREAST FEEDING**
  - Avoid.

- **RENAI IMPAIRMENT**
  - Avoid if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Correct hypocalcaemia before starting.
  - Correct other disturbances of bone and mineral metabolism (e.g. vitamin-D deficiency) at onset of treatment.

- **DIRECTIONS FOR ADMINISTRATION**
  - Swallow tablets whole with full glass of water; on rising, take on an empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising.

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer risedronate sodium tablets.
  - Oesophageal reactions
  - Patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - **Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160**
      - **Risedronate** is recommended as an alternative for women:
        - in whom alendronate is contra-indicated or not tolerated and
        - who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance.
        - **www.nice.org.uk/TA160**
    - **Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161**
      - This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.
      - **Risedronate** is recommended as an alternative for women:
        - in whom alendronate is contra-indicated or not tolerated and
        - who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis, as indicated in the full NICE guidance.
        - **www.nice.org.uk/TA161**

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Tablet**
  - **Risedronate sodium (Non-proprietary)**
    - **Risedronate sodium 5 mg**
      - Risedronate sodium 5mg tablets | 28 tablet (pom) £24.78 DT price = £18.85
    - **Risedronate sodium 30 mg**
      - Risedronate sodium 30mg tablets | 28 tablet (pom) £143.95 DT price = £143.83
    - **Risedronate sodium 35 mg**
      - Risedronate sodium 35mg tablets | 4 tablet (pom) £19.12 DT price = £0.89
  - **Actonel** (Warner Chilcott UK Ltd, Teva UK Ltd)
    - **Risedronate sodium 5 mg**
      - Actonel 5mg tablets | 28 tablet (pom) £17.99 DT price = £18.85
    - **Risedronate sodium 30 mg**
      - Actonel 30mg tablets | 28 tablet (pom) £143.95 DT price = £143.83
    - **Risedronate sodium 35 mg**
      - Actonel Once a Week 35mg tablets | 4 tablet (pom) £19.12 DT price = £0.89

- **Risedronate with calcium carbonate and colecalciferol**
  - The properties listed below are those particular to the combination only. For the properties of the components please consider, risedronate sodium above, calcium carbonate p. 919, colecalciferol p. 953.

- **INDICATIONS AND DOSE**
  - **Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures**
    - **BY MOUTH**
    - Adult: 1 tablet once weekly on day 1 of the weekly cycle, followed by 1 sachet daily on days 2–6 of the weekly cycle.
DIRECTIONS FOR ADMINISTRATION  Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet. Granules should be stirred into a glass of water and after dissolution complete taken immediately.

PRESCRIBING AND DISPENSING INFORMATION  Actonel Combi® effervescent granules contain calcium carbonate 2.5g (calcium 1g or Ca²⁺ 25 mmol) and colecaltferol 22 micrograms (880 units)/sachet.

PATIENT AND CARER ADVICE  Patients or carers should be given advice on how to administer calcium carbonate with colecaltferol and risedronate tablets and granules.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet/Granules
- Actonel Combi (Teva UK Ltd)
  - Actonel Combi 35mg tablets and 1000mg/880unit effervescent granules sachets | 4 week supply  £19.12

Sodium clodronate

INDICATIONS AND DOSE
Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma
- BY MOUTH
  - Adult: 1.6 g daily in 1–2 divided doses, then increased if necessary up to 3.2 g daily in 2 divided doses

LORON 520®
Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma
- BY MOUTH
  - Adult: Initially 2 tablets daily in 1–2 divided doses, increased if necessary up to 4 tablets daily

CONTRA-INDICATIONS  Acute gastro-intestinal inflammatory conditions

CAUTIONS  Atypical femoral fractures - maintain adequate fluid intake during treatment

INTERACTIONS  → Appendix 1 (bisphosphonates). Renal dysfunction reported in patients receiving concomitant NSAIDs.

SIDE-EFFECTS
- Common or very common  Bronchospasm • diarrhoea • nausea • skin reactions • vomiting
- Rare  Atypical femoral fractures
- Very rare  Osteonecrosis of the external auditory canal • osteonecrosis of the jaw
- Frequency not known  Renal impairment • uveitis

PREGNANCY  Avoid.

BREAST FEEDING  Manufacturer advises avoid—no information available.

RENAL IMPAIRMENT  Max. initial dose 1200 mg daily if eGFR 30–50 mL/minute/1.73m² . Use half normal dose if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².

MONITORING REQUIREMENTS  Monitor renal function, serum calcium and serum phosphate before and during treatment.

DIRECTIONS FOR ADMINISTRATION  Avoid food for 2 hours before and 1 hour after treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake.

PATIENT AND CARER ADVICE  Patients or carers should be given advice on how to administer sodium clodronate capsules and tablets.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS  10
- Sodium clodronate (Non-proprietary)
  - Sodium clodronate 800 mg Sodium clodronate 800mg tablets | 60 tablet  £116.72 DT price = £146.43
  - Bonefos (Bayer Plc)
    - Sodium clodronate 800 mg Bonefos 800mg tablets | 60 tablet  £146.43 DT price = £146.43
    - Clasteon (Beacon Pharmaceuticals Ltd)
      - Sodium clodronate 800 mg Clasteon 800mg tablets | 60 tablet  £146.43 DT price = £146.43
  - Loron (Intrapharm Laboratories Ltd)
    - Sodium clodronate 520 mg Loron 520mg tablets | 60 tablet  £152.59 DT price = £152.59

Capsule
- Sodium clodronate (Non-proprietary)
  - Sodium clodronate 400 mg Sodium clodronate 400mg capsules | 30 capsule £40.49 | 120 capsule £161.97 DT price = £139.83
  - Bonefos (Bayer Plc)
    - Sodium clodronate 400 mg Bonefos 400mg capsules | 120 capsule £139.83 DT price = £139.83
    - Clasteon (Beacon Pharmaceuticals Ltd)
      - Sodium clodronate 400 mg Clasteon 400mg capsules | 30 capsule £34.96 | 120 capsule £139.83 DT price = £139.83

Zoledronic acid

INDICATIONS AND DOSE
ACLASTA®
Treatment of Paget’s disease of bone
- BY INTRAVENOUS INFUSION
  - Adult: 5 mg as a single dose, to be administered over at least 15 minutes, at least 500 mg elemental calcium twice daily (with vitamin D) for at least 10 days is recommended following infusion

Treatment of postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis)
- BY INTRAVENOUS INFUSION
  - Adult: 5 mg once yearly as a single dose, to be administered over at least 15 minutes, in patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair; before first infusion give 5000–125000 units of vitamin D

ZOMETA® INFUSION
Reduction of bone damage in advanced malignancies involving bone
- BY INTRAVENOUS INFUSION
  - Adult: 4 mg every 3–4 weeks, to be administered over at least 15 minutes, calcium 500 mg daily and vitamin D 400 units daily should also be taken

Hypercalcaemia of malignancy
- BY INTRAVENOUS INFUSION
  - Adult: 4 mg for 1 dose, to be administered over at least 15 minutes

CAUTIONS  Atypical femoral fractures • cardiac disease (avoid fluid overload) • concomitant medicines that affect renal function

INTERACTIONS  → Appendix 1 (bisphosphonates).

SIDE-EFFECTS
- Common or very common  Anaemia • arthralgia • atrial fibrillation • bone pain • conjunctivitis • dizziness • fever •
Endocrine system

Disorders of bone metabolism

668 Disorders of bone metabolism

BNF 73

†Indental disturbances • headache • hypophosphataemia • influenza-like symptoms • myalgia • renal impairment • rigors

> Uncommon Angioedema • anorexia • anxiety • asthenia • blurred vision • chest pain • cough • dry mouth • dyspnoea • haematuria • hypersensitivity reactions • hypertension • hypokalaemia • hypomagnesaemia • hypotension • injection-site reactions • lethargy • leucopenia • muscle cramps • paraesthesia • peripheral oedema • proteinuria • pruritus • rash • sleep disturbance • stomatitis • sweating • taste disturbance • thrombocytopenia • tremor • urinary frequency • weight gain

> Rare Acute renal failure • atypical femoral fractures • bradycardia • confusion • hyperkalaemia • hypernatraemia • osteonecrosis of the jaw • pancytopenia

> Very rare Episcleritis • osteonecrosis of the external auditory canal • uveitis

Side-effects, Further Information

Renal impairment and renal failure have been reported; ensure patient is hydrated before each dose and assess renal function.

Conception and Contraception

Contra-indicated in women of child-bearing potential.

Pregnancy

Avoid—toxicity in animal studies.

Breast Feeding

Avoid—no information available.

Hepatic Impairment

Caution in severe hepatic impairment—limited information available.

Renal Impairment

In advanced malignancies involving bone, if eGFR 50–60 ml/minute/1.73 m² reduce dose to 3.5 mg every 3–4 weeks; if eGFR 40–50 ml/minute/1.73 m² reduce dose to 3.3 mg every 3–4 weeks; if eGFR 30–40 ml/minute/1.73 m² reduce dose to 3 mg every 3–4 weeks; if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value. Avoid in tumour-induced hypercalcaemia if serum creatinine above 400 micromol/litre. Avoid in advanced malignancies involving bone if eGFR less than 30 ml/minute/1.73 m² (or if serum creatinine greater than 265 micromol/litre).

Avoid in Paget’s disease, treatment of postmenopausal osteoporosis and osteoporosis in men if eGFR less than 35 ml/minute/1.73 m².

Monitoring Requirements

Correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting. Monitor serum electrolytes, calcium, phosphate and magnesium.

Monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated.

Directions for Administration

For intravenous infusion (Zometa®), give intermittently in Glucose 5% or Sodium chloride 0.9%; dilute requisite dose according to product literature; infuse over at least 15 minutes; administer as a single intravenous solution in a separate infusion line.

Patient and Carer Advice

A patient reminder card should be provided (risk of osteonecrosis of the jaw).

National Funding/Access Decisions

Zometa® Infusion

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (May 2003) that for the prevention of skeletal related events Zometa® is accepted for restricted use within NHS Scotland for the treatment of patients with breast cancer and multiple myeloma if prescribed by an oncologist.

Aclasta®

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2008) that in postmenopausal women Aclasta® is accepted for restricted use within the NHS Scotland for the treatment of osteoporosis in those for whom oral treatment options for osteoporosis are inappropriate and when initiated by a specialist.

Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

Infusion

Aclasta® (Novartis Pharmaceuticals UK Ltd)

Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml Aclasta 5mg/100ml infusion bottles £125.38

Zometa® (Novartis Pharmaceuticals UK Ltd)

Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml Zometa 4mg/100ml infusion bottles £174.14

Solution for Infusion

Zometa® (Novartis Pharmaceuticals UK Ltd)

Zoledronic acid (as Zoledronic acid monohydrate) 800 microgram per 1 ml Zometa 4mg/5ml solution for infusion vials £174.14

Calcitonin (salmon)

(Salcatonin)

Indications and Dose

Hypercalcaemia of malignancy

By Subcutaneous Injection, or By Intramuscular Injection

Adult: 100 units every 6–8 hours (max. per dose 400 units every 6–8 hours), adjusted according to response

By Intravenous Infusion

Adult: Up to 10 units/kg, in severe or emergency cases, to be administered by slow intravenous infusion over at least 6 hours

Paget’s Disease of Bone

By Subcutaneous Injection, or By Intramuscular Injection

Adult: 100 units daily, adjusted according to response for maximum 3 months (6 months in exceptional circumstances), a minimum dosage regimen of 50 units three times a week has been shown to achieve clinical and biochemical improvement

Prevention of Acute Bone Loss Due to Sudden Immobility

By Subcutaneous Injection, or By Intramuscular Injection

Adult: Initially 100 units daily in 1–2 divided doses, then reduced to 50 units daily at the start of mobilisation, usual duration of treatment is 2 weeks; maximum 4 weeks

Contra-Indications

Hypocalcaemia

Caution

Heart failure • history of allergy (skin test advised) • risk of malignancy—avoid prolonged use (use lowest effective dose for shortest possible time)

Side-effects

Common or Very Common

Abdominal pain • diarrhea • dizziness • fatigue • flushing • headache • malignancy (with long-term use) • musculoskeletal pain • nausea • taste disturbances • vomiting

Uncommon

Cough • hypersensitivity reactions • hypertension • injection-site reactions • oedema • polyuria • pruritus • rash • visual disturbances

Frequency Not Known

Tremor

Pregnancy

Avoid unless potential benefit outweighs risk (toxicity in animal studies).

Breast Feeding

Avoid; inhibits lactation in animals.
Strontium ranelate

- **DRUG ACTION** Stimulates bone formation and reduces bone resorption.

- **INDICATIONS AND DOSE**
  Treatment of severe osteoporosis in postmenopausal women or men at high risk of fracture for whom other treatments are contra-indicated or not tolerated (initiated under specialist supervision)

  - **By mouth**
  - Adult: 2 g once daily, dose to be taken in water, preferably at bedtime

- **CONTRA-INDICATIONS** Cerebrovascular disease · current or previous venous thromboembolic event · ischaemic heart disease · peripheral arterial disease · temporary or prolonged immobilisation · uncontrolled hypertension

- **CAUTIONS** Predisposition to cardiovascular disease—assess risk before and every 6–12 months during treatment

- **INTERACTIONS** → Appendix 1 (strontium ranelate).

- **SIDE-EFFECTS**
  - Common or very common Dermatitis · diarrhoea · eczema · headache · myocardial infarction · nausea · venous thromboembolism
  - Very rare Angioedema · hypersensitivity reactions · pruritus · rash · urticaria
  - Frequency not known Abdominal pain · alopecia · bone marrow suppression · constipation · dyspepsia · flatulence · gastro-oesophageal reflux · peripheral oedema · stomatitis · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  Severe allergic reactions Including drug rash with eosinophilia and systemic symptoms (DRESS), have been reported in patients taking strontium ranelate. DRESS starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal. Treatment with strontium ranelate should not be restarted.

- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².

- **EFFECT ON LABORATORY TESTS** Interferes with colorimetric measurements of calcium in blood and urine.

- **MEDICINAL FORMS**

  **Solution for injection**
  - Calcitonin (salmon) (Non-proprietary) Calcitonin (salmon) 50 unit per 1 ml Calcitonin (salmon) 50 units/1 ml solution for injection ampoules | 5 ampoule £167.20
  - Calcitonin (salmon) 100 unit per 1 ml Calcitonin (salmon) 100 units/1 ml solution for injection ampoules | 5 ampoule £220.00
  - Calcitonin (salmon) 200 unit per 1 ml Calcitonin (salmon) 200 units/1 ml solution for injection ampules | 1 vial £352.00
  - Miacalcic (Essential Pharma Ltd) Miacalcic (salmon) 50 units/ml solution for injection ampules | 5 ampoule £17.10
  - Miacalcic (salmon) 100 unit per 1 ml Miacalcic 100 units/ml solution for injection ampules | 5 ampoule £34.21
  - Miacalcic (salmon) 200 unit per 1 ml Miacalcic 200 units/ml multidose solution for injection vials | 1 vial £24.60

- **DIRECTIONS FOR ADMINISTRATION** Avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.

- **PATIENT AND CARER ADVICE**
  Patients or carers should be given advice on how to administer strontium ranelate granules. Severe allergic reactions Patients should be advised to stop taking strontium ranelate and consult their doctor immediately if skin rash develops.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  **NICE technology appraisals (TAs)**
  - Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160
  - Strontium ranelate is recommended as an alternative for women:
    - in whom alendronate and risedronate are contra-indicated or not tolerated and
    - who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance.
  - www.nice.org.uk/TA160
  - Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161
  - This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.
  - Strontium ranelate is recommended as an alternative for women:
    - in whom alendronate and risedronate are contra-indicated or not tolerated and
    - who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance.
  - www.nice.org.uk/TA161

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Granules**
  - **CAUTIONARY AND ADVISORY LABELS** 5, 13
  - **EXCIPIENTS:** May contain Aspartame
  - **Protelos** (Servier Laboratories Ltd)
  - **Strontium ranelate 2 g** Protelos 2 g granules sachets sugar-free | 28 sachet £27.08 DT price = £27.08

- **BNF 73** Disorders of bone metabolism 669

- **Endocrine system**
**Teriparatide**

- **INDICATIONS AND DOSE**
  Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures | Treatment of corticosteroid-induced osteoporosis
  - By subcutaneous injection
  - Adult: 20 micrograms daily for maximum duration of treatment 24 months (course not to be repeated)

- **CONTRA-INDICATIONS**
  Bone metastases • hyperparathyroidism • metabolic bone diseases • Paget’s disease • pre-existing hypercalcaemia • previous radiation therapy to the skeleton • skeletal malignancies • unexplained raised alkaline phosphatase

- **SIDE-EFFECTS**
  - Common or very common
    - Anaemia • arthralgia • asthenia • depression • dizziness • dyspnoea • fatigue • gastrointestinal disorders • haemorrhoids • headache • increased sweating • muscle cramps • myalgia • nausea • palpititation • reflux • sciatica • vertigo
  - Uncommon
    - Hypercalcaemia • injection-site reactions • urinary disorders
  - Rare
    - Hypersensitivity reactions

- **PREGNANCY**
  Avoid.

- **BREAST FEEDING**
  Avoid.

- **RENAL IMPAIRMENT**
  Caution in moderate impairment; avoid if severe.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  NICE technology appraisals (TAs)
  - Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161
  This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.

  **Teriparatide** is recommended as an alternative for women:
  - In whom alendronate or risedronate, or strontium ranelate are contra-indicated or not tolerated, or where treatment with alendronate or risedronate has been unsatisfactory (indicated by another fragility fracture and a decline in bone mineral density despite treatment for 1 year) and
  - Who comply with particular combinations of bone mineral density measurement, age, and number of fractures, as indicated in the full NICE guidance.

  www.nice.org.uk/TA161

  **Scottish Medicines Consortium (SMC) Decisions**
  The Scottish Medicines Consortium has advised (December 2003) that the use of teriparatide (Forsteo®) in postmenopausal women should be restricted to the treatment of established (severe) osteoporosis and should be initiated by specialists experienced in the treatment of osteoporosis.

- **MEDICINAL FORMS**
  There is variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - Forsteo (Eli Lilly and Company Ltd)
    Teriparatide 250 microgram per 1 ml Forsteo 20 microlitres solution for injection 2.4ml pre-filled disposable devices | 1 pre-filled disposable injection £71.88

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**Denosumab**

- **DRUG ACTION**
  Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.

- **INDICATIONS AND DOSE**
  **PROLIA®**
  Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures | Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures
  - By subcutaneous injection
  - Adult: 60 mg every 6 months, supplement with calcium and vitamin D

  **XGEVA®**
  Prevention of skeletal related events in patients with bone metastases from solid tumours
  - By subcutaneous injection
  - Adult: 120 mg every 4 weeks, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present

  **Treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity in adults and skeletally mature adolescents**
  - By subcutaneous injection
  - Adult: 120 mg every 4 weeks, give additional dose on days 8 and 15 of the first month of treatment only, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present

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**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: DENOSUMAB: ATYPICAL FEMORAL FRACTURES (FEBRUARY 2013)**

Atypical femoral fractures have been reported rarely in patients receiving denosumab for the long-term treatment (2.5 or more years) of postmenopausal osteoporosis.

Patients should be advised to report any new or unusual thigh, hip, or groin pain during treatment with denosumab.

Discontinuation of denosumab in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.


Denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia.

**Osteonecrosis of the jaw**

Osteonecrosis of the jaw is a well-known and common side-effect in patients receiving denosumab 120 mg for cancer. Risk factors include smoking, old age, poor oral hygiene, invasive dental procedures (including tooth extractions, dental implants, oral surgery), comorbidity (including dental disease, anaemia, coagulopathy, infection), advanced cancer, previous treatment with bisphosphonates, and concomitant treatments (including chemotherapy, anti-angiogenic biologics, corticosteroids, and radiotherapy to head and neck). The following precautions are now recommended to reduce the risk of ONJ:

Denosumab 120 mg (cancer indication)
● A dental examination and appropriate preventative dentistry before starting treatment are now recommended for all patients

● Do not start denosumab in patients with a dental or jaw condition requiring surgery, or in patients who have unhealed lesions from dental or oral surgery

Denosumab 60 mg (osteooporosis indication)

● Check for ONJ risk factors before starting treatment. A dental examination and appropriate preventative dentistry are now recommended for patients with risk factors

All patients should be given a patient reminder card and informed of the risk of ONJ. Advise patients to tell their doctor if they have any problems with their mouth or teeth before starting treatment, if they wear dentures they should make sure their dentures fit properly before starting treatment, to maintain good oral hygiene, receive routine dental check-ups during treatment, and immediately report any oral symptoms such as dental mobility, pain, swelling, non-healing sores or discharge to a doctor and dentist. Patients should tell their doctor and dentist that they are receiving denosumab if they need dental treatment or dental surgery.

Hypocalcaemia

Denosumab is associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment. Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later in treatment.

Plasma-calcium concentration monitoring is recommended for denosumab 120 mg (cancer indication):

● before the first dose

● within two weeks after the initial dose

● if suspected symptoms of hypocalcaemia occur

● consider monitoring more frequently in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance less than 30 mL/minute)

Plasma-calcium concentration monitoring is recommended for denosumab 60 mg (osteoporosis indication):

● before each dose

● within two weeks after the initial dose in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance less than 30 mL/minute)

● if suspected symptoms of hypocalcaemia occur

All patients should be advised to report symptoms of hypocalcaemia to their doctor (e.g. muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth).

● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Denosumab for the prevention of osteoporotic fractures in postmenopausal women (October 2010) NICE TA204

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures:

● who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contra-indication to, those treatments and

● who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance.

Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contra-indication to, those treatments.

www.nice.org.uk/TA204

Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012) NICE TA265

Denosumab is recommended for the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours other than prostate if:

● bisphosphonates would otherwise be prescribed, and

● the manufacturer provides denosumab with the discount agreed in the patient access scheme.

Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

Patients with bone metastases from solid tumours currently receiving denosumab whose disease does not meet the above criteria can continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA265
5 Dopamine responsive conditions

DOPAMINERGIC DRUGS > DOPAMINE RECEPTOR AGONISTS

Dopamine-receptor agonists

Overview

Bromocriptine p. 391 is used for the treatment of galactorrhoea, and for the treatment of prolactinomas (when it reduces both plasma prolactin concentration and tumour size). Bromocriptine also inhibits the release of growth hormone and is sometimes used in the treatment of acromegaly, but somatostatin analogues (such as octreotide p. 846) are more effective.

Cabergoline p. 393 has similar side-effects to bromocriptine, however patients intolerant of bromocriptine may be able to tolerate cabergoline (and vice versa).

Quinagolide below has actions and uses similar to those of ergot-derived dopamine agonists, but its side-effects differ slightly.

Suppression of lactation

Although bromocriptine and cabergoline are licensed to suppress lactation, they are not recommended for routine suppression (or for the relief of symptoms of postpartum pain and engorgement) that can be adequately treated with simple analogics and breast support. If a dopamine-receptor agonist is required, cabergoline is preferred. Quinagolide is not licensed for the suppression of lactation.

Quinagolide

- DRUG ACTION Quinagolide is a non-ergot dopamine D2 agonist.

- INDICATIONS AND DOSE

Hyperprolactinaemia

- BY MOUTH

- Adult: Initially 25 micrograms once daily for 3 days, dose to be taken at bedtime, increased in steps of 25 micrograms every 3 days; usual dose 75–150 micrograms daily, for doses higher than 300 micrograms daily increase in steps of 75–150 micrograms at intervals of not less than 4 weeks.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Prolixa (Amgen Ltd)
  - Denosumab 60 mg per 1 ml Prolixa 60mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PAM) £183.00
  - Xgeva (Amgen Ltd)
  - Denosumab 70 mg per 1 ml Xgeva 120mg/1.7ml solution for injection vials | 1 vial (PAM) £309.86

- UNLICENSED USE Not licensed for the suppression of lactation.

- CAUTIONS Acute porphyrias p. 930 · history of psychotic illness · history of serious mental disorders

- INTERACTIONS → Appendix 1 (quinagolide). Tolerance may be reduced by alcohol.

- SIDE-EFFECTS

- Common or very common Abdominal pain · anorexia · constipation or diarrhoea · dizziness · fatigue · flushing · headache · hypotension · insomnia · nasal congestion · nausea · oedema · syncope · vomiting

- Very rare Psychosis

SIDE-EFFECTS, FURTHER INFORMATION

- Gastro-intestinal bleeding · Treatment should be withdrawn if gastro-intestinal bleeding occurs.

- ALLERGY AND CROSS-SENSITIVITY Quinagolide should not be used in patients with hypersensitivity to quinagolide (does not apply to hypotension to ergot alcohol).

- CONCEPTION AND CONTRACEPTION Advise non-hormonal contraception if pregnancy not desired.

- PREGNANCY Discontinue when pregnancy confirmed unless medical reason for continuing (specialist advice needed).

- BREAST FEEDING Suppresses lactation.

- HEPATIC IMPAIRMENT Avoid—no information available.

- RENAL IMPAIRMENT Avoid—no information available.

- MONITORING REQUIREMENTS Monitor blood pressure for a few days after starting treatment and following dosage increase.

- PATIENT AND CARER ADVICE

Driving and skilled tasks

Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions Hypotensive reactions can be disturbing in some patients during the first few days of treatment with dopamine-receptor agonists, particular care should be exercised when driving or operating machinery.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 10, 21

- Quinagolide (Non-proprietary)

  | Quinagolide (as Quinagolide hydrochloride) |
  | 25 microgram | Quinagolide 25microgram tablets | 3 tablet (PAM) no price available |
  | 50 microgram | Quinagolide 50microgram tablets | 3 tablet (PAM) no price available |
  | 75 microgram | Quinagolide 75microgram tablets | 30 tablet (PAM) £54.57 DT price = £27.00 |
Breast pain (mastalgia)

Once any serious underlying cause for breast pain has been ruled out, most women will respond to reassurance and withdrawal of an oral contraceptive or of hormone replacement therapy to resolve the symptoms. Recurrence of symptoms that persist for longer than 6 months may require analgesics; moderate to severe pain, cyclical pain or pain of hormone replacement therapy may help to resolve the reduction in dietary fat; withdrawal of an oral contraceptive ruled out, most women will respond to reassurance and continued if necessary. Symptoms recur in 50% of women within 2 years of withdrawal of therapy but may be less severe.

6 Gonadotrophin responsive conditions

Gonadotrophins

Drugs affecting gonadotrophins

Danazol p. 678 is licensed for the treatment of endometriosis and for the relief of severe pain and tenderness in benign fibrocystic breast disease where other measures have proved unsatisfactory. It may also be effective in the long-term management of hereditary angioedema [unlicensed indication].

Cetrorelix, below, and ganirelix, below, are luteinising hormone releasing hormone antagonists, which inhibit the release of gonadotrophins (luteinising hormone and follicle stimulating hormone). They are used in the treatment of infertility by assisted reproductive techniques.

Gonadorelin analogues

Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility, male hypospermatogenesis with severe sexual deviation, anaemia due to uterine fibroids (together with iron supplementation), breast cancer, prostate cancer and before intra-uterine surgery. Use of leuporelin acetate and triptorelin for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding. For women undergoing hysterectomy or myomectomy, a vaginal procedure is made more feasible following the use of a gonadorelin analogue.

Breast pain (mastalgia)

Once any serious underlying cause for breast pain has been ruled out, most women will respond to reassurance and reduction in dietary fat; withdrawal of an oral contraceptive or of hormone replacement therapy may help to resolve the pain.

Mild, non-cyclical breast pain is treated with simple analgesics; moderate to severe pain, cyclical pain or symptoms that persist for longer than 6 months may require specific drug treatment.

Danazol is licensed for the relief of severe pain and tenderness in benign fibrocystic breast disease which has not responded to other treatment.

Tamoxifen p. 848 may be a useful adjunct in the treatment of mastalgia [unlicensed indication] especially when symptoms can definitely be related to cyclic oestrogen production; it may be given on the days of the cycle when symptoms are predicted.

Treatment for breast pain should be reviewed after 6 months and continued if necessary. Symptoms recur in about 50% of women within 2 years of withdrawal of therapy but may be less severe.

PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > ANTI-GONADOTROPHIN-RELEASING HORMONES

Cetrorelix

- **INDICATIONS AND DOSE**
  - Adjunct in the treatment of female infertility (initiated under specialist supervision)
    - *by subcutaneous injection*
      - Adult (female): 250 micrograms once daily, dose to be administered in the morning, starting on day 5 or 6 of ovarian stimulation with gonadotrophins (or each evening starting on day 5 of ovarian stimulation), continue throughout administration of gonadotrophin including day of ovulation induction (or evening before ovulation induction), dose to be injected into the lower abdominal wall.

- **SIDE-EFFECTS**
  - Common or very common
    - Headache, injection site reactions, nausea
  - Rare
    - Hypersensitivity reactions

- **PREGNANCY**
  - Avoid in confirmed pregnancy.

- **BREAST FEEDING**
  - Avoid.

- **HEPATIC IMPAIRMENT**
  - Avoid in moderate or severe liver impairment.

- **RENAL IMPAIRMENT**
  - Avoid in moderate or severe renal impairment.

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Ganirelix

- **INDICATIONS AND DOSE**
  - Adjunct in the treatment of female infertility (initiated under specialist supervision)
    - *by subcutaneous injection*
      - Adult: 250 micrograms once daily, dose to be administered in the morning, starting on day 5 or 6 of ovarian stimulation with gonadotrophins, continue throughout administration of gonadotrophins including day of ovulation induction (in administering in afternoon, give last dose in afternoon before ovulation induction), dose to be injected preferably into the upper leg (rotate injection sites to prevent lipoatrophy).

- **SIDE-EFFECTS**
  - Very rare
    - Facial oedema, hypersensitivity reactions, rash
  - Frequency not known
    - Dyspnoea, headache, injection site reactions, malaise, nausea

- **PREGNANCY**
  - Avoid in confirmed pregnancy—toxicity in animal studies.

- **BREAST FEEDING**
  - Avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Avoid in moderate or severe hepatic impairment.

- **RENAL IMPAIRMENT**
  - Avoid in moderate to severe renal impairment.

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**BNF 73**

Gonadotrophin responsive conditions 673

Endocrine system

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**Quinagolide 50 microgram tablets and Quinagolide 25 microgram tablets | 6 tablet pack £8.25–£10.83**

- **Norprolac**: (Ferring Pharmaceuticals Ltd)
  - 25 microgram Norprolac 25 microgram tablets | 3 tablet pack no price available
  - 50 microgram Norprolac 50 microgram tablets | 3 tablet pack no price available

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**Cetrorelix (as Cetrorelix acetate)** 250 microgram Cetrorelix 250 microgram powder and solvent for solution for injection vials | 1 vial pack £22.61

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**Ganirelix (as Ganirelix acetate)** 250 microgram powders and solvent for solution for injection vials | 1 vial pack £37.41

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**Pituitary and hypothalamic hormones and analogues** > Anti-gonadotrophin releasing hormones

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**Anti-gonadotrophin releasing hormones**

- **Gonadotrophins**
  - **Drugs affecting gonadotrophins**
  - **Gonadorelin analogues**
  - **Breast pain (mastalgia)**

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**Gonadotrophin responsive conditions**

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**BNF 73**

Gonadotrophin responsive conditions 673

Endocrine system
**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > GONADOTROPIN-RELEASING HORMONES**

**Buserelin**

**DRUG ACTION** Administration of gonadotropin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotropin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

**Endometriosis**

- **BY INTRanasal ADMINISTRATION**
  - Adult: 300 micrograms 3 times a day maximum duration of treatment 6 months (do not repeat), to be started on days 1 or 2 of menstruation; administer one 150 microgram spray into each nostril

**Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under expert supervision)**

- **BY SUBcutaneous INJECTION**
  - Adult: 200–500 micrograms once daily, increased if necessary up to 500 micrograms twice daily, starting in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually 1–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

- **BY INTRanasal ADMINISTRATION**
  - Adult: 150–300 micrograms 4 times a day, (150 micrograms equivalent to one spray), to be administered during waking hours. Start in early follicular phase (day 1) or, after exclusion of pregnancy, in the midluteal phase (day 21) and continued until down-regulation achieved (usually about 2–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

**Advanced prostate cancer**

- **INITIALLY BY SUBcutaneous INJECTION**
  - Adult: 500 micrograms every 8 hours for 7 days, then (by intranasal administration) 200 micrograms 6 times a day, (a single 100 microgram spray to be administered into each nostril)

**CONTRA-INDICATIONS**

- When used for endometriosis Hormone dependent tumours - undiagnosed vaginal bleeding - use longer than 6 months (do not repeat)
- When used for pituitary desensitisation Hormone dependent tumours - undiagnosed vaginal bleeding

**CAUTIONS** Depression - diabetes - hypertension - patients with metabolic bone disease (decrease in bone mineral density can occur) - polycystic ovarian disease

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**


**SPECIFIC SIDE-EFFECTS**

- With intranasal use Altered sense of taste and smell - nasal irritation - nose bleeds

**SIDE-EFFECTS, FURTHER INFORMATION**

- Tumour flare (when used for advanced prostate cancer) During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain.

**CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

**PREGNANCY** Avoid.

**BREAST FEEDING** Avoid.

**DIRECTIONS FOR ADMINISTRATION**

- With intranasal use Avoid use of nasal decongestants before and for at least 30 minutes after treatment.
- With subcutaneous use Rotate injection site to prevent atrophy and nodule formation.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer buserelin nasal spray.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Orgalutran** (Merck Sharp & Dohme Ltd)
  - Ganirelix 500 microgram per 1 ml Orgalutran 250 microgram/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £21.48

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**


**SPECIFIC SIDE-EFFECTS**

- With intranasal use Altered sense of taste and smell - nasal irritation - nose bleeds

**SIDE-EFFECTS, FURTHER INFORMATION**

- Tumour flare (when used for advanced prostate cancer) During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain.

**CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

**PREGNANCY** Avoid.

**BREAST FEEDING** Avoid.

**DIRECTIONS FOR ADMINISTRATION**

- With intranasal use Avoid use of nasal decongestants before and for at least 30 minutes after treatment.
- With subcutaneous use Rotate injection site to prevent atrophy and nodule formation.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer buserelin nasal spray.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Suprecur (Sanofi)**
  - Buserelin (as Buserelin acetate) 1 mg per 1 ml Suprecur 5.5mg/5.5ml solution for injection vials | 2 vial | £33.02
- **Suprecurfact (Sanofi)**
  - Buserelin (as Buserelin acetate) 1 mg per 1 ml Suprecurfact 5.5mg/5.5ml solution for injection vials | 2 vial | £34.37

**Spray**

- **Suprecur (Sanofi)**
  - Buserelin (as Buserelin acetate) 150 microgram per 1 dose Suprecur 150micrograms/dose nasal spray | 168 dose | £105.16
- **Suprecurfact (Sanofi)**
  - Buserelin (as Buserelin acetate) 100 microgram per 1 dose Suprecurfact 100micrograms/dose nasal spray | 336 dose | £122.24
Goserelin

**DRUG ACTION** Administration of goserelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle-stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

**ZOLADEX LA**
- Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer
  - BY SUBCUTANEOUS INJECTION
    - Adult: 10.8 mg every 12 weeks, to be administered into the anterior abdominal wall

**ZOLADEX**
- Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer | Advanced breast cancer | Oestrogen-receptor-positive early breast cancer
  - BY SUBCUTANEOUS INJECTION
    - Adult: 3.6 mg every 28 days, to be administered into the anterior abdominal wall

**Endometriosis**
  - BY SUBCUTANEOUS INJECTION
    - Adult: 3.6 mg every 28 days maximum duration of treatment 6 months (do not repeat), to be administered into the anterior abdominal wall

**Endometrial thinning before intra-uterine surgery**
  - BY SUBCUTANEOUS INJECTION
    - Adult: 3.6 mg, dose may be repeated after 28 days if uterus is large or to allow flexible surgical timing, to be administered into the anterior abdominal wall

**Before surgery in women who have anaemia due to uterine fibroids**
  - BY SUBCUTANEOUS INJECTION
    - Adult: 3.6 mg every 28 days maximum duration of treatment 3 months, to be given with supplementary iron, to be administered into the anterior abdominal wall

**Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (after exclusion of pregnancy) (under expert supervision)**
  - BY SUBCUTANEOUS INJECTION
    - Adult: 3.6 mg, dose given to achieve pituitary down-regulation (usually 1–3 weeks) then gonadotrophin is administered (stopping gonadotrophin on administration of chorionic gonadotrophin at appropriate stage of follicular development), to be administered into the anterior abdominal wall

**CONTRA-INDICATIONS** Undiagnosed vaginal bleeding · use longer than 6 months in endometriosis (do not repeat)

**CAUTIONS** Depression · diabetes · hypertension · patients with metabolic bone disease (decrease in bone mineral density can occur) · polycystic ovarian disease · risk of spinal cord compression in men · risk of ureteric obstruction in men

**SIDE-EFFECTS**
- Rare Hypercalcaemia (in women)
- Frequency not known Anaphylaxis · arthralgia · asthma · breast tenderness · changes in blood pressure · changes in breast size · changes in scalp and body hair · decrease in trabecular bone density · depression · dizziness · dyspareunia (when used for gynaecological conditions) · gastro-intestinal disturbances · gynaecomastia · headache · heart failure (when used for prostate or breast cancer) · hot flushes · hypersensitivity reactions · increased sweating · local reactions at injection site · loss of libido · menopausal-like symptoms · migraine · mood changes · musculoskeletal pain (when used for gynaecological conditions) · musculoskeletal weakness (when used for gynaecological conditions) · myalgia · myocardial infarction (when used for prostate or breast cancer) · oedema of the face and extremities (when used for gynaecological conditions) · ovarian cysts (may require withdrawal) · palpitation (when used for gynaecological conditions) · paraesthesia · paraesthesia · pruritus · rash · sexual dysfunction · sleep disorders · urticaria · vaginal bleeding · vaginal dryness · visual disturbances · weight change · withdrawal bleeding

**SIDE-EFFECTS, FURTHER INFORMATION**
- Tumour flare (when used for advanced prostate cancer) During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain.
- CONCEPTION AND CONTRACEPTION Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.
- PREGNANCY Avoid.
- BREAST FEEDING Avoid.
- MONITORING REQUIREMENTS Men at risk of tumour ‘flare’ should be monitored closely during the first month of therapy for prostate cancer.
- DIRECTIONS FOR ADMINISTRATION Rotate injection site to prevent atrophy and nodule formation.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Implant**
- Zoladex (AstraZeneca UK Ltd)
- Goserelin (as Goserelin acetate) 3.6 mg Zoladex 3.6mg implant
  - SafeSystem pre-filled syringes | 1 pre-filled disposable iron injection £65.00 DT price = £65.00
- Zoladex LA (AstraZeneca UK Ltd)
- Goserelin (as Goserelin acetate) 10.8 mg Zoladex LA 10.8mg implant
  - SafeSystem pre-filled syringes | 1 pre-filled disposable injection £235.00 DT price = £235.00
Leuprolrelin acetate

**DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

**PROSTAP 3 DCS**
Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 11.25 mg every 3 months

Endometriosis

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 11.25 mg for 1 dose, dose to be given as a single dose in first 5 days of menstrual cycle, then 11.25 mg every 3 months for maximum 6 months (course not to be repeated)

**PROSTAP SR DCS**
Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 3.75 mg every month

Endometriosis

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 3.75 mg for 1 dose, dose to be given as a single dose in first 5 days of menstrual cycle, then 3.75 mg every month for maximum 6 months (course not to be repeated)

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Tumour flare** (when used for advanced prostate cancer) During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain.

**CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

**PREGNANCY** Avoid—teratogenic in animal studies.

**BREAST FEEDING** Avoid.

**MONITORING REQUIREMENTS**

- Monitor liver function.
- Men at risk of tumour ‘flare’ should be monitored closely during the first month of therapy.

**DIRECTIONS FOR ADMINISTRATION** Rotate injection site to prevent atrophy and nodule formation.

**MEDIcINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**

- **Prostap 3 DCS** (Takeda UK Ltd)
  - Leuprolrelin acetate 11.25 mg Prostap 3 DCS 11.25mg powder and solvent for suspension for injection pre-filled disposable injection \( \text{P} \& \text{S} \) £225.72 DT price = £225.72

- **Prostap SR DCS** (Takeda UK Ltd)
  - Leuprolrelin acetate 3.75 mg Prostap SR DCS 3.75mg powder and solvent for suspension for injection pre-filled disposable injection \( \text{P} \& \text{S} \) £75.24 DT price = £75.24

Nafarelin

**DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

**Endometriosis**

- **BY INTRANASAL ADMINISTRATION**
  - Adult (female): 200 micrograms twice daily for maximum 6 months (do not repeat), one spray in one nostril in the morning, and one spray in the other nostril in the evening (starting on days 2–4 of menstruation).
Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under expert supervision)

- **BY INTRANASAL ADMINISTRATION**
  - Adult: 400 micrograms twice daily, one spray in each nostril, to be started in early follicular phase (day 2) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down regulation achieved (usually within 4 weeks) then maintained (usually for 8–12 days) during gonadotrophin administration (stopping gonadotrophin and nafarelin on administration of chorionic gonadotrophin at follicular maturity), discontinue if down-regulation not achieved within 12 weeks

- **CONTRA-INDICATIONS** Undiagnosed vaginal bleeding - use longer than 6 months in the treatment of endometriosis (do not repeat)
- **CAUTIONS** Patients with metabolic bone disease (decrease in bone mineral density can occur)
- **SIDE-EFFECTS** Acne · anaphylaxis · asthma · changes in breast size · changes in scalp and body hair · decrease in trabecular bone density · depression · dyspareunia · headache · hot flushes · hypersensitivity reactions · hypertension · increased sweating · irritation of the nasal mucosa · loss of libido · menopausal-like symptoms · migraine · mood changes · musculoskeletal pain · musculoskeletal weakness · oedema of the face and extremities · ovariian cysts (may require withdrawal) · palpitation · paraesthesia · pruritus · rash · urticaria · vaginal dryness · visual disturbances · weight changes
- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Menopausal-like symptoms: These effects can be reduced by hormone replacement (e.g. with an oestrogen and a progestogen or with tibolone).
- **CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first dose should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.
- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.
- **DIRECTIONS FOR ADMINISTRATION** Avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer nafarelin nasal spray.

**MEDICINAL FORMS**

There can be variation in thelicensing of different medicines containing the same drug.

Spray

- CAUTIONARY AND ADVISORY LABELS 10
  - Synarel (Pfizer Ltd)
    - Nafarelin (as Nafarelin acetate) 200 microgram per 1 dose Synarel 200micrograms/dose nasal spray | 60 dose Pod | £52.43

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**Triptorelin**

- **DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

- **INDICATIONS AND DOSE**
  - **DECAPEPTYL® SR 11.25MG**
    - Locally advanced non-metastatic prostate cancer as an alternative to surgical castration | Metastatic prostate cancer | Adjuvant treatment to radiotherapy in high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression
    - BY INTRAMUSCULAR INJECTION
    - Adult: 11.25 mg every 3 months
  - **DECAPEPTYL® SR 22.5MG**
    - Locally advanced non-metastatic prostate cancer as an alternative to surgical castration | Metastatic prostate cancer | Adjuvant treatment to radiotherapy in high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression
    - BY INTRAMUSCULAR INJECTION
    - Adult: 22.5 mg every 6 months
  - **DECAPEPTYL® SR 3MG**
    - Locally advanced non-metastatic prostate cancer as an alternative to surgical castration | Metastatic prostate cancer | Adjuvant treatment to radiotherapy in high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression
    - BY INTRAMUSCULAR INJECTION
    - Adult: 3 mg every 4 weeks

**Endometriosis**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 3 mg every 4 weeks maximum duration of 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**Reduction in size of uterine fibroids**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 3 mg every 4 weeks for at least 3 months, maximum duration of treatment 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**GONAPEPTYL DEPOT®**

**Advanced prostate cancer**

- **BY SUBCUTANEOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 3.75 mg every 4 weeks

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Endocrine system
Endometriosis | Reduction in size of uterine fibroids
▶ BY SUBCUTANEOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION
▶ Adult: 3.75 mg every 4 weeks maximum duration of 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**SALVACYL®**

Male hypersexuality with severe sexual deviation
▶ BY INTRAMUSCULAR INJECTION
▶ Adult: 11.25 mg every 12 weeks

**CONTRA-INDICATIONS** In endometriosis do not use for longer than 6 months (do not repeat) - undiagnosed vaginal bleeding

**SALVACYL®** Severe osteoporosis

**CAUTIONS**

**GENERAL CAUTIONS**
Patients with metabolic bone disease (decrease in bone mineral density can occur)

**SPECIFIC CAUTIONS**
▶ When used for prostate cancer Risk factors for osteoporosis - risk of spinal cord compression in men - risk of ureteric obstruction in men

**SALVACYL®** Increased risk of sensitivity to restored testosterone if treatment interrupted - consider administration of an antiandrogen before stopping treatment - transient increase in serum testosterone occurs on initiation - consider administration of an antiandrogen

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
Anaphylaxis - arthralgia - asthenia - asthma - breast tenderness (males and females) - changes in blood pressure - changes in breast size - changes in scalp and body hair - depression - gastrointestinal disturbances - headache - hot flushes - hypersensitivity reactions - increased sweating - local reactions at injection site - mood changes - ovarian cysts (may require withdrawal) - paraesthesia - pruritus - rash - urticaria - visual disturbances - weight changes

**SPECIFIC SIDE-EFFECTS**
▶ When used for endometriosis Decrease in trabecular bone density - dyspareunia - loss of libido - menopausal-like symptoms - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation - vaginal dryness - withdrawal bleeding (may occur in the first month of treatment)

▶ When used for male hypersexuality with severe sexual deviation Decrease in trabecular bone density - dyspareunia - loss of libido - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation

▶ When used for prostate cancer Dizziness - dry mouth - hair loss - increased dysuria - myalgia - peripheral oedema - sexual dysfunction - sleep disorders

▶ When used for reduction in size of uterine fibroids Bleeding associated with fibroid degeneration - decrease in trabecular bone density - dyspareunia - loss of libido - menopausal-like symptoms - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation - vaginal dryness - withdrawal bleeding (may occur in the first month of treatment)

**SIDE-EFFECTS, FURTHER INFORMATION**
▶ Tumour flare (when used for advanced prostate cancer) During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain.

▶ CONCEPTION AND CONTRACEPTION Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

▶ PREGNANCY Avoid.

▶ BREAST FEEDING Avoid.

▶ MONITORING REQUIREMENTS
When used for Prostate cancer Men at risk of tumour ‘flare’ should be monitored closely during the first month of therapy.

▶ DIRECTIONS FOR ADMINISTRATION Rotate injection site to prevent atrophy and nodule formation.

▶ PRESCRIBING AND DISPENSING INFORMATION

**DECAPEPTYL® SR 11.25MG** Each vial includes an overage to allow accurate administration of an 11.25 mg dose.

**DECAPEPTYL® SR 22.5MG** Each vial includes an overage to allow accurate administration of a 22.5 mg dose.

**DECAPEPTYL® SR 3MG** Each vial includes an overage to allow accurate administration of 3 mg dose.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**
▶ **Decapeptyl SR** (Ipsen Ltd) Triptorelin (as Triptorelin acetate) 3 mg Decapeptyl SR 3mg powder and solvent for suspension for injection vials | 1 vial (Ipsen) £69.00 DT price = £63.00

Triptorelin (as Triptorelin acetate) 11.25 mg Decapeptyl SR 11.25mg powder and solvent for suspension for injection vials | 1 vial (Ipsen) £207.00 DT price = £207.00

Triptorelin (as Triptorelin acetate) 22.5 mg Decapeptyl SR 22.5mg powder and solvent for suspension for injection vials | 1 vial (Ipsen) £414.00 DT price = £414.00

▶ **Gonapeptyl Depot** (Ferring Pharmaceuticals Ltd) Triptorelin (as Triptorelin acetate) 3.75 mg Gonapeptyl Depot 3.75mg powder and solvent for suspension for injection pre-filled disposable devices | 1 pre-filled disposable injection (Ferring) £81.69

▶ **Salvacyl** (Ipsen Ltd) Triptorelin (as Triptorelin acetate) injection vials | 1 vial (Ipsen) £248.00

6.1 Hereditary angioedema

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES**
▶ ANTI-GONADOTROPIN-RELEASING HORMONES

**Danazol**

▶ DRUG ACTION Danazol inhibits pituitary gonadotrophins; it combines androgenic activity with antioestrogenic and antiprogestogenic activity.

▶ INDICATIONS AND DOSE

**Endometriosis**
▶ **BY MOUTH**
▶ Adult: 200–800 mg daily in up to 4 divided doses usually for 3–6 months, dose to be adjusted to achieve amenorrhoea, in women of child-bearing potential, treatment should start during menstruation, preferably on day 1

**Severe pain and tenderness in benign fibrocystic breast disease not responding to other treatment**
▶ **BY MOUTH**
▶ Adult: 300 mg daily in divided doses usually for 3–6 months, in women of child-bearing potential, treatment should start during menstruation, preferably on day 1
**Hypothalamic and anterior pituitary hormone related disorders**

### Hypothalamic and anterior pituitary hormones

#### Anterior pituitary hormones

### Corticotrophins

Tetracosactide p. 680 (tetracosactrin), an analogue of corticotropin (ACTH), is used to test adrenocortical function; failure of the plasma cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency.

Both corticotropin and tetracosactide were formerly used as alternatives to corticosteroids in conditions such as Crohn’s disease or rheumatoid arthritis; their value was limited by the variable and unpredictable therapeutic response and by the waning of their effect with time.

### Gonadotrophins

Follicle-stimulating hormone (FSH) and luteinising hormone (LH) together, follicle-stimulating hormone alone (as in follitropin), or chorionic gonadotrophin p. 681, are used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene citrate p. 702, or in superovulation treatment for assisted conception (such as in vitro fertilisation).

The gonadotrophins are also occasionally used in the treatment of hypogonadotrophic hypogonadism and associated oligosperma. There is no justification for their use in primary gonadal failure.

Chorionic gonadotrophin has also been used in delayed puberty in the male to stimulate endogenous testosterone production, but has little advantage over testosterone.

### Growth hormone

Growth hormone is used to treat deficiency of the hormone in children and in adults. In children it is used in Prader-Willi syndrome, Turner syndrome, chronic renal insufficiency, short children considered small for gestational age at birth, and short stature homeobox-containing gene (SHOX) deficiency.

Growth hormone of human origin (HGH; somatotrophin) has been replaced by a growth hormone of human sequence, somatropin p. 685, produced using recombinant DNA technology.

Mecasermin, a human insulin-like growth factor-1 (rIGF-I), is licensed to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency.

### Hypothalamic hormones

Gonadorelin p. 681 when injected intravenously in normal subjects leads to a rapid rise in plasma concentrations of both luteinising hormone (LH) and follicle-stimulating hormone (FSH). It has not proved to be very helpful, however, in distinguishing hypothalamic from pituitary lesions. Gonadorelin analogues are indicated in endometriosis and infertility and in breast and prostate cancer.
7.1 Adrenocortical function testing

PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > CORTICOTROPHINS

Tetracosactide (Tetracosactrin)

- **INDICATIONS AND DOSE**
  
  **Diagnosis of adrenocortical insufficiency (diagnostic 30-minute test)**
  - By intravenous injection, or by intramuscular injection
  - Adult: 250 micrograms for 1 dose
  
  **Diagnosis of adrenocortical insufficiency (diagnostic 5-hour test)**
  - By intramuscular injection using depot injection
  - Adult: 1 mg for 1 dose
  
  **Alternative to corticosteroids in conditions such as Crohn’s disease or rheumatoid arthritis (formerly used but value was limited by the variable and unpredictable therapeutic response and by the waning of effect with time)**
  - By intramuscular injection using depot injection
  - Adult: Initially 1 mg daily, alternatively initially 1 mg every 12 hours, (in acute cases), then reduced to 1 mg every 2–3 days, followed by 1 mg once weekly, alternatively 500 micrograms every 2–3 days

- **CONTRA-INDICATIONS**
  Acute psychosis • adrenogenital syndrome • allergic disorders • asthma • avoid injections containing benzyl alcohol in neonates • Cushing’s syndrome • infectious diseases • peptic ulcer • primary adrenocortical insufficiency • refractory heart failure

- **CAUTIONS**
  Active infectious diseases (should not be used unless adequate disease-specific therapy is being given) • active systemic diseases (should not be used unless adequate disease-specific therapy is being given) • diabetes mellitus • diverticulitis • history of asthma • history of atopic allergy • history of eczema • history of hayfever • history of hypersensitivity • hypertension • latent amoebiasis (may become activated) • latent tuberculosis (may become activated) • myasthenia gravis • ocular herpes simplex • osteoporosis • predisposition to thromboembolic • psychological disturbances may be triggered • recent intestinal anastomosis • reduced immune response (should not be used unless adequate disease-specific therapy is being given) • ulcerative colitis

**CAUTIONS, FURTHER INFORMATION**

- Risk of anaphylaxis. Should only be administered under medical supervision. Consult product literature.
- Hypertension. Patients already receiving medication for moderate to severe hypertension must have their dosage adjusted if treatment started.
- Diabetes mellitus. Patients already receiving medication for diabetes mellitus must have their dosage adjusted if treatment started.

- **SIDE-EFFECTS** → Appendix 1 (corticosteroids).
- **INTERACTIONS**

hypersensitivity reactions (tend to be more severe in patients susceptible to allergies, especially asthma) • hypertension • hypokalaemia • hypokalaemic alkalosis • impaired healing • increased appetite • increased intraocular pressure • infection susceptibility increased • insomnia • irregular menstruation • leukocytosis • malaise • manifestations of latent diabetes mellitus • mood swings • muscle atrophy • muscular weakness • myopathy • nausea • necrotising vasculitis • negative nitrogen balance • osteoporosis • pancreatitis • pathological fracture of long bones • peptic ulcer • personality changes • petechiae • posterior subcapsular cataracts • pruritus • psychotic manifestations • Quincke’s oedema • secondary adrenocortical unresponsiveness • secondary pituitary unresponsiveness • severe depression • skin atrophy • skin hyperpigmentation • skin reactions at injection site • sodium retention • spinal compression fractures • tendon rupture • thromboembolism • ulcerative oesophagitis • urticaria • vertigo • vomiting • weight increase

- **ALLERGY AND CROSS-SENSITIVITY**
  Contra-indicated in patients with history of hypersensitivity to tetracosactide/corticotrophins or excipients.

- **PREGNANCY**
  Avoid (but may be used diagnostically if essential).

- **BREAST FEEDING**
  Avoid (but may be used diagnostically if essential).

- **HEPATIC IMPAIRMENT**
  An enhanced effect of tetracosactide therapy may occur in patients with cirrhosis of the liver. Use with caution in hepatic impairment. Monitor hepatic function closely during treatment.

- **RENAL IMPAIRMENT**
  Use with caution in patients with renal impairment.

- **EFFECT ON LABORATORY TESTS**
  May suppress skin test reactions.

  Post administration total plasma cortisol levels during 30-minute test for diagnosis of adrenocortical insufficiency might be misleading due to altered cortisol binding globulin levels in some special clinical situations including, patients on oral contraceptives, post-operative patients, critical illness, severe liver disease and nephrotic syndrome.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  - Synacthen (Mallinckrodt Specialty Pharmaceuticals Ireland Ltd)
    - Tetracosactide acetate 250 microgram per 1 ml Synacthen
      - 250micrograms/1ml solution for injection ampoules | 1 ampoule [Pud] £38.00

  **Suspension for injection**

  **EXCIPIENTS:** May contain Benzyl alcohol

  - Synacthen Depot (Mallinckrodt Specialty Pharmaceuticals Ireland Ltd)
    - Tetracosactide acetate 1 mg per 1 ml Synacthen Depot 1mg/1ml suspension for injection ampoules | 1 ampoule [Pud] £346.28
7.2 Assessment of pituitary function

PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES ➔ GONADOTROPIN-RELEASING HORMONES

**Gonadorelin**
(Gonadotrophin-releasing hormone; GnRH; LH-RH)

- **INDICATIONS AND DOSE**
  - Assessment of pituitary function
    - By subcutaneous injection, or by intravenous injection
  - Adult: 100 micrograms for 1 dose

- **CAUTIONS**
  - Pituitary adenoma
  - Side-effects: Abdominal pain, headache, hypersensitivity reaction on repeated administration of large doses, increased menstrual bleeding, irritation at injection site, nausea

- **PREGNANCY**
  - Avoid.

- **BREAST FEEDING**
  - Avoid.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Powder and solvent for solution for injection
    - Excipients: May contain Benzyl alcohol
      - Gonadorelin (Non-proprietary)
      - Gonadorelin (as Gonadorelin hydrochloride)
        - 100 microgram Gonadorelin 100 microgram powder and solvent for solution for injection vials | 1 vial £75.00 (Hospital only)

7.3 Gonadotrophin replacement therapy

GONADOTROPHINS

**Choriogonadotropin alfa**
(Human chorionic gonadotropin)

- **INDICATIONS AND DOSE**
  - Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene
  - Superoxivan treatment for assisted conception (such as in vitro fertilisation)
  - By subcutaneous injection
  - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Active thromboembolic disorders
  - Ovarian enlargement or cyst (unless caused by polycystic ovarian disease)
  - Ovarian malignancy
  - Pituitary malignancy
  - Uterine malignancy

- **CAUTIONS**
  - Acute porphyrias p. 930
  - Side-effects: Abdominal pain, breast pain, depression, diarrhoea, ectopic pregnancy, headache, injection-site reactions, irritability, nausea, ovarian hyperstimulation syndrome, ovarian torsion, tiredness, vomiting

**Chorionic gonadotrophin**
(Human chorionic gonadotrophin; HCG)

- **DRUG ACTION**
  - A preparation of a glycoprotein fraction secreted by the placenta and obtained from the urine of pregnant women having the action of the pituitary luteinising hormone.

- **INDICATIONS AND DOSE**
  - Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene
  - Superoxivan treatment for assisted conception (such as in vitro fertilisation)
  - By intramuscular injection, or by subcutaneous injection
  - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Androgen-dependent tumours

- **CAUTIONS**
  - Asthma, cardiac impairment, epilepsy, migraine, prepubertal boys (risk of premature epiphyseal closure or precocious puberty)
  - Gynaecomastia, headache, local reactions, may aggravate ovarian hyperstimulation, mood changes, multiple pregnancy, oedema (particularly in males—reduce dose), tiredness

- **RENAL IMPAIRMENT**
  - Use with caution.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Powder and solvent for solution for injection
    - Choragon (Ferring Pharmaceuticals Ltd)
      - Chorionic gonadotrophin human 5000 unit Choragon 5,000 unit powder and solvent for solution for injection ampoules | 3 ampoules £9.77 (CD4-2)
    - Pregnyl (Merck Sharp & Dohme Ltd)
      - Chorionic gonadotrophin human 5000 unit Pregnyl 5,000 unit powder and solvent for solution for injection ampoules | 1 ampoule £15.00 (CD4-2)

- **Corifollitropin alfa**

- **INDICATIONS AND DOSE**
  - Controlled ovarian stimulation in combination with a gonadotrophin-releasing hormone antagonist
  - By subcutaneous injection
  - Adult (body-weight up to 60 kg): 100 micrograms
  - Adult (body-weight 60 kg and above): 150 micrograms

- **CONTRA-INDICATIONS**
  - History of ovarian hyperstimulation syndrome, ovarian enlargement or cyst, polycystic ovarian syndrome, tumours of breast, tumours of hypothalamus, tumours of ovaries, tumours of pituitary, tumours of uterus, vaginal bleeding of unknown cause

- **CAUTIONS**
  - Acute porphyrias p. 930—risk factors for thromboembolism, risk of ovarian hyperstimulation syndrome
## Folitropin alfa
*(Recombinant human follicle stimulating hormone)*

### INDICATIONS AND DOSE

Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)

- **BY SUBCUTANEOUS INJECTION**
  - Adult (female): Adjusted according to response.

### CONTRA-INDICATIONS

Ovarian cysts (not caused by polycystic ovarian syndrome) | ovarian enlargement (not caused by polycystic ovarian syndrome) | tumours of breast | tumours of hypothalamus | tumours of ovaries | tumours of pituitary | tumours of prostate | tumours of testes | tumours of uterus | vaginal bleeding of unknown cause

### CAUTIONS

Acute porphyrias p. 930 | history of tubal disease

### SIDE-EFFECTS

- **Common or very common** Fever | gastro-intestinal disturbances | headache | hyperstimulation | injection site reactions | joint pain | ovarian hyperstimulation | varicocele
  - **Very rare** Exacerbation or aggravation of asthma | thromboembolism
  - **Frequency not known** Acne | gynaecomastia | increased risk of miscarriage | increased risk of multiple pregnancy | weight gain

### PREGNANCY

Avoid.

### BREAST FEEDING

Avoid.

### PRESCRIBING AND DISPENSING INFORMATION

Folitropin alfa is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see *Biological medicines* and *Biosimilar medicines*, under Guidance on prescribing p. 1.

### PATIENT AND CARER ADVICE

Patient advice required around conception and contraception

Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

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### MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection

- **Bemfola** *(Finox Biotech UK)*
  - Folitropin alfa 600 unit per 1 ml | Bemfola 225units/0.375ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £70.50
  - Bemfola 300units/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £94.00
  - Bemfola 150units/0.25ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £23.50

- **Gonal-f** *(Merck Sharp & Dohme Ltd)*
  - Folitropin alfa 600 unit per 1 ml | Gonal-f 900units/1.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £282.00
  - Gonal-f 300units/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £94.00
  - Gonal-f 450units/0.75ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £141.00

- **Ovaleap** *(Teva UK Ltd)*
  - Folitropin alfa 600 unit per 1 ml | Ovaleap 450units/0.75ml solution for injection cartridges | 1 cartridge | £112.80
  - Ovaleap 900units/1.5ml solution for injection cartridges | 1 cartridge | £225.60
  - Ovaleap 300units/0.5ml solution for injection cartridges | 1 cartridge | £75.20

#### Powder and solvent for solution for injection

- **Gonal-f** *(Merck Serono Ltd)*
  - Folitropin alfa 75 unit | Gonal-f 75unit powder and solvent for solution for injection vials | 1 vial | £126.10
  - Folitropin alfa 450 unit | Gonal-f 450unit powder and solvent for solution for injection vials | 1 vial | £294.22

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### Folitropin alfa with lutropin alfa

The properties listed below are those particular to the combination only. For the properties of the components please consider, folitropin alfa above, lutropin alfa p. 683.

#### INDICATIONS AND DOSE

Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)

- **BY SUBCUTANEOUS INJECTION**
  - Adult (female): Adjusted according to response.

#### MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Powder and solvent for solution for injection

**ELECTROLYTES:** May contain Sodium

- **Pergovers** *(Merck Serono Ltd)*
  - Lutropin alfa 75 unit, Folitropin alfa 150 unit | Pergovers 150unit/75unit powder and solvent for solution for injection vials | 1 vial | £60.29 | 10 vial | £602.90
Follitropin beta
(Recombinant human follicle stimulating hormone)

- **INDICATIONS AND DOSE**
  - Infertility in women with proven hypopituitarism or who have not responded to clomifene | Supereovulation treatment for assisted conception (such as in vitro fertilisation)
    - By intramuscular injection, or by subcutaneous injection
  - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Ovarian cysts (not caused by polycystic ovarian syndrome) - ovarian enlargement (not caused by polycystic ovarian syndrome) - tumours of breast - tumours of hypothalamus - tumours of ovaries - tumours of pituitary - tumours of prostate - tumours of testes - tumours of uterus - vaginal bleeding of unknown cause

- **CAUTIONS**
  - Acute porphyrias p. 930 - history of tubal disease

- **SIDE-EFFECTS**
  - Common or very common: Fever - gastro-intestinal disturbances - headache - hypersensitivity reactions - injection site reactions - joint pain - ovarian hyperstimulation
  - Very rare: Thromboembolism
  - Frequency not known: Acne - gynaecomastia - increased risk of miscarriage - increased risk of multiple pregnancy - weight gain

- **PREGNANCY**
  - Avoid.

- **BREAST FEEDING**
  - Avoid.

- **DIRECTIONS FOR ADMINISTRATION**
  - Cartridges and vials are used for subcutaneous administration; vials are used for intramuscular injection.

- **PATIENT AND CARER ADVICE**
  - Patient advice required around conception and contraception
  - Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - EXCIPIENTS: May contain Neomycin, streptomycin
    - Puregon (Merck Sharp & Dohme Ltd)
      - Follitropin beta 100 unit per 1 ml
        - Puregon 50units/0.5ml solution for injection vials | 1 vial £18.03
      - Follitropin beta 200 unit per 1 ml
        - Puregon 100units/0.5ml solution for injection vials | 1 vial £36.06
      - Follitropin beta 833 unit per 1 ml
        - Puregon 900units/1.08ml solution for injection cartridges | 1 cartridge £292.23
        - Puregon 600units/0.72ml solution for injection cartridges | 1 cartridge £194.82
        - Puregon 300units/0.36ml solution for injection cartridges | 1 cartridge £97.41

Lutropin alfa
(Recombinant human luteinising hormone)

- **INDICATIONS AND DOSE**
  - Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene | Supereovulation treatment for assisted conception (such as in vitro fertilisation)
    - By subcutaneous injection
    - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Mammary carcinoma - ovarian carcinoma - ovarian enlargement or cyst (unless caused by polycystic ovarian disease) - tumours of hypothalamus - tumours of pituitary - undiagnosed vaginal bleeding - uterine carcinoma

- **CAUTIONS**
  - Acute porphyrias p. 930

- **SIDE-EFFECTS**

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Powder and solvent for solution for injection**
  - Luveris (Merck Serono Ltd)
    - Lutropin alfa 75 unit
      - Luveris 75unit powder and solvent for solution for injection vials | 1 vial £31.38

Menotrophin

- **INDICATIONS AND DOSE**
  - Infertility in women with proven hypopituitarism or who have not responded to clomifene | Supereovulation treatment for assisted conception (such as in vitro fertilisation)
    - By subcutaneous injection, or by deep intramuscular injection
    - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Ovarian cysts (not caused by polycystic ovarian syndrome) - ovarian enlargement (not caused by polycystic ovarian syndrome) - tumours of breast - tumours of hypothalamus - tumours of ovaries - tumours of pituitary - tumours of prostate - tumours of testes - tumours of uterus - vaginal bleeding of unknown cause

- **CAUTIONS**
  - Acute porphyrias p. 930 - history of tubal disease

- **SIDE-EFFECTS**
  - Very rare: Thromboembolism
  - Frequency not known: Acne - fever - gastro-intestinal disturbances - gynaecomastia - headache - hypersensitivity reactions - increased risk of multiple pregnancy and miscarriage - injection site reactions - joint pain - ovarian hyperstimulation - weight gain

- **PREGNANCY**
  - Avoid.

- **BREAST FEEDING**
  - Avoid.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Menotrophin is purified extract of human post-menopausal urine containing follicle-stimulating hormone (FSH) and luteinising hormone (LH) in a ratio of 1:1.
684 Hypothalamic and anterior pituitary hormone related disorders

**PATIENT AND CARER ADVICE**

Patient advice required around conception and contraception

Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- **Menotrophin** (Ferring Pharmaceuticals Ltd)
  - Menotrophin 75 unit Menotrophin 75 unit powder and solvent for solution for injection vials | 1 vial (Pom) £16.38 | 10 vial (Pom) £163.80
  - Menotrophin 150 unit Menotrophin 150 unit powder and solvent for solution for injection vials | 5 vial (Pom) £163.80 | 10 vial (Pom) £327.60
- **Menotrophin 600 unit** Menotrophin 600 unit powder and solvent for solution for injection vials | 1 vial (Pom) £131.04
- **Menotrophin 1200 unit** Menotrophin 1200 unit powder and solvent for solution for injection vials | 1 vial (Pom) £262.08
  - **Merional** (BSA Farmaceutici Italia Srl)
    - **Menotrophin 75 unit** Merional 75 unit powder and solvent for solution for injection vials | 10 vial (Pom) £279.00
    - **Menotrophin 150 unit** Merional 150 unit powder and solvent for solution for injection vials | 10 vial (Pom) £558.00

**Urofollitropin**

**INDICATIONS AND DOSE**

Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superoovulation treatment for assisted conception (such as in vitro fertilisation)

- **BY SUBCUTANEOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult (female): Adjusted according to response.

**CONTRA-INDICATIONS**

Ovarian cysts (not caused by polycystic ovarian syndrome) - tumours of breast - tumours of hypothalamus - tumours of ovaries - tumours of pituitary - tumours of prostate - tumours of testes - tumours of uterus - vaginal bleeding of unknown cause

**CAUTIONS**

Acute porphyrias p. 930

**SIDE-EFFECTS**

- Very rare: Thromboembolism
- Frequency not known: Fever - gastro-intestinal disturbances - headache - hypersensitivity reactions - increased risk of miscarriage - increased risk of multiple pregnancy - injection site reactions - joint pain - ovarian hyperstimulation

**PREGNANCY**

Avoid.

**BREAST FEEDING**

Avoid.

**PRESCRIBING AND DISPENSING INFORMATION**

Urofollitropin is purified extract of human post-menopausal urine containing follicle-stimulating hormone (FSH).

**PATIENT AND CARER ADVICE**

Patient advice required around conception and contraception

Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- **Bravelle** (Ferring Pharmaceuticals Ltd)
  - **Follicle stimulating hormone human (as Urofollitropin)**
    - **75 unit** Bravelle 75 unit powder and solvent for solution for injection vials | 10 vial (Pom) £270.00
  - **Fostimon** (BSA Farmaceutici Italia Srl)
    - **Follicle stimulating hormone human (as Urofollitropin)**
      - **75 unit** Fostimon 75 unit powder and solvent for solution for injection vials | 10 vial (Pom) £279.00

**7.4 Growth hormone disorders**

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > GROWTH HORMONE RECEPTOR ANTAGONISTS**

**Pegvisomant**

- **DRUG ACTION** Pegvisomant is a genetically modified analogue of human growth hormone and is a highly selective growth hormone receptor antagonist.

**INDICATIONS AND DOSE**

Treatment of acromegaly in patients with inadequate response to surgery, radiation, or both, and to treatment with somatostatin analogues (initiated by a specialist)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 80 mg for 1 dose, followed by 10 mg daily, then increased in steps of 5 mg daily, adjusted according to response; maximum 30 mg per day

**CAUTIONS**

Diabetes mellitus (adjustment of antidiabetic therapy may be necessary) - liver disease

**SIDE-EFFECTS**

- Uncommon: Bleeding tendency - leucocytosis - leucopenia - thrombocytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**

Injection-site reactions: Rotate injection sites to avoid lipohypertrophy.

**CONCEPTION AND CONTRACEPTION**

Possible increase in female fertility.

**PREGNANCY**

Avoid.

**BREAST FEEDING**

Avoid.

**MONITORING REQUIREMENTS**

Monitor liver enzymes every 4–6 weeks for 6 months or if symptoms of hepatitis develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- **Somavert** (Pfizer Ltd)
  - **Pegvisomant 10 mg** Somavert 10mg powder and solvent for solution for injection vials | 30 vial (Pom) £1,500.00 (Hospital only)
  - **Pegvisomant 15 mg** Somavert 15mg powder and solvent for solution for injection vials | 30 vial (Pom) £2,250.00 (Hospital only)
  - **Pegvisomant 20 mg** Somavert 20mg powder and solvent for solution for injection vials | 1 vial (Pom) £100.00 (Hospital only) | 30 vial (Pom) £3,000.00 (Hospital only)
  - **Pegvisomant 25 mg** Somavert 25mg powder and solvent for solution for injection vials | 30 vial (Pom) £3,750.00 (Hospital only)
  - **Pegvisomant 30 mg** Somavert 30mg powder and solvent for solution for injection vials | 30 vial (Pom) £4,500.00 (Hospital only)
PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > HUMAN GROWTH HORMONES

Somatropin
(Recombinant Human Growth Hormone)

- INDICATIONS AND DOSE
  Gonadal dysgenesis (Turner syndrome)
  > BY SUBCUTANEOUS INJECTION
  > Adult: 1.4 mg/m² daily, alternatively 45–50 micrograms/kg daily

- Deficiency of growth hormone
  > BY SUBCUTANEOUS INJECTION
  > Adult: Initially 150–300 micrograms daily, then increased if necessary up to 1 mg daily, dose to be increased gradually, use minimum effective dose (requirements may decrease with age)

- DOSE EQUIVALENCE AND CONVERSION
  > Dose formerly expressed in units; somatropin 1 mg = 3 units.

- CONTRA-INDICATIONS
  Evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting) - not to be used after renal transplantation - severe obesity in Prader-Willi syndrome - severe respiratory impairment in Prader-Willi syndrome

- CAUTIONS
  Diabetes mellitus (adjustment of antidiabetic therapy may be necessary) - disorders of the epiphysis of the hip (monitor for limping) - history of malignant disease - hypothyroidism - manufacturers recommend periodic thyroid function tests but limited evidence of clinical value - initiation of treatment close to puberty not recommended in child born small for corrected gestational age - papilloedema - relative deficiencies of other pituitary hormones - resolved intracranial hypertension (monitor closely) - Silver-Russell syndrome

- INTERACTIONS
  > Appendix 1 (somatropin).

- SIDE-EFFECTS
  Antibody formation - arthralgia - benign intracranial hypertension - carpal tunnel syndrome - fluid retention (peripheral oedema) - headache - hyperglycaemia - hypoglycaemia - hypothyroidism - insulin resistance - leukaemia in children with growth hormone deficiency - myalgia - nausea - papilloedema - paraesthesia - reactions at injection site - visual problems - vomiting

- SIDE-EFFECTS, FURTHER INFORMATION
  Papilloedema - Fundoscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur - if papilloedema confirmed consider benign intracranial hypertension (rare cases reported).

- PREGNANCY
  Discontinue if pregnancy occurs - no information available.

- BREAST FEEDING
  No information available. Absorption from milk unlikely.

- DIRECTIONS FOR ADMINISTRATION
  Rotate subcutaneous injection sites to prevent lipoatrophy.

- SAIZEN® SOLUTION FOR INJECTION
  For use by subcutaneous injection.

- NUTROPINAQ®
  For use by subcutaneous injection.

- OMNITROPE®
  For use by subcutaneous injection.

- NORDITROPIN® PREPARATIONS
  For use by subcutaneous injection.

- ZOMACTON®
  For use by subcutaneous injection.

- GENOTROPIN® PREPARATIONS
  For use by subcutaneous injection.

- SAIZEN® POWDER AND SOLVENT FOR SOLUTION FOR INJECTION
  For use by subcutaneous injection.

- HUMATROPE®
  Cartridges for use by subcutaneous injection.

- PRESCRIBING AND DISPENSING INFORMATION
  Somatropin is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

- SAIZEN® SOLUTION FOR INJECTION
  For use with cool.click® needle-free autoinjector device or easypod® autoinjector device (non-NHS but available free of charge from clinics).

- NUTROPINAQ®
  For use with NutropinAg® Pen device (non-NHS but available free of charge from clinics).

- OMNITROPE®
  For use with Omnitrope Pen 5® and Omnitrope Pen 10® devices (non-NHS but available free of charge from clinics).

- NORDITROPIN® PREPARATIONS
  Cartridges are for use with appropriate NordiPen® device (non-NHS but available free of charge from clinics).

- ZOMACTON®
  4 mg vial for use with ZomaJet 2® Vision needle-free device (non-NHS but available free of charge from clinics) or with needles and syringes.

- GENOTROPIN® PREPARATIONS
  Cartridges are for use with Genotropin® Pen device (non-NHS but available free of charge from clinics).

- SAIZEN® POWDER AND SOLVENT FOR SOLUTION FOR INJECTION
  For use with one. click® autoinjector device or cool.click® needle-free autoinjector device or easypod® autoinjector device (non-NHS but available free of charge from clinics).

- NATIONAL FUNDING/ACCESS DECISIONS

- NICE technology appraisals (TAs)

  Somatropin for the treatment of growth failure in children
  (May 2010) NICE TA188
  Somatropin is recommended for children with growth failure who:
  - have growth-hormone deficiency
  - have Turner syndrome
  - have Prader-Willi syndrome
  - have chronic renal insufficiency
  - are born small for gestational age with subsequent growth failure at 4 years of age or later
  - have short stature homeobox-containing gene (SHOX) deficiency.
  Treatment should be discontinued if growth velocity increases by less than 50% from baseline in the first year of treatment.
  www.nice.org.uk/TA188

  Somatropin for adults with growth hormone deficiency
  (August 2003) NICE TA64
  Somatropin is recommended in adults only if the following 3 criteria are fulfilled:
  - Severe growth hormone deficiency, established by an appropriate method,
  - Impaired quality of life, measured by means of a specific questionnaire,
  - Already receiving treatment for another pituitary hormone deficiency.
  Somatropin treatment should be discontinued if the quality of life has not improved sufficiently by 9 months.
  Severe growth hormone deficiency developing after linear growth is complete but before the age of 25 years should be treated with growth hormone; treatment should continue until adult peak bone mass has been achieved.
  Treatment for adult-onset growth hormone deficiency should be stopped only when the patient and the patient’s physician consider it appropriate.
  Treatment with somatropin should be initiated and managed by a physician with expertise in growth hormone
Sex hormone responsive conditions

**Sex hormones**

**Oestrogens and HRT**

Oestrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia. 

In terms of oestrogenic activity, natural oestrogens (estradiol p. 690 (oestradiol), estrone (oestrone), and estriol p. 761 (oestriol)) have a more appropriate profile for hormone replacement therapy (HRT) than synthetic oestrogens (ethinylestradiol p. 694 (ethinylestrodiol) and mestranol). Tibolone p. 695 has oestrogenic, progestogenic and weak androgenic activity.

Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. If long-term therapy is required in women with a uterus, a prostegestone should normally be added to reduce the risk of cystic hyperplasia of the endometrium (or of endometriotic foci in women who have had a hysterectomy) and possible transformation to cancer.

Oestrogens are no longer used to suppress lactation because of their association with thromboembolism.

**Hormone replacement therapy**

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability. Oestrogen given systemically in the perimenopausal and postmenopausal period or tibolone given in the postmenopausal period also diminish postmenopausal

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**Disorders**

Maintenance treatment can be prescribed in the community under a shared-care protocol.

www.nice.org.uk/TA64

**Medicinal forms**

- **Genotropin MiniQuick**
- **Genotropin GoQuick**
- **Powder and solvent for solution for injection**
- **Saizen**
- **NutropinAq**
- **Norditropin NordiFlex**
- **Solution for injection containing the same drug.**

There can be variation in the licensing of different medicines within a community under a shared-care protocol.

**Sex hormone responsive conditions**

- **Genotropin (rbe) 1.2 mg** Genotropin MiniQuick 1.2 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £48.68 (D4-2)
- **Genotropin (rbe) 1.4 mg** Genotropin MiniQuick 1.4 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £57.37 (D4-2)
- **Genotropin (rbe) 1.6 mg** Genotropin MiniQuick 1.6 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £121.71 (D4-2)
- **Genotropin (rbe) 1.8 mg** Genotropin MiniQuick 1.8 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £110.09 (D4-2)
- **Genotropin (rbe) 2 mg** Genotropin MiniQuick 2 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £170.39 (D4-2)
- **Genotropin (rbe) 2.5 mg** Genotropin MiniQuick 2.5 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £191.08 (D4-2)
- **Genotropin (rbe) 2.8 mg** Genotropin MiniQuick 2.8 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £216.00 (D4-2)
- **Genotropin (rbe) 3 mg** Genotropin MiniQuick 3 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £24.35 (D4-2)
- **Genotropin (rbe) 3.3 mg** Genotropin MiniQuick 3.3 mg powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £73.03 (D4-2)
- **Humatrope (Eli Lilly and Company Ltd)**
- **Genotropin (rbe) 6 mg** Humatrope 6 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £108.00 (D4-2)
- **Genotropin (rbe) 12 mg** Humatrope 12 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £185.44 (D4-2)
- **Genotropin (rbe) 24 mg** Humatrope 24 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £432.00 (D4-2)
- **Saizen**
- **Genotropin (rbe) 4 mg** Saizen 4 mg powder and solvent for solution for injection vials | 1 vial (Pom) £79.69 (D4-2)
- **Zomacton (Ferring Pharmaceuticals Ltd)**
- **Genotropin (rbe) 10 mg** Zomacton 10 mg powder and solvent for solution for injection vials | 1 vial (Pom) £119.25 (D4-2)

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**Genetropin (Pfizer Ltd)**

- **Genotropin (rbe) 5 mg** Genetropin 5 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £92.15 (D4-2)
- **Genotropin (rbe) 10 mg** Genetropin 10 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £192.08 (D3-2)
- **Genotropin GoQuick (Pfizer Ltd)**
- **Genotropin (rbe) 5.3 mg** Genotropin GoQuick 5.3 mg powder and solvent for solution for injection pre-filled disposable devices | 1 pre-filled disposable injection (Pom) £92.15 (D4-2)
- **Genotropin (rbe) 12 mg** Genotropin GoQuick 12 mg powder and solvent for solution for injection pre-filled disposable devices | 1 pre-filled disposable injection (Pom) £208.65 (D4-2)
- **Genetropin MiniQuick (Pfizer Ltd)**
- **Genotropin (rbe) 400 microgram** Genetropin MiniQuick 400 microgram powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £146.06 (D4-2)
- **Genotropin (rbe) 800 microgram** Genetropin MiniQuick 800 microgram powder and solvent for solution for injection pre-filled disposable devices | 7 pre-filled disposable injection (Pom) £97.37 (D4-2)

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**Genotropin (Novo Nordisk Ltd)**

- **Genotropin (rbe) 6 mg** Genotropin 6 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £319.05 (D4-2)
- **Genotropin (rbe) 10 mg** Genotropin 10 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £537.49 (D4-2)
- **Genotropin (rbe) 15 mg** Genotropin 15 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £800.00 (D4-2)
- **Genotropin (rbe) 20 mg** Genotropin 20 mg powder and solvent for solution for injection cartridges | 1 cartridge (Pom) £1000.00 (D4-2)

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**Oestrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia.**

In terms of oestrogenic activity, natural oestrogens (estradiol p. 690 (oestradiol), estrone (oestrone), and estriol p. 761 (oestriol)) have a more appropriate profile for hormone replacement therapy (HRT) than synthetic oestrogens (ethinylestradiol p. 694 (ethinylestrodiol) and mestranol). Tibolone p. 695 has oestrogenic, progestogenic and weak androgenic activity.

Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. If long-term therapy is required in women with a uterus, a progestogen should normally be added to reduce the risk of cystic hyperplasia of the endometrium (or of endometriotic foci in women who have had a hysterectomy) and possible transformation to cancer.

Oestrogens are no longer used to suppress lactation because of their association with thromboembolism. **Hormone replacement therapy**

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability. Oestrogen given systemically in the perimenopausal and postmenopausal period or tibolone given in the postmenopausal period also diminish postmenopausal
vaginal oestrogen preparation used for a few weeks and osteoporosis but other drugs are preferred. Menopausal atrophic vaginitis may respond to a short course of a topical vaginal oestrogen preparation used for a few weeks and repeated if necessary.

Systemic therapy with an oestrogen or drugs with oestrogenic properties alleviates the symptoms of oestrogen deficiency such as vasomotor symptoms. Tibolone combines oestrogenic and progestogen activity with weak androgenic activity; it is given continuously, without cyclical progestogen.

HRT may be used in women with early natural or surgical menopause (before age 45 years), since they are at high risk of osteoporosis. For early menopause, HRT can be given until the approximate age of natural menopause (i.e. until age 50 years). Alternatives to HRT should be considered if osteoporosis is the main concern.

Clonidine hydrochloride p. 136 may be used to reduce vasomotor symptoms in women who cannot take an oestrogen, but clonidine hydrochloride may cause unacceptable side-effects.

HRT increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. For details of these risks see HRT Risk table.

The minimum effective dose of HRT should be used for the shortest duration. Treatment should be reviewed at least annually and for osteoporosis alternative treatments considered. HRT does not prevent coronary heart disease or protect against a decline in cognitive function and it should not be prescribed for these purposes. Experience of treating women over 65 years with HRT is limited.

For the treatment of menopausal symptoms the benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years.

Risk of breast cancer
It is estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping. Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use; tibolone has only a limited effect on mammographic density.

Risk of endometrial cancer
The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT. In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

Risk of ovarian cancer
Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer; this excess risk disappears within a few years of stopping.

Risk of venous thromboembolism
Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary

### HRT Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>Age range (years)</th>
<th>Background incidence per 1000 women in Europe not using HRT</th>
<th>Additional cases per 1000 women using oestrogen only HRT (estimated)</th>
<th>Additional cases per 1000 women using combined (oestrogen-progesterone) HRT (estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over 5 years</td>
<td>Over 10 years</td>
<td>For 5 years’ use</td>
<td>For 10 years’ use</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>50–59</td>
<td>10</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>15</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>50–59</td>
<td>2</td>
<td>4</td>
<td>32</td>
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<tr>
<td></td>
<td>60–69</td>
<td>3</td>
<td>6</td>
<td>48</td>
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<td>Ovarian cancer</td>
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<td>&lt;1</td>
<td>1</td>
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<tr>
<td></td>
<td>60–69</td>
<td>3</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>50–59</td>
<td>5</td>
<td>–</td>
<td>2</td>
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<tr>
<td></td>
<td>60–69</td>
<td>8</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>50–59</td>
<td>4</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>9</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>70–79</td>
<td>29–44</td>
<td>NS</td>
<td>–</td>
</tr>
</tbody>
</table>

Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference. Taken from MHRA/CHM (Drug Safety 2007; 1 (2): 2–6) available at www.gov.uk/drug-safety-update

1. Tibolone increases the risk of breast cancer but to a lesser extent than with combined HRT.
2. Evidence suggests an increased risk of endometrial cancer with tibolone. After 2.7 years of use (in women of average age 68 years), 1 extra case of endometrial hyperplasia and 4 extra cases of endometrial cancer were diagnosed compared with placebo users.
3. The risk of endometrial cancer cannot be reliably estimated in those using combined HRT because the addition of progestogen for at least 10 days per 28-day cycle greatly reduces the additional risk, and addition of a daily progestogen eliminates the additional risk. The risk of endometrial cancer in women who have not used HRT increases with body mass index (BMI); the increased risk of endometrial cancer in users of oestrogen-only HRT or tibolone is more apparent in women who are not overweight.
4. Tibolone increases the risk of breast cancer within 2 years of use (in women of average age 68 years), 1 extra case of endometrial hyperplasia and 4 extra cases of endometrial cancer were diagnosed compared with placebo users.
5. Limited data does not suggest an increased risk of thromboembolism with tibolone compared with combined HRT or women not taking HRT.
6. Although the level of risk of thromboembolism associated with non-oral routes of administration of HRT has not been established, it may be lower for the transdermal route.
7. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment; risk of stroke is age-dependent and therefore the absolute risk of stroke with tibolone increases with age.
8. There is insufficient data to draw a conclusion on the risk of coronary heart disease with tibolone.
Endocrine system

involving prolonged immobility further increases the risk of deep vein thrombosis.

Risk of stroke
Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment.

Risk of coronary heart disease
HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

Choice
The choice of HRT for an individual depends on an overall balance of indication, risk, and convenience. A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle or a preparation which involves continuous administration of an oestrogen and a progestogen (or one which provides both oestrogenic and progestogenic activity in a single preparation). Continuous combined preparations or tibolone are not suitable for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT.

An oestrogen alone is suitable for continuous use in women without a uterus. However, in endometriosis, endometrial foci may remain despite hysterectomy and the addition of a progestogen should be considered in these circumstances. An oestrogen may be given by mouth or by transdermal administration, which avoids first-pass metabolism.

Surgery
Major surgery under general anaesthesia, including orthopaedic and vascular leg surgery, is a predisposing factor for venous thromboembolism and it may be prudent to stop HRT 4–6 weeks before surgery; it should be restarted only after full mobilisation. If HRT is continued or if discontinuation is not possible (e.g. in non-elective surgery), prophylaxis with unfractionated or low molecular weight heparin and graduated compression hosiery is advised.

Reasons to stop HRT
Hormone replacement therapy should be stopped (pending investigation and treatment), if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg;
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment

Ethinylestradiol
Ethinylestradiol p. 694 (ethinyleoestradiol) is licensed for short-term treatment of symptoms of oestrogen deficiency, for osteoporosis prophylaxis if other drugs cannot be used and for the treatment of female hypogonadism and menstrual disorders.

Ethinylestradiol is occasionally used under specialist supervision for the management of hereditary haemorrhagic telangiectasia (but evidence of benefit is limited). It is also used licensed for the palliative treatment of prostate cancer.

Raloxifene
Raloxifene hydrochloride p. 689 is licensed for the treatment and prevention of postmenopausal osteoporosis; unlike hormone replacement therapy, raloxifene hydrochloride does not reduce menopausal vasomotor symptoms.

Progestogens and progesterone receptor modulators
There are two main groups of progestogen, progesterone and its analogues (dydrogesterone and medroxyprogesterone acetate p. 741) and testosterone analogues (norethisterone p. 699 and norgestrel). The newer progestogens (desogestrel p. 737, norgestimate, and gestodene) are all derivatives of norgestrel; levonorgestrel p. 737 is the active isomer of norgestrel and has twice its potency. Progesterone p. 701 and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.

Where endometriosis requires drug treatment, it may respond to a progestogen, e.g. norethisterone, administered on a continuous basis. Danazol p. 678 and gonadorelin analogues are also available.

Although oral progestogens have been used widely for menorrhagia they are relatively ineffective compared with tranexamic acid p. 104 or, particularly where dysmenorrhoea is also a factor, mefenamic acid p. 1004; the levonorgestrel-releasing intra-uterine system may be particularly useful for women also requiring contraception. Oral progestogens have also been used for severe dysmenorrhoea, but where contraception is also required in younger women the best choice is a combined oral contraceptive.

Progestogens have also been advocated for the alleviation of premenstrual symptoms, but no convincing physiological basis for such treatment has been shown.

Progestogens have been used for the prevention of miscarriage in women with a history of recurrent miscarriage but there is no evidence of benefit and they are not recommended for this purpose. In pregnant women with antiphospholipid antibody syndrome who have suffered recurrent miscarriage, administration of low-dose aspirin p. 114 and a prophylactic dose of a low molecular weight heparin may decrease the risk of fetal loss (use under specialist supervision only).

Hormone replacement therapy
In women with a uterus a progestogen needs to be added to long-term oestrogen therapy for hormone replacement, to prevent cystic hyperplasia of the endometrium and possible transformation to cancer; it can be added on a cyclical or a continuous basis. Combined packs incorporating suitable progestogen tablets are available.

Oral contraception
Desogestrel, gestodene, levonorgestrel, norethisterone, and norgestimate are used in combined oral contraceptives and in progestogen-only contraceptives.
Cancer
Progestogens also have a role in neoplastic disease.

**Progestrone receptor modulators**
Ulipristal acetate p. 736 is a progesterone receptor modulator with a partial progesterone antagonist effect. Ulipristal acetate is used in the pre-operative treatment of moderate to severe symptoms of uterine fibroids; it is also used as an hormonal emergency contraceptive.

8.1 Female sex hormone responsive conditions

**CALCIUM REGULATING DRUGS** > BONE RESORPTION INHIBITORS

**Raloxifene hydrochloride**

- **INDICATIONS AND DOSE**
  - Treatment and prevention of postmenopausal osteoporosis
  - **BY MOUTH**
  - Adult: 60 mg once daily

- **CONTRA-INDICATIONS**
  - Cholestatic • endometrial cancer • history of venous thromboembolism • undiagnosed uterine bleeding

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930 • breast cancer (manufacturer advises avoid during treatment for breast cancer) • history of oestrogen-induced hypertriglyceridaemia (monitor serum triglycerides) • risk factors for stroke • risk factors for venous thromboembolism (discontinue if prolonged immobilisation)

- **INTERACTIONS**
  - Common or very common Hot flushes • influenza-like symptoms • leg cramps • peripheral oedema
  - Uncommon Thrombophlebitis • venous thromboembolism
  - Rare Arterial thromboembolism • breast discomfort • gastro-intestinal disturbances • headache • hypertension • migraine • rashes • thrombocytopenia

- **HEPATIC IMPAIRMENT**
  - Avoid.

- **RENAL IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**
  - Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160
    - Raloxifene is not recommended as a treatment option in postmenopausal women for primary prevention of osteoporotic fractures.
    - www.nice.org.uk/TA160
  - Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fracture fragility fractures in postmenopausal women (October 2008) NICE TA161
    - This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.
    - **Raloxifene** is recommended as an alternative treatment option for women:
      - in whom alendronate and risedronate are contra¬indicated or not tolerated and

**OESTROGENS**

**Conjugated oestrogens (equine)**

- **INDICATIONS AND DOSE**
  - **PREMARIN ® TABLETS**
    - Menopausal symptoms
      - **BY MOUTH**
      - Adult: 0.3—1.25 mg daily continuously; with cyclical progesterone for 12—14 days of each cycle in women with a uterus
    - Osteoporosis prophylaxis
      - **BY MOUTH**
      - Adult: 0.625—1.25 mg daily continuously; with cyclical progesterone for 12—14 days of each cycle in women with a uterus

- **CONTRA-INDICATIONS**
  - Active arterial thromboembolic disease (e.g. angina or myocardial infarction) • active thrombophlebitis • Dubin-Johnson syndromes (or monitor closely) • history of breast cancer • history of recurrent venous thromboembolism (unless already on anticoagulant treatment) • liver disease (where liver function tests have failed to return to normal) • oestrogen-dependent cancer • recent arterial thromboembolic disease (e.g. angina or myocardial infarction) • Rotor syndromes (or monitor closely) • thrombophilic disorder • undiagnosed vaginal bleeding • untreated endometrial hyperplasia • venous thromboembolism

- **CAUTIONS**
  - Acute porphyrias p. 930 • diabetes (increased risk of heart disease) • factors predisposing to thromboembolism • history of breast nodules (closely monitor breast status—risk of breast cancer) • history of endometrial hyperplasia • history of fibrocystic disease (closely monitor breast status—risk of breast cancer) • hypophyseal tumours • increased risk of gall-bladder disease reported • migraine • migraine-like headaches • presence of antiphospholipid antibodies (increased risk of thrombotic events) • risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) • risk of breast cancer

**CAUTIONS, FURTHER INFORMATION**

- Risk of breast cancer It is estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1—2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at
which HRT is started) and this excess risk disappears within 5 years of stopping.

Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

- **Risk of endometrial cancer** The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.

  - In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

- **Risk of ovarian cancer** Long-term use of combined HRT or oestrogen–only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

- **Risk of venous thromboembolism** Women using combined or oestrogen–only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.

  - In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

  - **Travel** involving prolonged immobility further increases the risk of deep vein thrombosis.

- **Risk of stroke** Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen–only HRT slightly increases the risk of stroke.

- **Risk of coronary heart disease** HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

- **Other conditions** The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **INTERACTIONS** → Appendix 1 (oestrogens).

- **SIDE-EFFECTS** Abdominal bloating · abdominal cramps · altered blood lipids (may lead to pancreatitis, rashes and chloasma) · breast enlargement · breast tenderness · changes in libido · cholestatic jaundice · contact lenses may irritate · depression · dizziness · fluid retention · glucose intolerance · headache · headache (on vigorous exercise) · leg cramps (rule out venous thrombosis) · migraine · mood changes · nausea · premenstrual-like syndrome · prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer · sodium retention · symptoms of endometriosis may be exacerbated · uterine fibroids may increase in size · vaginal candidiasis · vomiting · weight changes

**SIDE-EFFECTS, FURTHER INFORMATION**

- Withdrawal bleeding Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

- **CONCEPTION AND CONTRACEPTION** HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Avoid until weaning or for 6 months after birth (adverse effects on lactation).

- **HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin–Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Premarin** (Pfizer Ltd)
  - **Conjugated oestrogens 300 microgram** Premarin 0.3mg tablets | 84 tablet (P) £6.07 DT price = £6.07
  - **Conjugated oestrogens 625 microgram** Premarin 0.625mg tablets | 84 tablet (P) £4.02 DT price = £4.02
  - **Conjugated oestrogens 1.25 mg** Premarin 1.25mg tablets | 84 tablet (P) £3.58 DT price = £3.58

Combinations available: **Conjugated oestrogens with medroxyprogesterone**, p. 696 · **Conjugated oestrogens with norgestrel**, p. 696

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**Estradiol**

- **INDICATIONS AND DOSE**
  - **BEDOL**
    - **Menopausal symptoms | Osteoporosis prophylaxis**
      - **BY MOUTH**
        - Adult: 2 mg daily, started on day 1–5 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progestogen for 12–14 days of each cycle in women with a uterus
      - **CLIMAVAL**
        - **Menopausal symptoms (if patient has had a hysterectomy)**
          - **BY MOUTH**
            - Adult: 1–2 mg daily
          - **ELLESTE SOLO** ®
            - **MX**
        - Menopausal symptoms
          - **BY TRANSDERMAL APPLICATION**
            - Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progestogen for 12–14 days of each cycle in women with a uterus, initiate therapy with MX 40, subsequently adjust according to response
Menopausal symptoms

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with MX 80, subsequently adjust according to response

ELLESTE-SOLO® 1-MG

Menopausal symptoms

BY MOUTH

Adult: 1 mg daily, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

ELLESTE-SOLO® 2-MG

Menopausal symptoms not controlled with lower strength

BY MOUTH

Adult: 2 mg daily, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be given with cyclical progesterone for 12–14 days of each cycle in women with a uterus

ESTRADERM MX®

Menopausal symptoms

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for at least 12 days of each cycle in women with a uterus, initiate therapy with MX25 for first 3 months; subsequently adjust according to response

Osteoporosis prophylaxis

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for at least 12 days of each cycle in women with a uterus, initiate therapy with MX50; subsequently adjust according to response

ESTRADOT®

Menopausal symptoms

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with 25 patch for 3 months; subsequently adjust according to response

Osteoporosis prophylaxis

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with 50 patch; subsequently adjust according to response

EVOREL®

Menopausal symptoms | Osteoporosis prophylaxis

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, therapy should be initiated with Evorel 50 patch; subsequently adjust according to response; dose may be reduced to Evorel 25 patch after first month if necessary for menopausal symptoms only

FEMSEVEN®

Menopausal symptoms | Osteoporosis prophylaxis

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch once weekly continuously, to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with FemSeven 50 patches for the first few months, subsequently adjust according to response

OSTREGEL®

Menopausal symptoms

TO THE SKIN

Adult: Apply 1.5 mg once daily continuously, increased if necessary up to 3 mg after 1 month continuously, to be applied over an area twice that of the template provided, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), to be used with cyclical progesterone for at least 12 days of each cycle in women with a uterus

Osteoporosis prophylaxis

TO THE SKIN

Adult: Apply 1.5 mg once daily continuously, to be applied over an area twice that of the template provided, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), to be used with cyclical progesterone for at least 12 days of each cycle in women with a uterus

DOSE EQUIVALENCE AND CONVERSION

For Oestrogel®: 2 measures is equivalent to estradiol 1.5 mg.

PROGYNOVA®

Menopausal symptoms

BY MOUTH

Adult: 1–2 mg daily continuously, to be started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

Osteoporosis prophylaxis

BY MOUTH

Adult: 2 mg daily continuously, to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

PROGYNOVA® TS

Menopausal symptoms | Osteoporosis prophylaxis

BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch once weekly continuously, followed by a 7-day patch-free interval (cyclical), to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with Progynova TS 50, subsequently adjust according to response, women receiving Progynova TS 100 patches for menopausal symptoms may continue with this strength for osteoporosis prophylaxis

SANDRENA®

Menopausal symptoms | Osteoporosis prophylaxis

BY MOUTH

Adult: 50 µg daily, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus, therapy should be initiated with Sandrena 50 patch; subsequently adjust according to response; dose may be reduced to Sandrena 10 patch after first month if necessary for menopausal symptoms only

ZUMENON®

Menopausal symptoms

BY MOUTH

Adult: Initially 1 mg daily, to be started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), increased if continued →
necessary to 2 mg daily, to be taken with a cyclical progestogen for 12–14 days of each cycle in women with a uterus

Osteoporosis prophylaxis

▶ BY MOUTH

Adult: 2 mg daily, to be taken with a cyclical progestogen for 12–14 days of each cycle in women with a uterus

- CONTRA-INDICATIONS Active arterial thromboembolic disease (e.g. angina or myocardial infarction) • active thrombophlebitis • Dubin-Johnson syndrome (or monitor closely) • history of breast cancer • history of recurrent venous thromboembolism (unless already on anticoagulant treatment) • oestrogen-dependent cancer • recent arterial thromboembolic disease (e.g. angina or myocardial infarction) • Rotor syndrome (or monitor closely) • thrombophilic disorder • undiagnosed vaginal bleeding • untreated endometrial hyperplasia • venous thromboembolism

- CAUTIONS Acute porphyrrias p. 930 • diabetes (increased risk of heart disease) • history of breast nodules—closely monitor breast status (risk of breast cancer) • history of endometrial hyperplasia; factors predisposing to thromboembolism • history of fibrocystic disease—closely monitor breast status (risk of breast cancer) • hypophyseal tumours • increased risk of gall-bladder disease • migraine (or migraine-like headaches) • presence of antiphospholipid antibodies (increased risk of thrombotic events) • prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer • risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) • symptoms of endometriosis may be exacerbated • uterine fibroids may increase in size

CAUTIONS, FURTHER INFORMATION

- Risk of breast cancer It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.

- Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

- Risk of endometrial cancer The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.

In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

- Risk of ovarian cancer Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

- Risk of venous thromboembolism Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.

In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

- Risk of stroke Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke.

Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

- Risk of coronary heart disease HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

- Other conditions The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- INTERACTIONS → Appendix 1 (oestrogens).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Abdominal bloating • abdominal cramps • altered blood lipids (may lead to pancreatitis, rashes and chloasma) • breast enlargement • breast tenderness • changes in libido • cholestatic jaundice • contact lenses may irritate • depression • dizziness • fluid retention • glucose intolerance • headache • headache (on vigorous exercise) • leg cramps (rule out venous thrombosis) • migraine • mood changes • nausea • premenstrual-like syndrome • sodium retention • vaginal candidiasis • vomiting • weight changes

SPECIFIC SIDE-EFFECTS

- With transdermal use Cause contact sensitisation (possible severe hypersensitivity reaction on continued exposure)

SIDE-EFFECTS, FURTHER INFORMATION

- Withdrawal bleeding Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

CONCEPTION AND CONTRACEPTION HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

- PREGNANCY Not known to be harmful.

- BREAST FEEDING Avoid; adverse effects on lactation.

- HEPATIC IMPAIRMENT Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.
MONITORING REQUIREMENTS

- History of breast nodules or fibrocystic disease—closely monitor breast status (risk of breast cancer).
- The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

DIRECTIONS FOR ADMINISTRATION

- With transdermal use Patch should be removed after 3–4 days (or once a week in case of 7-day patch) and replaced with fresh patch on slightly different site; recommended sites: clean, dry, unbroken areas of skin on trunk below waistline; not to be applied on or near breasts or under waistband. If patch falls off in bath allow skin to cool before applying new patch.

PATIENT AND CARER ADVICE

- With transdermal use Patient counselling is advised for estradiol patches (administration).
- With topical use Patient counselling is advised for estradiol gels (administration).

OESTROGEL® Apply gel to clean, dry, intact skin such as arms, shoulders or inner thighs and allow to dry for 5 minutes before covering with clothing. Not to be applied on or near breasts or on vulval region. Avoid skin contact with another person (particularly male) and avoid other skin products or washing the area for at least 1 hour after application.

SANDRENA® Apply gel to intact areas of skin such as lower trunk or thighs, using right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Bedol (ReSource Medical UK Ltd)
  Estradiol 2 mg Bedol 2mg tablets | 84 tablet Per | £5.07 DT price = £5.06
- Elleste Solo (Meda Pharmaceuticals Ltd)
  Estradiol 1 mg Elleste Solo 1mg tablets | 84 tablet Per | £5.06 DT price = £5.06
- Elleste Solo 2 mg Elleste Solo 2mg tablets | 84 tablet Per | £5.06 DT price = £5.06
- Progynova (Bayer Plc)
  Estradiol valerate 1 mg Progynova 1mg tablets | 84 tablet Per | £7.30 DT price = £7.30
- Estradiol valerate 2 mg Progynova 2mg tablets | 84 tablet Per | £7.30 DT price = £7.30
- Zumenon (BGP Products Ltd)
  Estradiol 1 mg Zumenon 1mg tablets | 84 tablet Per | £6.89 DT price = £5.06
  Estradiol 2 mg Zumenon 2mg tablets | 84 tablet Per | £6.89 DT price = £5.06

Transdermal patch

- Elleste Solo MX (Meda Pharmaceuticals Ltd)
  Estradiol 40 microgram per 24 hour Elleste Solo MX 40 transdermal patches | 8 patch Per | £5.19
  Estradiol 80 microgram per 24 hour Elleste Solo MX 80 transdermal patches | 8 patch Per | £5.99
- Estraderm MX (Merus Labs Luxco S.a.R.L.)
  Estradiol 25 microgram per 24 hour Estraderm MX 25 patches | 24 patch Per | £6.42
  Estradiol 50 microgram per 24 hour Estraderm MX 50 patches | 8 patch Per | £5.51
  Estradiol 75 microgram per 24 hour Estraderm MX 75 patches | 8 patch Per | £5.51
  Estradiol 100 microgram per 24 hour Estraderm MX 100 patches | 8 patch Per | £5.99

Estradiol with estriol and estrone

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 690, estriol p. 761.

INDICATIONS AND DOSE

Menopausal symptoms | Osteoporosis prophylaxis

- BY MOUTH
  - Adult: 1–2 tablets daily continuously or cyclically (21 days out of 28), started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Hormonin (AMCo)
  Estriol 270 microgram, Estradiol 600 microgram, Estrone 1.4 mg Hormonin tablets | 84 tablet Per | £7.93
Ethinylestradiol
(ETHINYL estradiol)

**INDICATIONS AND DOSE**

**Short-term treatment of symptoms of oestrogen deficiency**/Osteoporosis prophylaxis if other drugs cannot be used
- **BY MOUTH**
  - Adult (female): 10–50 micrograms daily for 21 days, repeated after 7-day tablet-free period, to be given with progesterogen for 12–14 days per cycle in women with intact uterus.

**Female hypogonadism**
- **BY MOUTH**
  - Adult (female): 10–50 micrograms daily usually on cyclical basis, initial oestrogen therapy should be followed by combined oestrogen and progesterogen therapy.

**Menstrual disorders**
- **BY MOUTH**
  - Adult (female): 20–50 micrograms daily from day 5 to 25 of each cycle, to be given with progesterogen, added either throughout the cycle or from day 15 to 25.

**Palliative treatment of prostate cancer**
- **BY MOUTH**
  - Adult (male): 0.15–1.5 mg daily.

**CONTRA-INDICATIONS** Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) / active thrombophlebitis / acute porphyrias p. 930 / Dubin-Johnson and Rotor syndromes (or monitor closely) / gallstones / heart disease associated with pulmonary hypertension / heart disease associated with risk of embolus / history during pregnancy of cholestatic jaundice / history during pregnancy of convulsions / history during pregnancy of pemphigoid gestationis / history during pregnancy of pruritus / history of breast cancer / history of haemolytic uraemic syndrome / liver disease (where liver function tests have failed to return to normal) / migraine with aura / oestrogen-dependent cancer / thrombophlebitis / thromboembolic disease / systemic lupus erythematosus with (or unknown) antiphospholipid antibodies / thrombophilic disorder / transient cerebral ischaemic attacks without headaches / undiagnosed vaginal bleeding / untreated endometrial hyperplasia / venous thromboembolism, or history of recurrent venous thromboembolism (unless already on anticoagulant treatment)

**CAUTIONS** Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice / cardiovascular disease (sodium retention with oedema, thromboembolism) / Crohn’s disease / diabetes (increased risk of heart disease) / gene mutations associated with breast cancer (e.g. BRCA 1) / heart disease associated with risk of embolus / history during pregnancy of cholestatic jaundice / heart disease associated with risk of embolus / history during pregnancy of cholestatic jaundice / renal disease (where liver function tests have failed to return to normal) / migraine with aura / oestrogen-dependent cancer / thrombophlebitis / thromboembolic disease / systemic lupus erythematosus with (or unknown) antiphospholipid antibodies / thrombophilic disorder / transient cerebral ischaemic attacks without headaches / undiagnosed vaginal bleeding / untreated endometrial hyperplasia / venous thromboembolism, or history of recurrent venous thromboembolism (unless already on anticoagulant treatment)

**SIDE-EFFECTS**

- Other conditions: The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, osteosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present, see above). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **Risk of venous thromboembolism** Use with caution if any of the following factors present but avoid if two or more factors present:
  - family history of venous thromboembolism in first-degree relative aged under 45 years (avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
  - obesity—body mass index ≥ 30 kg/m² (avoid if body mass index ≥ 35 kg/m² unless no suitable alternative); (In adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
  - long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
  - history of superficial thrombophlebitis;
  - age over 35 years (avoid if over 50 years);
  - smoking.

- Risk factors for arterial disease Use with caution if any one of the following factors present but avoid if two or more factors present:
  - family history of arterial disease in first degree relative aged under 45 years (avoid if other genetic lipid profile);
  - diabetes mellitus (avoid if diabetes complications present);
  - hypertension—blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (In adolescents, avoid if blood pressure very high);
  - smoking (avoid if smoking 40 or more cigarettes daily);
  - age over 35 years (avoid if over 50 years);
  - obesity (avoid if body mass index ≥ 35 kg/m² unless no suitable alternative); (In adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
  - migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

- Migraine: Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).

**INTERACTIONS** → Appendix 1 (oestrogens).

- Rare: Gallstones / systemic lupus erythematosus
- **Frequency not known** Abdominal bloating / abdominal cramps / absence of withdrawal bleeding / altered blood lipids (may lead to pancreatitis) / amenorrhoea after discontinuation / breast enlargement / breast secretion / breast tenderness / cervical erosion / changes in libido / changes in lipid metabolism / changes in vaginal discharge / chloasma / cholestatic jaundice / chorea / contact lenses may irritate / depression / dizziness / feminising effects / fluid retention / glucose intolerance / headache / hepatic tumours / hypertension / irritability / leg cramps (rule out venous thrombosis) / liver impairment / migraine / mood changes / nausea / nervousness / photosensitivity / premenstrual-like syndrome / rashes / reduced menstrual
loss • skin reactions • sodium retention • symptoms of endometriosis may be exacerbated • thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB) • uterine fibroids may increase in size • vaginal candidiasis • visual disturbances • vomiting • weight changes • ‘spotting’ in early cycles

SIDE-EFFECTS, FURTHER INFORMATION

Withdrawal bleeding  Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

PREGNANCY  Not known to be harmful.

BREAST FEEDING  Avoid until weaning or for 6 months after birth (adverse effects on lactation).

HEPATIC IMPAIRMENT  Avoid.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension

**Tablet**

- Ethinylestradiol (Non-proprietary)
  - Ethinylestradiol 1 mg Ethinylestradiol 1mg tablets | 28 tablet £200.00 DT price = £200.00
  - Ethinylestradiol 10 microgram Ethinylestradiol 10microgram tablets | 21 tablet £200.00 DT price = £200.00
  - Ethinylestradiol 50 microgram Ethinylestradiol 50microgram tablets | 21 tablet £200.00 DT price = £200.00

**Tibolone**

INDICATIONS AND DOSE

Short-term treatment of symptoms of oestrogen deficiency (including women being treated with gonadotrophin releasing hormone analogues) • Osteoporosis prophylaxis in women at high risk of fractures when other prophyaxis contra-indicated or not tolerated

BY MOUTH

- Adult: 2.5 mg daily

CONTRA-INDICATIONS  Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) • active thrombophlebitis • Acute porphyrias p. 930 • Dubin–Johnson andRotor syndrome (or monitor closely) • history of breast cancer • history of cardiovascular disease • history of cerebrovascular disease • history of recurrent venous thromboembolism (unless already on anticoagulant treatment) • history of thromboembolism • history of thrombophlebitis • hormone-dependent tumours • liver disease (where liver function tests have failed to return to normal) • oestrogen-dependent cancer • thrombohaemolytic disorder • uninvestigated or undiagnosed vaginal bleeding • untreated endometrial hyperplasia • venous thromboembolism

CAUTIONS  Acute porphyrias p. 930 • diabetes (increased risk of heart disease) • epilepsy • factors predisposing to thromboembolism • history of breast nodules—closely monitor breast status (risk of breast cancer) • history of endometrial hyperplasia • history of fibrocystic disease—closely monitor breast status (risk of breast cancer) • history of liver disease • hypertriglyceridaemia • hypophyseal tumours • migraine (or migraine-like headaches) • presence of antiphospholipid antibodies (increased risk of thrombotic events) • prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer • risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) • risk of stroke

CAUTIONS, FURTHER INFORMATION

Other conditions  The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, atherosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

INTERACTIONS  Appendix 1 (tibolone).

SIDE-EFFECTS

- Common or very common  Abdominal pain • facial hair • leucorrhoea • vaginal bleeding • weight changes

- Rare  Amnesia

- Frequency not known  Arthralgia • breast cancer • depression • dizziness • gastro-intestinal disturbances • headache • increased risk of gall-bladder disease • migraine • myalgia • oedema • pruritus • rash • seborrhoeic dermatitis • symptoms of endometriosis may be exacerbated • uterine fibroids may increase in size • visual disturbances

SIDE-EFFECTS, FURTHER INFORMATION

Vaginal bleeding  Investigate for endometrial cancer if bleeding continues beyond 6 months or after stopping treatment.

Reasons to withdraw treatment  Withdraw treatment if signs of thromboembolic disease, abnormal liver function tests, or signs of cholestatic jaundice.

PREGNANCY  Avoid; toxicity in animal studies.

BREAST FEEDING  Avoid.

HEPATIC IMPAIRMENT  Avoid in acute liver disease or if history of liver disease and liver function tests not returned to normal.

RENAL IMPAIRMENT  Patients with renal impairment should be closely monitored (risk of fluid retention).

PRESCRIBING AND DISPENSING INFORMATION  Unsuitable for use in the premenopause (unless being treated with gonadotrophin-releasing hormone analogue) and as (or with) an oral contraceptive.

Also unsuitable for use within 12 months of last menstrual period (may cause irregular bleeding). If transferring from cyclical HRT, start at end of regimen; if transferring from continuous–combined HRT, start at any time.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- T__ibolone (Non-proprietary)
  - T__ibolone 2.5 mg Tibolone 2.5mg tablets | 28 tablet £10.36–£10.95 DT price = £10.36 | 84 tablet £31.08–£32.63
  - L__ivial (Merck Sharp & Dohme Ltd)
    - T__ibolone 2.5 mg Livial 2.5mg tablets | 28 tablet £10.36 DT price = £10.36 | 84 tablet £31.08

**Female sex hormone responsive conditions** 695

Endocrine system

BNF 73
OESTROGENS COMBINED WITH PROGESTOGENS

Conjugated oestrogens with medroxyprogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, conjugated oestrogens (equine) p. 689, medroxyprogesterone acetate p. 741.

- **INDICATIONS AND DOSE**
  - PREMIQUE®
    - Menopausal symptoms in women with a uterus
    - Osteoporosis prophylaxis in women with a uterus
      - **BY MOUTH**
      - Adult: 1 tablet daily continuously
  - PREMIQUE® LOW DOSE TABLETS
    - Menopausal symptoms in women with a uterus
      - **BY MOUTH**
      - Adult: 1 tablet daily continuously

- **INTERACTIONS** → Appendix 1 (oestrogens, progestogens).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Premique (Pfizer Ltd)
      - Conjugated oestrogens 625 microgram, Medroxyprogesterone acetate 5 mg Premique 0.625mg/5mg tablets | 84 tablet [POM] £10.61 DT price = £10.61
    - Modified-release tablet
      - Premique (Pfizer Ltd)
        - Conjugated oestrogens 300 microgram, Medroxyprogesterone acetate 1.5 mg Premique Low Dose 0.3mg/1.5mg modified-release tablets | 84 tablet [POM] £6.52 DT price = £6.52

Conjugated oestrogens with norgestrel

The properties listed below are those particular to the combination only. For the properties of the components please consider, conjugated oestrogens (equine) p. 689.

- **INDICATIONS AND DOSE**
  - PREMPAK C® 0.625
    - Menopausal symptoms in women with a uterus
    - Osteoporosis prophylaxis in women with a uterus
      - **BY MOUTH**
      - Adult: 1 tablet daily continuously, maroon tablet to taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) and 1 tablet daily, brown tablet to be taken and started on days 17–28 of each 28-day treatment cycle, subsequent courses are repeated without interval
  - PREMPAK C® 1.25
    - Menopausal symptoms in women with a uterus (if symptoms not fully controlled with lower strength pack)
    - Osteoporosis prophylaxis in women with a uterus (if symptoms not fully controlled with lower strength pack)
      - **BY MOUTH**
      - Adult: 1 tablet daily continuously, (yellow tablet) to taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) and 1 tablet daily, (brown tablet) to be taken and started on days 17–28 of each 28-day treatment cycle, subsequent courses are repeated without interval

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablets**
    - PREmpak-C (Pfizer Ltd)
      - PREmpak-C 1.25mg/0.15mg tablets | 120 tablet [POM] £7.40 DT price = £7.40
      - PREmpak-C 0.625mg/0.15mg tablets | 120 tablet [POM] £6.25 DT price = £6.25

Estradiol with drospirenone

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 690.

- **INDICATIONS AND DOSE**
  - Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously
  - Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously
      - **BY MOUTH**
      - Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase

- **CAUTIONS**
  - Use with care if an increased concentration of potassium might be hazardous
  - **RENNAL IMPAIRMENT**
    - Avoid if eGFR less than 30 mL/minute/1.73 m².

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Angeliq (Bayer Plc)
      - Estradiol (as Estradiol hemihydrate) 1 mg, Drospirenone 2 mg Angeliq tablets | 84 tablet [POM] £29.00 DT price = £29.00

Estradiol with dydrogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 690.

- **INDICATIONS AND DOSE**
  - Menopausal symptoms in women with a uterus
      - **BY MOUTH**
      - Adult: 1 tablet daily for 14 days, white tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, grey tablet to be taken, subsequent courses repeated without interval, Femoston® 1 mg/10 mg given initially and Femoston® 2 mg/10 mg substituted if symptoms not controlled

  - Osteoporosis prophylaxis in women with a uterus
      - **BY MOUTH**
      - Adult: 1 tablet daily for 14 days, red tablet to be taken and started within 5 days of onset of menstruation (or...
any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, yellow tablet to be taken, subsequent courses repeated without interval, Femoston® 1 mg/10 mg given initially and Femoston® 2 mg/10 mg substituted if symptoms not controlled

**Osteoporosis prophylaxis in women with a uterus**
- **BY MOUTH**
  - Adult: 1 tablet daily for 14 days, red tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, yellow tablet to be taken, subsequent courses repeated without interval

**FEMOSTON® CONTI 0.5 MG/2.5MG**
Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously
- **BY MOUTH**
  - Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progesterone phase

**FEMOSTON® CONTI 1 MG/5MG**
Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously
- **BY MOUTH**
  - Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progesterone phase

**CONTRA-INDICATIONS**
- Acute porphyrias p. 930 | genital or breast cancer | history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis | history of liver tumours | severe arterial disease | undiagnosed vaginal bleeding

**CAUTIONS**
- Conditions that may worsen with fluid retention e.g. epilepsy, hypertension, migraine, asthma, or cardiac dysfunction | diabetes (progestogens can decrease glucose tolerance) | history of depression | in those susceptible to thromboembolism (particular caution with high dose)

**INTERACTIONS**
- Appendix 1 (progestogens).

**SIDE-EFFECTS**
- Acne | alopecia | anaphylactoid reactions | bloating | breast tenderness | change in libido | depression | dizziness | drowsiness | fluid retention | headache | hirsutism | insomnia | jaundice | menstrual disturbances | nausea | premenstrual-like syndrome | pruritus | rash | skin reactions | urticaria | weight change

**HEPATIC IMPAIRMENT**
- Avoid.

**RENAL IMPAIRMENT**
- Use with caution.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Transdermal patch**
- FemSeven Conti (Teva UK Ltd)
  - Levonorgestrel 7 microgram per 24 hour, Estradiol 50 microgram per 24 hour
  - FemSeven Conti patches | 4 patch | £15.48 | 12 patch | £44.12
- FemSeven Sequi (Teva UK Ltd)
  - FemSeven Sequi patches | 4 patch | £13.18 | 12 patch | £37.54

**Estradiol with levonorgestrel**
The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 690, levonorgestrel p. 737.

**INDICATIONS AND DOSE**

**FEMSEVEN CONTI®**
- Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch once weekly continuously

**FEMSEVEN SEQUI®**
- Menopausal symptoms in women with a uterus
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch once weekly for 2 weeks, phase 1 patches to be applied, then apply 1 patch once weekly for 2 weeks, phase 2 patches to be applied, subsequent courses are repeated without interval

**PATIENT AND CARER ADVICE**
- Patient counselling is advised for estradiol with levonorgestrel patches (application).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**INDIVINA® TABLETS**
- Menopausal symptoms in women with a uterus whose last menstrual period occurred over 3 years previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 3 years previously
- **BY MOUTH**
  - Adult: Initially 1/2.5 mg daily taken continuously, adjust according to response, to be started at end of scheduled bleed if changing from cyclical HRT

**TRIDESTRA®**
- Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus
- **BY MOUTH**
  - Adult: 1 tablet daily for 70 days, white tablet to be taken, then 1 tablet daily for 14 days, blue tablet to be taken, then 1 tablet daily for 7 days, yellow tablet to be taken, subsequent courses are repeated without interval

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Indivina (Orion Pharma (UK) Ltd)
  - Estradiol valerate 1 mg, Medroxyprogesterone acetate
  - 2.5 mg Indivina 1mg/2.5mg tablets | 84 tablet | £20.58 DT price = £20.58
Estradiol with notherhisterone

The properties listed below are those particular to the combination only. For the properties of the components please see, estradiol p. 690, notherhisterone p. 699.

**INDICATIONS AND DOSE**

CLIMAGEST® 1-MG

Menopausal symptoms

- **BY MOUTH**
  - Adult: 1 tablet daily for 16 days, grey tablet to be taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 12 days, white tablet to be taken, subsequent courses are repeated without interval

CLIMAGEST® 2-MG

Menopausal symptoms (if symptoms not controlled with lower strength)

- **BY MOUTH**
  - Adult: 1 tablet daily for 16 days, blue tablet to be taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 12 days, white tablet to be taken, subsequent courses are repeated without interval

CLIMESSE®

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- **BY MOUTH**
  - Adult: 1 tablet daily continuously

CLINORETTE®

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

- **BY MOUTH**
  - Adult: 1 tablet daily for 16 days, white tablets to be taken, starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 12 days, pink tablets to be taken, subsequent courses are repeated without interval

ELLESTE-DUET® 1-MG

Menopausal symptoms

- **BY MOUTH**
  - Adult: 1 tablet daily for 16 days, white tablet to be taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 12 days, green tablets to be taken, subsequent courses are repeated without interval

ELLESTE-DUET® 2-MG

Menopausal symptoms | Osteoporosis prophylaxis

- **BY MOUTH**
  - Adult: 1 tablet daily for 16 days, orange tablet to be taken, to be started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 12 days, grey tablet to be taken, subsequent courses are repeated without interval

ELLESTE-DUET® CONTI

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- **BY MOUTH**
  - Adult: 1 tablet daily continuous basis, if changing from cyclical HRT begin treatment at the end of scheduled bleed

EVOREL® CONTI

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch twice weekly continuously

EVOREL® SEQUI

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch twice weekly for 2 weeks, Evorel® 50 patch to be applied and started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), then apply 1 patch twice weekly, Evorel® Conti patch to be applied, subsequent courses are repeated without interval.

KLIOfem®

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- **BY MOUTH**
  - Adult: 1 tablet daily continuously, to be started at end of scheduled bleed if changing from cyclical HRT

KLOVANCE®

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- **BY MOUTH**
  - Adult: 1 tablet daily continuously, to be started at end of scheduled bleed if changing from cyclical HRT

NOVOFEM®

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

- **BY MOUTH**
  - Adult: 1 tablet daily for 16 days, red tablets to be taken, then 1 tablet daily for 12 days, white tablets to be taken, subsequent courses are repeated without interval; start treatment with red tablet at any time or if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase

NUVELLE® CONTINUOUS

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- **BY MOUTH**
  - Adult: 1 tablet daily continuously, if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinorette (ReSource Medical UK Ltd)</td>
<td>£9.23</td>
</tr>
<tr>
<td>Elleste Duet (Meda Pharmaceuticals Ltd)</td>
<td>£9.20</td>
</tr>
<tr>
<td>Kliovance (Novo Nordisk Ltd)</td>
<td>£17.02</td>
</tr>
<tr>
<td>Kliofem (Novo Nordisk Ltd)</td>
<td>£11.43</td>
</tr>
<tr>
<td>Norethisterone acetate 1 mg, Estradiol 2 mg</td>
<td>£13.20</td>
</tr>
<tr>
<td>Nuvelle Continuous (Bayer Plc)</td>
<td>£11.43</td>
</tr>
<tr>
<td>Trisequens (Novo Nordisk Ltd)</td>
<td>£19.00</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>£11.10</td>
</tr>
</tbody>
</table>

**Estradiol with norgestrel**

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 690.

### INDICATIONS AND DOSE

**Cyclo-Progynova 2mg Tablets**

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

- **BY MOUTH**
- **Adult:** 1 tablet daily for 11 days, white tablet to be taken; start on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 10 days, brown tablet to be taken, followed by a 7-day tablet free interval

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**

Avoid in patients with a history of liver tumours · breast cancer (unless progestogens are being used in the management of this condition) · genital cancer (unless progestogens are being used in the management of this condition) · history during pregnancy of idiopathic jaundice · history during pregnancy of pemphigoid gestations (non-contraceptive indications) · history during pregnancy of severe pruritus (non-contraceptive indications) · when used as a contraceptive, history of breast cancer (can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable)

**SPECIFIC CONTRA-INDICATIONS**

- With oral use | Acute porphyrias p. 930 · severe arterial disease · undiagnosed vaginal bleeding

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**TRISEQUENS**

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

- **BY MOUTH**
- **Adult:** 1 tablet daily for 12 days, blue tablets to be taken, followed by 1 tablet daily for 10 days, white tablet to be taken, then 1 tablet daily for 6 days, red tablet to be taken, subsequent courses are repeated without interval

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evorel Sequi patches (Meda Pharmaceuticals Ltd)</td>
<td>£8.43</td>
</tr>
</tbody>
</table>

**EVOREL® SEQUI** Patients and carers should be advised on the application of Evorel® Sequi patches.

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**PROGESTOGENS**

**Norethisterone**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometriosis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BY MOUTH</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Adult:</strong> 10–15 mg daily for 4–6 months or longer, to be started on day 5 of cycle; increased to 20–25 mg daily if required, dose only increased if spotting occurs and reduced once bleeding has stopped</td>
<td></td>
</tr>
</tbody>
</table>

**Dysfunctional uterine bleeding (to arrest bleeding) | Menorrhagia (to arrest bleeding)**

- **BY MOUTH**
- **Adult:** 5 mg 3 times a day for 10 days

**Dysfunctional uterine bleeding (to prevent bleeding) | Menorrhagia (to prevent bleeding)**

- **BY MOUTH**
- **Adult:** 5 mg twice daily, to be taken from day 19 to day 26 of cycle

**Dysmenorrhoea**

- **BY MOUTH**
- **Adult:** 5 mg 3 times a day for 3–4 days to be started 3 days before expected onset (menstruation occurs 2–3 days after stopping)

**Premenstrual syndrome (not recommended)**

- **BY MOUTH**
- **Adult:** 5 mg 2–3 times a day for several cycles, to be taken from day 19–26 of cycle

**Postponement of menstruation**

- **BY MOUTH**
- **Females of childbearing potential:** 5 mg 3 times a day, to be started 3 days before expected onset (menstruation occurs 2–3 days after stopping)

**Breast cancer**

- **BY MOUTH**
- **Adult:** 40 mg daily, increased if necessary to 60 mg daily

**Short-term contraception**

- **BY DEEP INTRAMUSCULAR INJECTION**
- **Females of childbearing potential:** 200 mg, to be administered within first 5 days of cycle or immediately after parturition (duration 8 weeks). To be injected into the gluteal muscle, then 200 mg after 8 weeks if required

**Contraception**

- **BY MOUTH**
- **Females of childbearing potential:** 350 micrograms daily, dose to be taken at same time each day, starting on day 1 of cycle then continuously, if administration delayed for 3 hours or more it should be regarded as a ‘missed pill’
CAUTIONS

GENERAL CAUTIONS
Asthma • cardiac dysfunction • conditions that may worsen with fluid retention • diabetes (progestogens can decrease glucose tolerance—monitor patient closely) • epilepsy • history of depression • hypertension • migraine • susceptibility to thromboembolism (particular caution with high dose)

SPECIFIC CAUTIONS

• When used for contraception Active trophoblastic disease (until return to normal of urine- and plasma-gondotrophin concentration)—seek specialist advice • arterial disease • functional ovarian cysts • history of jaundice in pregnancy • malabsorption syndromes • past ectopic pregnancy • sex-steroid dependent cancer • systemic lupus erythematosus with positive (or unknown) anti-phospholipid antibodies

• With intramuscular use for contraception Disturbances of lipid metabolism • history during pregnancy of deterioration of otoosclerosis • history during pregnancy of pruritus • possible risk of breast cancer

CAUTIONS, FURTHER INFORMATION

• Use as a contraceptive in co-morbidities The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory.

• Breast cancer risk with contraceptive use There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

INTERACTIONS

• With intramuscular use Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. The effectiveness of norethisterone intramuscular injection is not affected by enzyme-inducing drugs and may be continued as normal during courses of these drugs.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
Acne • alopecia • anaphylactoid reactions • breast tenderness • change in libido • depression • disturbance of appetite • dizziness • fluid retention • headache • hirsutism • insomnia (non-contraceptive indications) • jaundice • menstrual disturbances • nausea • premenstrual-like syndrome • pruritus • rash • skin reactions • urticaria • vomiting • weight change

SPECIFIC SIDE-EFFECTS

• With intramuscular use Injection-site reactions

SIDE-EFFECTS, FURTHER INFORMATION

• Cervical cancer Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives (use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years). The risk of cervical cancer with other progestogen-only contraceptives is not yet known.

PREGNANCY

• With oral use Masculinisation of female fetuses and other defects reported with non-contraceptive use.

BREAST FEEDING

Progestogen-only contraceptives do not affect lactation. Higher doses (used in malignant conditions) may suppress lactation and alter milk composition—use lowest effective dose.

• With intramuscular use Withhold breast-feeding for neonates with severe or persistent jaundice requiring medical treatment.

HEPATIC IMPAIRMENT

When used as a contraceptive; caution in severe liver disease and recurrent cholestatic jaundice, avoid in liver tumour. Avoid in non-contraceptive indications.

RENAL IMPAIRMENT

Use with caution in non-contraceptive indications.

PATIENT AND CARER ADVICE

Missed oral contraceptive pill The following advice is recommended: ’If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than three hours overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days.’

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

Diarrhoea and vomiting with oral contraceptives Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

Starting routine for oral contraceptives One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not required if norethisterone is started up to and including day 5 of the menstrual cycle; if started after this time, additional contraceptive precautions are required for 2 days.

Changing from a combined oral contraceptive Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

After childbirth Oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

Contraceptives by injection Full counselling backed by patient information leaflet required before administration—likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

• Norethisterone (Non-proprietary)
  Norethisterone 5 mg Norethisterone 5mg tablets | 30 tablet £2.48 DT price = £2.09

• Micronor (Janssen-Cilag Ltd)
  Micronor 350 microgram Micronor 350 microgram tablets | 84 tablet £1.80 DT price = £1.80
**Progestosterone**

**INDICATIONS AND DOSE**

**CRINONE® VAGINAL GEL**

Infertility due to inadequate luteal phase

- **BY VAGINA**
  - Adult: 1 applicatorful daily, to be started either after documented ovulation or on day 18–21 of cycle, in vitro fertilisation, daily application continued for 30 days after laboratory evidence of pregnancy

**CYCLOGEST® PESSARIES**

Premenstrual syndrome / Post-natal depression

- **BY VAGINA, OR BY RECTUM**
  - Adult: 200–800 mg daily, doses above 200 mg to be given in 2 divided doses, for premenstrual syndrome start on day 12–14 and continue until onset of menstruation (but not recommended); rectally if barrier methods of contraception are used, in patients who have recently given birth or in those who suffer from vaginal infection or recurrent cystitis

**GESTONE® SOLUTION FOR INJECTION**

Dysfunctional uterine bleeding

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 5–10 mg daily for 5–10 days until 2 days before expected onset of menstruation, to be administered into buttocks

Recurrence miscarriage due to inadequate luteal phase (but not recommended) or following in vitro fertilisation or gamete intra-fallopian transfer

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 25–100 mg 2–7 times a week from day 15, or day of embryo or gamete transfer, until 8–16 weeks of pregnancy, to be administered into buttocks; maximum 200 mg per day

**LUBION®**

Supplementation of luteal phase during assisted reproductive technology (ART) treatment in women for whom vaginal preparations are inappropriate

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 25 mg once daily from day of oocyte retrieval up to week 12 of pregnancy

**UTROGESTAN® CAPSULES**

Progestogen opposition of oestrogen HRT

- **BY MOUTH**
  - Adult: 200 mg once daily on days 15–26 of each 28-day oestrogen HRT cycle, alternatively 100 mg once daily on days 1–25 of each 28-day oestrogen HRT cycle

**UTROGESTAN® VAGINAL CAPSULES**

Supplementation of luteal phase during assisted reproductive technology (ART) cycles

- **BY VAGINA**
  - Adult: 1 capsule 3 times a day from day of embryo transfer until at least week 7 of pregnancy up to week 12 of pregnancy

**CONTRA-INDICATIONS**

Acute porphyrias p. 930 - avoid in patients with a history of liver tumours - breast cancer (unless progestogens are being used in the management of this condition) - genital cancer (unless progestogens are being used in the management of this condition) - history during pregnancy of idiopathic jaundice - history during pregnancy of pemphigoid gestations - history during pregnancy of severe pruritus - incomplete miscarriage - missed miscarriage - severe arterial disease - undiagnosed vaginal bleeding

**CAUTIONS**

- Asthma - cardiac dysfunction - conditions that may worsen with fluid retention - diabetes (progestogens can decrease glucose tolerance—monitor patient closely) - epilepsy - history of depression - hypertension - migraine - susceptibility to thromboembolism (particular caution with high dose)

**INTERACTIONS**

- Appendix 1 (progestogens).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**


**SPECIFIC SIDE-EFFECTS**

- With intramuscular use or subcutaneous use - Injection-site reactions
  - With rectal use - Diarrhoea - flatulence - pain
  - With vaginal use - Local irritation

**PREGNANCY**

Not known to be harmful.

**BREAST FEEDING**

Avoid — present in milk.

**HEPATIC IMPAIRMENT**

Avoid in hepatic impairment. Avoid in active liver disease including disorders of hepatic excretion (e.g. Dublin-Johnson or Rotor Syndromes), infective hepatitis (until liver function returns to normal) and liver tumours.

**RENAL IMPAIRMENT**

Use with caution.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use - Capsules should be taken at bedtime on an empty stomach.

**PATIENT AND CARER ADVICE**

- With oral use - Patient counselling is advised for progestosterone capsules (administration).

**LESS SUITABLE FOR PRESCRIBING**

- With vaginal use - Progestosterone pessaries are less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **EXCIPIENTS:** May contain Arachis (peanut) oil
  - **Utrogestan** (Besins Healthcare (UK) Ltd)
    - Progesterone 100 mg Utrogestan 100mg capsules | 30 capsule | £5.13
    - Progesterone 200 mg Utrogestan 200mg capsules with applicators | 21 capsule | £21.00

**Solution for injection**

- **Gestone** (Nordic Pharma Ltd)
  - Gestone 50 mg per 1 ml Gestone 50mg/1ml solution for injection ampoules | 10 ampoule | £45.00
  - Gestone 100mg/2ml solution for injection ampoules | 10 ampoule | £45.00
8.1a Anti-oestrogens

OVULATION STIMULANTS

Clomifene citrate

(Clomiphene citrate)

- **DRUG ACTION** Anti-oestrogen which induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin is sometimes used as an adjunct.

- **INDICATIONS AND DOSE**
  
  Treatment of female infertility due to oligomenorrhoea or secondary amenorrhoea (e.g. associated with polycystic ovarian disease)
  
  - **BY MOUTH**
  - Adult (female): 50 mg daily for 5 days, to be started within about 5 days of onset of menstruation (preferably on 2nd day) or at any time (normally preceded by a progesterogen-induced withdrawal bleed) if cycles have ceased, followed by 100 mg daily if required for a further 5 days, this second course may be given in absence of ovulation; most patients who are going to respond will do so to first course, 3 courses should constitute adequate therapeutic trial; long-term cyclical therapy not recommended.

- **IMPORTANT SAFETY INFORMATION**

  The CSM has recommended that clomifene should not normally be used for longer than 6 cycles (possibly increased risk of ovarian cancer).

- **CONTRA-INDICATIONS** Abnormal uterine bleeding of undetermined cause • hormone-dependent tumours • ovarian cysts

- **CAUTIONS** Ectopic pregnancy • incidence of multiple births increased (consider ultrasound monitoring) • ovarian hyperstimulation syndrome • polycystic ovary syndrome (cysts may enlarge during treatment, also risk of exaggerated response to usual doses) • uterine fibroids

- **SIDE-EFFECTS** Abdominal discomfort • breast tenderness • convulsions • depression • dizziness • endometriosis • hair loss • headache • hot flushes • insomnia • intermenstrual spotting • menorrhagia • nausea • ovarian hyperstimulation (withdraw) • rashes • visual disturbances (withdraw and initiate ophthalmological examination) • vomiting • weight gain

- **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment.

- **PREGNANCY** Possible effects on fetal development.

- **BREAST FEEDING** May inhibit lactation.

- **HEPATIC IMPAIRMENT** Avoid in severe liver disease.

- **PATIENT AND CARER ADVICE**

  Patient advice required around conception and contraception

  Patients planning to conceive should be warned that there is a risk of multiple pregnancy (rarely more than twins).

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - Clomifene citrate (Non-proprietary)
    - Clomifene citrate 50 mg Clomifene 50 mg tablets | 30 tablet
    - £21.74 DT price = £10.15
  - Clomid (Sanofi)
    - Clomifene citrate 50 mg Clomid 50 mg tablets | 30 tablet
    - £10.15 DT price = £10.15

8.2 Male sex hormone responsive conditions

Androgens, anti-androgens and anabolic steroids

**Androgens**

Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids.

Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated. Treatment should be under expert supervision.

When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production.

Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, may be used.

**Anti-androgens**

Cyproterone acetate

Cyproterone acetate p. 704 is an anti-androgen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and produces reversible infertility (but is not a male contraceptive); abnormal sperm forms are produced. Fully informed consent is recommended and an initial spermogram. As hepatic tumours have been produced in animal studies, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also licensed for use alone in patients with metastatic prostate cancer refractory to gonadorelin analogue therapy and has been used as an adjunct in prostatic cancer and in the treatment of acne and hirsutism in women.

Dutasteride and finasteride

Dutasteride p. 720 and finasteride p. 720 are alternatives to alpha-blockers particularly in men with a significantly enlarged prostate. Finasteride is also licensed for use with doxazosin p. 716 in the management of benign prostatic hyperplasia.
A low strength of finasteride is licensed for treating male-pattern baldness in men.

**Anabolic steroids**

Anabolic steroids have some androgenic activity but they cause less virilisation than androgens in women. They are used in the treatment of some aplastic anaemias. Anabolic steroids have been given for osteoporosis in women but they are no longer advocated for this purpose.

The protein-building properties of anabolic steroids have not proved beneficial in the clinical setting. Their use as body builders or tonics is unjustified; some athletes abuse them.

**ANDROGENS**

**Androgens**

- **CONTRA-INDICATIONS** Breast cancer in males; history of liver tumours; hypercalcaemia; prostate cancer
- **CAUTIONS** Cardiac impairment; diabetes mellitus; elderly; epilepsy; hypertension; ischaemic heart disease; migraine; pre-pubertal boys (fusion of epiphyses is hastened and may result in short stature)—satural growth and sexual development should be monitored; skeletal metastases—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored); sleep apnoea; stop treatment or reduce dose if severe polycythaemia occurs—tumours—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored)
- **INTERACTIONS** → Appendix 1 (testosterone).
- **SIDE-EFFECTS**
  - **Common or very common** Acne; androgenic effects (to be assessed regularly in women); anxiety; arthralgia; asthenia; changes in libido; cholestatic jaundice; depression; electrolyte disturbances; excessive duration of penile erection; excessive frequency of penile erection; gastro-intestinal bleeding; gynaecomastia; headache; hirsutism; hypercalcaemia; hypertension; increased bone growth; irritability; male-pattern baldness; muscle cramps; nausea; nervousness; oedema; paraesthesia; polycythaemia—precocious sexual development in pre-pubertal males; premature closure of epiphyses in pre-pubertal males; prostate abnormalities; prostate cancer; pruritus; seborrhoea; sodium retention—suppression of virilism in women; vomiting—weight gain
  - **Rare** Liver tumours
  - **Frequency not known** Sleep apnoea
- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Polycythaemia—Stop treatment or reduce dose if severe polycythaemia occurs.
- **PREGNANCY** Avoid—causes masculinisation of female fetus.
- **BREAST FEEDING** Avoid.
- **HEPATIC IMPAIRMENT** Avoid if possible—fluid retention and dose-related toxicity.
- **RENAL IMPAIRMENT** Caution—potential for fluid retention.
- **MONITORING REQUIREMENTS**
  - Monitor haematocrit and haemoglobin before treatment, every three months for the first year, and yearly thereafter.
  - Monitor prostate and PSA in men over 45 years.
- **PATIENT AND CARER ADVICE**
  - Androgenic effects in women Women should be advised to report any signs of virilisation e.g. deepening of the voice or hirsutism.

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**Mesterolone**

- **INDICATIONS AND DOSE**
  - **Androgen deficiency | Male infertility associated with hypogonadism**
    - **BY MOUTH**
    - Adult: 25 mg 3–4 times a day for several months, then maintenance 50–75 mg daily in divided doses
  - **MEDICINAL FORMS**
    - **Tablet**
      - [Pro-Viron](Bayer Plc) Mesterolone 25 mg
      - Pro-Viron 25mg tablets | 30 tablet [P4M]
      - £4.19

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**Testosterone**

- **INDICATIONS AND DOSE**
  - **TESTIM®**
    - **Hypogonadism due to testosterone deficiency in men**
      - **BY TRANSDERMAL APPLICATION**
      - Adult: Apply 50 mg once daily, subsequent application adjusted according to response; maximum 100 mg per day
      - **DOSE EQUIVALENCE AND CONVERSION**
        - One tube of 5 g contains 50 mg testosterone.
  - **TESTOGEL®**
    - **Hypogonadism due to androgen deficiency in men**
      - **BY TRANSDERMAL APPLICATION**
      - Adult: Apply 50 mg once daily; increased in steps of 25 mg, adjusted according to response; maximum 100 mg per day
      - **DOSE EQUIVALENCE AND CONVERSION**
        - One sachet of 5 g contains 50 mg testosterone.
  - **TOSTRAN®**
    - **Hypogonadism due to testosterone deficiency in men**
      - **BY TRANSDERMAL APPLICATION**
      - Adult: Apply 60 mg once daily, subsequent application adjusted according to response; maximum 80 mg per day
      - **DOSE EQUIVALENCE AND CONVERSION**
        - 1 g of gel contains 20 mg testosterone.
  - **SIDE-EFFECTS** Allergic reactions—local irritation—suppression of spermatogenesis
  - **DIRECTIONS FOR ADMINISTRATION** Avoid skin contact with gel application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature.
  - **TESTOGEL®** Apply thin layer of gel on clean, dry, healthy skin such as shoulders, arms or abdomen, immediately after sachet is opened. Not to be applied on genital area as high alcohol content may cause local irritation. Allow to dry for 3–5 minutes before dressing. Wash hands with soap and water after applying gel, avoid shower or bath for at least 6 hours.
  - **TESTIM®** Squeeze entire content of tube on to one palm and apply as a thin layer on clean, dry, healthy skin of shoulder or upper arm, preferably in the morning after washing or bathing (if 2 tubes required use 1 per shoulder or upper arm); rub in and allow to dry before putting on clothing to cover site; wash hands with soap after application; avoid washing application site for at least 6 hours.
Testosterone propionate

**INDICATIONS AND DOSE**

**Androgen deficiency**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 50 mg 2–3 times a week

**Delayed puberty in males**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 50 mg once weekly

**Breast cancer in women**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 100 mg 2–3 times a week

**SIDE-EFFECTS** Suppression of spermatogenesis

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection.

Testosterone undecanoate

**INDICATIONS AND DOSE**

**Androgen deficiency**

- **BY MOUTH**
  - Adult: 120–160 mg daily for 2–3 weeks; maintenance 40–120 mg daily

**Hypogonadism**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult (male): 1 g every 10–14 weeks, to be given over 2 minutes, if necessary, second dose may be given after 6 weeks to achieve rapid steady state plasma testosterone levels and then every 10–14 weeks.

**SIDE-EFFECTS** Suppression of spermatogenesis

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS** 21, 25

- **Restandol** (Merck Sharp & Dohme Ltd)

**Solution for injection**

- **Nebido** (Bayer Plc)

**Cyproterone acetate**

**INDICATIONS AND DOSE**

**Hyper-sexuality in males | Sexual deviation in males**

- **BY MOUTH**
  - Adult: 50 mg twice daily, to be taken after food

**Prevention of tumour flare with initial gonadorelin analogue therapy**

- **BY MOUTH**
  - Adult (male): 200 mg daily in 2–3 divided doses for 5–7 days before initiation of gonadorelin analogue, followed by 200 mg daily in 2–3 divided doses for...
CONTRA-INDICATIONS In hypersexuality, Dubin-Johnson syndrome - in hypersexuality, history of thromboembolic disorders - in hypersexuality, liver-disease - in hypersexuality, malignant diseases - in hypersexuality, previous or existing liver tumours - in hypersexuality, Rotor syndrome - in hypersexuality, severe depression - in hypersexuality, severe diabetes (with vascular changes) - in hypersexuality, sickle-cell anaemia - in hypersexuality, wasting diseases - meningioma or history of meningioma

SIDE-EFFECTS Diabetes mellitus - in prostate cancer, severe depression - in prostate cancer, sickle-cell anaemia - ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known)

SIDE-EFFECTS, FURTHER INFORMATION

Hepatotoxicity Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (fatalities reported, usually after several months, at dosages of 100 mg and above). If hepatotoxicity is confirmed, cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as metastatic disease (in which case cyproterone should be continued only if the perceived benefit exceeds the risk).

HEPATIC IMPAIRMENT Avoid (unless used for prostate cancer)—dose-related toxicity.

MONITORING REQUIREMENTS

Monitor blood counts initially and throughout treatment.

Monitor adrenocortical function regularly.

Monitor hepatic function regularly—liver function tests should be performed before and regularly during treatment and whenever symptoms suggestive of hepatotoxicity occur.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Fatigue and lassitude may impair performance of skilled tasks (e.g. driving).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 21

Cyproterone acetate (Non-proprietary)

Cyproterone acetate 50 mg Cyproterone 50mg tablets | 56 tablet £48.95 | 168 tablet £87.00 DT price = £87.00
Cyproterone acetate 100 mg Cyproterone 100mg tablets | 84 tablet £112.57 DT price = £55.19

Androcur (Bayer Plc)

Cyproterone acetate 50 mg Androcur 50mg tablets | 56 tablet £29.25
Cyprostat (Bayer Plc)

Cyproterone acetate 50 mg Cyprostat 50mg tablets | 168 tablet £87.00 DT price = £87.00
Cyproterone acetate 100 mg Cyprostat 100mg tablets | 84 tablet £87.00 DT price = £55.19

Hyperthyroidism

Overview

Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term...
management. In the UK carbimazole below is the most commonly used drug. Propylthiouracil p. 707 should be reserved for patients who are intolerant of carbimazole or for those who experience sensitivity reactions to carbimazole (sensitivity is not necessarily displayed to both drugs), and for whom other treatments are inappropriate. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

Over-treatment with antithyroid drugs can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy because it can cause fetal goitre.

A combination of carbimazole with levothyroxine sodium p. 708 daily, may be used in a blocking-replacement regimen; therapy is usually given for 18 months. The blocking-replacement regimen is not suitable during pregnancy.

Iodine has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.

Radioactive sodium iodide (¹³¹I) solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroideectomy.

Propranolol hydrochloride p. 142 is useful for rapid relief of thyrotoxic symptoms and may be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine. Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism.

Propranolol hydrochloride has been used in conjunction with iodine to prepare mildly thyrotoxic patients for surgery but it is preferable to make the patient euthyroid with carbimazole. Laboratory tests of thyroid function are not altered by beta-blockers. Most experience in treating thyrotoxicosis has been gained with propranolol hydrochloride but nadolol p. 141 is also used. Thyrotoxic crisis (‘thyroid storm’) requires emergency treatment with intravenous administration of fluids, propranolol hydrochloride and hydrocortisone p. 620 (as sodium succinate), as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

Pregnancy
Radioactive iodine therapy is contra-indicated during pregnancy. Propylthiouracil and carbimazole can be given but the blocking-replacement regimen is not suitable. Rarely, carbimazole has been associated with congenital defects, including aplasia cutis of the neonate, therefore propylthiouracil remains the drug of choice during the first trimester of pregnancy. In the second trimester, consider switching to carbimazole because of the potential risk of hepatotoxicity with propylthiouracil. Both propylthiouracil and carbimazole cross the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy).

Other drugs used for Hyperthyroidism Metoprolol tartrate, p. 145

### ANTITHYROID DRUGS > SULFUR-CONTAINING IMIDAZOLES

#### Carbimazole

- **INDICATIONS AND DOSE**
  - **Hyperthyroidism**
    - **BY MOUTH**
      - Adult: 15–40 mg daily continue until the patient becomes euthyroid, usually after 4 to 8 weeks, higher doses should be prescribed under specialist supervision only, then reduced to 5–15 mg daily, reduce dose gradually, therapy usually given for 12 to 18 months
    - **Hyperthyroidism (blocking-replacement regimen) in combination with levothyroxine**
      - **BY MOUTH**
        - Adult: 40–60 mg daily, therapy usually given for 18 months
  - **DOSE EQUIVALENCE AND CONVERSION**
    - When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

#### IMPORTANT SAFETY INFORMATION

**NEUTROPENIA AND AGRANULOCYTOSIS**

Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.

- Patient should be asked to report symptoms and signs suggestive of infection, especially sore throat.
- A white blood cell count should be performed if there is any clinical evidence of infection.
- Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

**SIDE-EFFECTS**

- **Common or very common** Arthralgia · fever · headache · jaundice · malaise · mild gastro-intestinal disturbances · nausea · pruritus · rash · taste disturbance
- **Rare** Agranulocytosis · alopecia · bone marrow suppression · jaundice · myopathy · pancytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**

Rashes and pruritus are common with carbimazole but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted.

**PREGNANCY** Carbimazole can be given but the blocking-replacement regimen is not suitable. Rarely, carbimazole has been associated with congenital defects, including aplasia cutis of the neonate. Carbimazole cross the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy).

**BREAST FEEDING** Present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk may be sufficient to affect neonatal thyroid function therefore lowest effective dose should be used.

**HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment.

**PATIENT AND CARER ADVICE** Warn patient or carers to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops.
Antithyroid drugs

Propylthiouracil

Indications and dose

Hyperthyroidism

- **By mouth**
  - Adults: Initially 200–400 mg daily in divided doses until the patient becomes euthyroid, then reduced to 50–150 mg daily in divided doses, initial dose should be gradually reduced to the maintenance dose.

Dose equivalence and conversion

- When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

Side-effects

- Common or very common: Arthralgia, fever, headache, jaundice, leucopenia, malaise, mild gastro-intestinal disturbances, nausea, pruritus, rash, taste disturbance.
- Rare: Agranulocytosis, alopecia, aplastic anaemia, bone marrow suppression, cutaneous vasculitis, encephalopathy, hepatic disorders, hepatic failure, hepatic necrosis, hepatitis, hypoprothrombinaemia, jaundice, lupus erythematosus-like syndromes, myopathy, nephritis, pancytopenia, thrombocytopenia.

Further information

- Hepatotoxicity: Severe hepatic reactions have been reported, including fatal cases and cases requiring liver transplant—discontinue if significant liver-enzyme abnormalities develop.

Pregnancy

Propylthiouracil can be given but the blocking-replacement regimen is not suitable. Propylthiouracil crosses the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy).

Breast feeding

Present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk probably too small to affect infant; high doses may affect neonatal thyroid function.

Monitor infant’s thyroid status.

Hepatic impairment

Reduce dose.

Renal impairment

Use three-quarters normal dose if eGFR 10–50 mL/minute/1.73 m². Use half normal dose if eGFR less than 10 mL/minute/1.73 m².

Monitoring requirements

Monitor for hepatotoxicity.

Patient and carer advice

Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, dark urine, or pruritus develop.

Vitamins and trace elements

Iodide with iodine

Indications and dose

Thyrotoxicosis (pre-operative)

- **By mouth using oral solution**
  - Adult: 0.1–0.3 mL 3 times a day.

Caution


Side-effects

- Bronchitis, conjunctivitis, coryza-like symptoms, depression (on prolonged treatment), goitre in infants of mothers taking iodides, headache, hypersensitivity reactions, impotence (on prolonged treatment), insomnia (on prolonged treatment), lacrimation, laryngitis, pain in salivary glands, rashes.

Pregnancy

Neonatal goitre and hypothyroidism.

Breast feeding

Stop breast-feeding. Danger of neonatal hypothyroidism or goitre. Appears to be concentrated in milk.

Directions for administration

For oral solution, dilute well with milk or water.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Oral solution

- Iodide with iodine (Non-proprietary)
  - Iodine 50 mg per 1 mL, Potassium iodide 100 mg per 1 mL, iodine aqueous oral solution | 500 mL P £9.58

9.2 Hypothyroidism

Thyroid hormones

Overview

Thyroid hormones are used in hypothyroidism (myxoedema), and also in diffuse non-toxic goitre, Hashimoto’s thyroiditis (lymphadenoid goitre), and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development. Levothyroxine sodium p. 708 (thyroxine sodium) is the treatment of choice for maintenance therapy.

In infants and children with congenital hypothyroidism and juvenile myxoedema, the dose of levothyroxine sodium should be titrated according to clinical response, growth assessment, and measurements of plasma thyroxine and thyroid-stimulating hormone.

Liothyronine sodium p. 708 has a similar action to levothyroxine sodium but is more rapidly metabolised and has a more rapid effect. Its effects develop after a few hours and disappear within 24 to 48 hours of discontinuing treatment. It may be used in severe hypothyroid states when a rapid response is desired.

Liothyronine sodium by intravenous injection is the treatment of choice in hypothyroid coma. Adjunctive therapy includes intravenous fluids, hydrocortisone p. 620, and treatment of infection; assisted ventilation is often required.
THYROID HORMONES

Levothyroxine sodium
(Thyroxine sodium)

● INDICATIONS AND DOSE

Hypothyroidism
▶ BY MOUTH
  ▶ Adult 18–49 years: Initially 50–100 micrograms once daily; adjusted in steps of 25–50 micrograms every 3–4 weeks, adjusted according to response; maintenance 100–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication
  ▶ Adult 50 years and over: Initially 25 micrograms once daily; adjusted in steps of 25 micrograms every 4 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication

Hypothyroidism in patients with cardiac disease | Severe hypothyroidism
▶ BY MOUTH
  ▶ Adult: Initially 25 micrograms once daily; adjusted in steps of 25 micrograms every 4 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication

Hyperthyroidism (blocking-replacement regimen) in combination with carbimazole
▶ BY MOUTH
  ▶ Adult: 50–150 micrograms daily therapy usually given for 18 months

● CONTRA-INDICATIONS
Thyrotoxicosis

● CAUTIONS
Cardiovascular disorders • diabetes insipidus • diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased) • elderly • hypertension • long-standing hypothyroidism • myocardial infarction • myocardial insufficiency • panhypopituitarism (initiate corticosteroid therapy before starting levothyroxine) • predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting levothyroxine)

CAUTIONS, FURTHER INFORMATION
Cardiovascular disorders Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia.

● INTERACTIONS → Appendix 1 (thryroid hormones).

● SIDE-EFFECTS
Anginal pain (usually at excessive dosage) • arrhythmias (usually at excessive dosage) • diarrhoea (usually at excessive dosage) • excitability (usually at excessive dosage) • fever • flushing • headache • heat intolerance • hypersensitivity reactions • insomnia (usually at excessive dosage) • muscle cramp • muscular weakness • oedema • palpitation (usually at excessive dosage) • pruritus • rash • restlessness (usually at excessive dosage) • sweating • tachycardia (usually at excessive dosage) • transient hair loss in children • tremor (usually at excessive dosage) • vomiting (usually at excessive dosage) • weight loss

SIDE-EFFECTS, FURTHER INFORMATION
Initial dosage in patients with cardiovascular disorders. If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose.

● PREGNANCY
Levothyroxine requirement may increase during pregnancy. Levothyroxine may cross the placenta. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus.
Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of levothyroxine).

● BREAST FEEDING
Amount too small to affect tests for neonatal hypothyroidism.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Tablet
▶ Levothyroxine sodium (Non-proprietary)
Levothyroxine sodium anhydrous 12.5 microgram | 28 tablet P<sub>om</sub> £15.00
Levothyroxine sodium anhydrous 25 microgram | 28 tablet P<sub>om</sub> £16.65
Levothyroxine sodium anhydrous 50 microgram | 100 tablet P<sub>om</sub> no price available
Levothyroxine sodium anhydrous 100 microgram | 100 tablet P<sub>om</sub> no price available
Levothyroxine sodium anhydrous 100 microgram lactose free | 100 tablet P<sub>om</sub> £48.95
Levothyroxine sodium anhydrous 100 microgram tablets lactose free | 100 tablet P<sub>om</sub> £56.21
Levothyroxine sodium anhydrous 75 microgram | 28 tablet P<sub>om</sub> £10.77 DT price = £1.65
Levothyroxine sodium anhydrous 50 microgram | 100 tablet P<sub>om</sub> £22.12
Levothyroxine sodium anhydrous 25 microgram | 100 tablet P<sub>om</sub> £46.39
Levothyroxine sodium anhydrous 12.5 microgram | 100 tablet P<sub>om</sub> £67.86

▶ Eltroxin (AMCo)
Eltroxin 25microgram tablets | 28 tablet P<sub>om</sub> £2.54 DT price = £2.85
Eltroxin 50microgram tablets | 28 tablet P<sub>om</sub> £4.77 DT price = £1.65
Eltroxin 75microgram tablets | 28 tablet P<sub>om</sub> £5.48

▶ Tirosint
Levothyroxine sodium anhydrous 5 microgram | 100 capsule P<sub>om</sub> £26.95
Levothyroxine sodium anhydrous 10 microgram | 100 capsule P<sub>om</sub> £45.00
Levothyroxine sodium anhydrous 20 microgram | 100 capsule P<sub>om</sub> £65.45

Levothyroxine sodium anhydrous 25 microgram | 100 capsule P<sub>om</sub> £85.74

DT price = £1.65

Levothyroxine sodium anhydrous 50 microgram | 100 capsule P<sub>om</sub> £19.52
Levothyroxine sodium anhydrous 75 microgram | 100 capsule P<sub>om</sub> £28.62
Levothyroxine sodium anhydrous 100 microgram | 100 capsule P<sub>om</sub> £42.02

Capsule
▶ Levothyroxine sodium (Non-proprietary)
Levothyroxine sodium anhydrous 25 microgram Tirosint 25microgram capsules | 28 capsule P<sub>om</sub> no price available
Levothyroxine sodium anhydrous 50 microgram Tirosint 50microgram capsules | 28 capsule P<sub>om</sub> no price available
Levothyroxine sodium anhydrous 100 microgram Tirosint 100microgram capsules | 28 capsule P<sub>om</sub> no price available

Oral solution
▶ Levothyroxine sodium (Non-proprietary)
Levothyroxine sodium anhydrous 5 microgram per 1 ml Levothyroxine sodium 5micrograms/5ml oral solution sugar free sugar-free | 100 ml P<sub>om</sub> £95.00 DT price = £94.26
Levothyroxine sodium anhydrous 10 microgram per 1 ml Levothyroxine sodium 10micrograms/5ml oral solution sugar free sugar-free | 100 ml P<sub>om</sub> £97.52 DT price = £95.81
Levothyroxine sodium anhydrous 20 microgram per 1 ml Levothyroxine sodium 20micrograms/5ml oral solution sugar free sugar-free | 100 ml P<sub>om</sub> £165.00 DT price = £162.45

Liothyronine sodium
(L-Tri-iodothyronine sodium)

● INDICATIONS AND DOSE

Hypothyroidism
▶ BY MOUTH
  ▶ Adult: Initially 10–20 micrograms daily; increased to 60 micrograms daily in 2–3 divided doses, dose should
be increased gradually, smaller initial doses given for the elderly

**Hypothyroid coma**
- **BY SLOW INTRAVENOUS INJECTION**
- Adult: 5–20 micrograms every 12 hours, increased to 5–20 micrograms every 4 hours if required, alternatively initially 50 micrograms for 1 dose, then 25 micrograms every 8 hours, reduced to 25 micrograms twice daily

**DOSE EQUIVALENC E AND CONVERSION**
- 20–25 micrograms of liothyronine sodium is equivalent to approximately 100 micrograms of levothyroxine sodium.
- Brands without a UK licence may not be bioequivalent and dose adjustment may be necessary.

**CONTRA-INDICATIONS** Thyrotoxicosis

**CAUTIONS** Cardiovascular disorders · diabetes insipidus · diabetes mellitus (dose of anti-diabetic drugs including insulin may need to be increased) · elderly · hypertension · long-standing hypothyroidism · myocardial infarction · myocardial insufficiency · panhypopituitarism (initiate corticosteroid therapy before starting liothyronine) · predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting liothyronine)

**CAUTIONS, FURTHER INFORMATION**
- Cardiovascular disorders  Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia.

**INTERACTIONS**  → Appendix 1 (thyroid hormones).

**SIDE-EFFECTS** Anginal pain (usually at excessive dosage) · arrhythmias (usually at excessive dosage) · diarrhoea (usually at excessive dosage) · excitability (usually at excessive dosage) · fever · flushing · headache · heat intolerance · hypersensitivity reactions · insomnia (usually at excessive dosage) · muscle cramp · muscular weakness · oedema · palpitation (usually at excessive dosage) · pruritus · rash · restlessness (usually at excessive dosage) · sweating · tachycardia (usually at excessive dosage) · tremor (usually at excessive dosage) · vomiting (usually at excessive dosage) · weight-loss

**SIDE-EFFECTS, FURTHER INFORMATION**
- Initial dosage in patients with cardiovascular disorders  If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose.

**PREGNANCY**  Liothyronine requirement may increase during pregnancy. Does not cross the placenta in significant amounts. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus.
- Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of liothyronine).

**BREAST FEEDING**  Amount too small to affect tests for neonatal hypothyroidism.

**PRESCRIBING AND DISPENSING INFORMATION**
- Patients switched to a different brand should be monitored (particularly if pregnant or if heart disease present) as brands without a UK licence may not be bioequivalent.
- Pregnant women or those with heart disease should undergo an early review of thyroid status, and other patients should have thyroid function assessed if experiencing a significant change in symptoms. If liothyronine is continued long-term, thyroid function tests should be repeated 1–2 months after any change in brand.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, solution for injection

**Tablet**
- Liothyronine sodium (Non-proprietary)
  - Liothyronine sodium 5 microgram  Cytomel 5microgram tablets | 100 tablet (POM) no price available
  - Liothyronine sodium 20 microgram  Liothyronine 20microgram tablets | 28 tablet (POM) £258.20 DT price = £258.20
  - Liothyronine sodium 25 microgram  Cytomel 25microgram tablets | 100 tablet (POM) no price available

**Powder for solution for injection**
- Liothyronine sodium (Non-proprietary)
  - Liothyronine sodium 20 microgram  Liothyronine 20microgram powder for solution for injection vials | 5 vial (POM) £1,425.00
Chapter 7  Genito-urinary system

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Urinary frequency, enuresis and incontinence

Urinary frequency and incontinence

Incontinence in adults which arises from detrusor instability is managed by combining drug therapy with conservative methods for managing urge incontinence such as pelvic floor exercises and bladder training; stress incontinence is generally managed by non-drug methods. Duloxetine p. 345 can be added and is licensed for the treatment of moderate to severe stress incontinence in women; it may be more effective when used as an adjunct to pelvic floor exercises.

Antimuscarinic drugs reduce symptoms of urgency and urge incontinence and increase bladder capacity. Oxybutynin hydrochloride p. 712 also has a direct relaxant effect on urinary smooth muscle. Side-effects limit the use of oxybutynin hydrochloride, but they may be reduced by starting at a lower dose. A modified-release preparation of oxybutynin hydrochloride is effective and has fewer side-effects; a transdermal patch is also available. The efficacy and side-effects of tolterodine tartrate p. 714 are comparable to those of modified-release oxybutynin hydrochloride.

Flavoxate hydrochloride p. 712 has less marked side-effects but it is also less effective. Darifenacin p. 711, fesoterodine fumarate p. 711, propiverine hydrochloride p. 714, solifenacin succinate p. 713, and trosiptium chloride p. 713 are newer antimuscarinic drugs licensed for urinary frequency, urgency, and incontinence. The need for continuing antimuscarinic drug therapy should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

Propantheline bromide p. 81 and tricyclic antidepressants were used for urge incontinence but they are little used now because of their side-effects. The use of imipramine hydrochloride p. 353 is limited by its potential to cause cardiac side-effects.

Mirabegron p. 715, a selective beta3 agonist, is licensed for the treatment of urinary frequency, urgency, and urge incontinence associated with overactive bladder syndrome.

Purified bovine collagen implant (Contigen®, Bard) is indicated for urinary incontinence caused by intrinsic sphincter deficiency (poor or non-functioning bladder outlet mechanism). The implant should be inserted only by surgeons or physicians trained in the technique for injection of the implant.

Nocturnal enuresis in children

Nocturnal enuresis is common in young children, but persists in a small proportion by 10 years of age. For children under 5 years, reassurance and advice on the management of nocturnal enuresis can be useful for some families. Treatment may be considered in children over 5 years depending on their maturity and motivation, the frequency of nocturnal enuresis, and the needs of the child and their family.

Initially, advice should be given on fluid intake, diet, toileting behaviour, and reward systems; for children who do not respond to this advice, further treatment may be necessary. An enuresis alarm should be first line treatment for motivated, well-supported children; alarms have a lower relapse rate than drug treatment when discontinued. Treatment should be reviewed after 4 weeks, and, if there are early signs of response, continued until a minimum of 2 weeks’ uninterrupted dry nights have been achieved. If complete dryness is not achieved after 3 months, only continue if the condition is still improving and the child remains motivated to use the alarm. If initial alarm treatment is unsuccessful, consider combination treatment with desmopressin p. 611, or desmopressin alone if the alarm is no longer appropriate or desirable.

Desmopressin is given by oral or by sublingual administration. Desmopressin alone can be offered to children over 5 years of age if an alarm is inappropriate or undesirable, or when rapid or short-term results are the
Antimuscarinics (systemic)

- **CONTRA-INDICATIONS** Gastro-intestinal obstruction - intestinal atony - myasthenia gravis (but some antimuscarinics may be used to decrease muscarinic side-effects of anticholinesterases) - paralytic ileus - prostatic enlargement (in adults) - pyloric stenosis - severe ulcerative colitis - significant bladder outflow obstruction - toxic megacolon - urinary retention

- **CAUTIONS** Acute myocardial infarction (in adults) - arrhythmias (may be worsened) - autonomic neuropathy - cardiac insufficiency (due to association with tachycardia) - cardiac surgery (due to association with tachycardia) - children (increased risk of side-effects) - conditions characterised by tachycardia - congestive heart failure (may be worsened) - coronary artery disease (may be worsened) - diaphoresis - elderly (especially if frail) - gastro-oesophageal reflux disease - hiatus hernia with reflux oesophagitis - hypertension - hyperthyroidism (due to association with tachycardia) - individuals susceptible to angle-closure glaucoma - prostatic hyperplasia (in adults) - pyrexia - ulcerative colitis

- **INTERACTIONS**

  Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation. Concomitant use of other drugs with antimuscarinic effects can also lead to confusion in the elderly.

- **SIDE-EFFECTS**

  - **Common or very common** Constipation - dilation of pupils with loss of accommodation - dry mouth - photophobia - reduced bronchial secretions - skin dryness - skin flushing - transient bradycardia (followed by tachycardia, palpitation and arrhythmias) - urinary retention - urinary urgency

  - **Uncommon** Confusion (particularly in the elderly) - dizziness - dryness - euphoria - fatigue - flatulence - hallucinations - headache - impaired memory - palpitation - photosensitivity - rash - reduced sweating (may lead to heat sensations and fainting in hot environments or patients with fever) - restlessness - taste disturbances

  - **Very rare** Angle-closure glaucoma


- **SIDE-EFFECTS**

  - **Common or very common** Insomnia

  - **Uncommon** Cough - nasal dryness - pharyngolaryngeal pain - vertigo

- **PREGNANCY** Manufacturer advises avoid — toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid — no information available.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Antimuscarinics can affect the performance of skilled tasks (e.g. driving).

**ANTIMUSCARINICS > URINARY**

### Darifenacin

- **INDICATIONS AND DOSE**

  **Urinary frequency / Urinary urgency / Incontinence**

  - **BY MOUTH**

    - **Adult:** Initially 7.5 mg once daily, increased if necessary to 15 mg after 2 weeks

  - **SIDE-EFFECTS**

    - **Uncommon**

      - Cough - dyspnoea - hypertension - impotence - insomnia - oedema - rhinitis - ulcerative stomatitis - vaginitis - weakness

  - **PREGNANCY** Manufacturer advises avoid — toxicity in animal studies.

### Fesoterodine fumarate

- **INDICATIONS AND DOSE**

  **Urinary frequency / Urinary urgency / Urge incontinence**

  - **BY MOUTH**

    - **Adult:** 4 mg once daily, increased if necessary up to 8 mg once daily

  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**

    Max. 4 mg daily with concomitant atazanavir, clarithromycin, indinavir, itraconazole, ritonavir, saquinavir, or telithromycin.

    In patients with hepatic or renal impairment, consult product literature before concomitant use with amnprevir, aprepitant, atazanavir, clarithromycin, diltiazem, erythromycin, fluconazole, fosamprenavir, indinavir, itraconazole, ritonavir, saquinavir, telithromycin, verapamil, or grapefruit juice.

  - **SIDE-EFFECTS**

    - **Common or very common**

      - Insomnia

    - **Uncommon**

      - Cough - nasal dryness - pharyngolaryngeal pain - vertigo
Oxybutynin hydrochloride

**INDICATIONS AND DOSE**

Urinary frequency | Urinary urgency | Urinary incontinence

- Neurogenic bladder instability
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Child 5–11 years: Initially 2.5–3 mg twice daily, increased to 5 mg 2–3 times a day
    - Child 12–17 years: Initially 5 mg 2–3 times a day, increased if necessary up to 5 mg 4 times a day
    - Adult: Initially 5 mg 2–3 times a day, increased if necessary up to 5 mg 4 times a day
    - Elderly: Initially 2.5–3 mg twice daily, increased if tolerated to 5 mg twice daily, adjusted according to response
  - **BY MOUTH USING MODIFIED-RELEASE TABLETS**
    - Child 5–17 years: Initially 5 mg once daily, adjusted in steps of 5 mg every week, adjusted according to response; maximum 15 mg per day
    - Adult: Initially 5 mg once daily, increased in steps of 5 mg every week, adjusted according to response; maximum 20 mg per day

Urinary frequency | Urinary urgency | Urinary incontinence

- **BY TRANSDERMAL APPLICATION USING PATCHES**
  - Adult: Apply 1 patch twice weekly, patch is to be applied to clean, dry, unbroken skin on abdomen, hip or buttock. Patch should be removed every 3–4 days and site replacement patch on a different area. The same area should be avoided for 7 days

Nocturnal enuresis associated with overactive bladder

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 5–17 years: 2.5–3 mg twice daily, increased to 5 mg 2–3 times a day, last dose to be taken before bedtime
  - **BY MOUTH USING MODIFIED-RELEASE TABLETS**
    - Child 5–17 years: Initially 5 mg once daily, adjusted in steps of 5 mg every week, adjusted according to response; maximum 15 mg per day

DOSE EQUIVALENCE AND CONVERSION

- Patients taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of Lyrinel® XL

**UNLICENSED USE** Not licensed for use in children under 5 years.

**CAUTIONS** Acute porphyrias p. 930

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Uncommon Anorexia · Facial flushing
- Rare Night terrors
- Frequency not known Cognitive impairment (in adults)

**SPECIFIC SIDE-EFFECTS**

- Rare
  - With transdermal use Application site reactions with patches
- **PREGNANCY** Manufacturers advise avoid unless essential—toxicity in animal studies.
- **BREAST FEEDING** Manufacturers advise avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution.
- **RENAL IMPAIRMENT** Manufacturer advises caution.

**DIRECTIONS FOR ADMINISTRATION**

- With transdermal use Apply patches to clean, dry, unbroken skin on abdomen, hip or buttock, remove after every 3–4 days and site replacement patch on a different area (avoid using same area for 7 days).
DOSE ADJUSTMENTS DUE TO INTERACTIONS
Max. 5 mg daily with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole, ketoconazole, omeprazole, or ritonavir).

CONTRA-INDICATIONS
- Narrow-angle glaucoma

CAUTIONS
- Neurogenic bladder disorder – susceptibility to QT-interval prolongation

SIDE-EFFECTS
- Uncommon Gastro-oesophageal reflux – oedema
- Frequency not known Dysphonia – hepatic impairment – hyperkalaemia – muscle weakness – reduced appetite – tachycardia

PREGNANCY
Manufacturer advises caution—no information available.

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Max. 5 mg daily in moderate impairment. Avoid in moderate impairment in those already taking potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole, ketoconazole or ritonavir).

RENAI IMPAIRMENT
Max. 5 mg daily if eGFR less than 30 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m² in those already taking potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole, ketoconazole or ritonavir).

PRESCRIBING AND DISPENSING INFORMATION
The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 3
- Oxybutynin hydrochloride (Non-proprietary)
  - Oxybutynin hydrochloride 2.5 mg Oxybutynin 2.5mg tablets | 56 tablet (£5.58 DT price = £1.25 | 84 tablet (£7.71
  - Oxybutynin hydrochloride 3 mg Oxybutynin 3mg tablets | 56 tablet (£6.80 DT price = £6.80
  - Oxybutynin hydrochloride 5 mg Oxybutynin 5mg tablets | 56 tablet (£13.85 DT price = £1.70 | 84 tablet (£20.77
- Cystrin (Zentiva)
  - Oxybutynin hydrochloride 5 mg Cystrin 5mg tablets | 84 tablet (£21.99
- Ditropan (Sanofi)
  - Oxybutynin hydrochloride 2.5 mg Ditropan 2.5mg tablets | 84 tablet (£1.60
  - Oxybutynin hydrochloride 5 mg Ditropan 5mg tablets | 84 tablet (£2.90
Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 3, 25
- Lyrinel XL (Janssen-Cilag Ltd)
  - Oxybutynin hydrochloride 5 mg Lyrinel XL 5mg tablets | 30 tablet (£13.77 DT price = £13.77
  - Oxybutynin hydrochloride 10 mg Lyrinel XL 10mg tablets | 30 tablet (£27.54 DT price = £27.54
Oral solution
CAUTIONARY AND ADVISORY LABELS 3
- Oxybutynin hydrochloride 500 microgram per 1 ml Oxybutynin 2.5mg/5ml oral solution sugar free sugar-free | 150 ml (POM £144.50 DT price = £144.50
- Oxybutynin hydrochloride 1 mg per 1 ml Oxybutynin 5mg/5ml oral solution sugar free sugar-free | 150 ml (POM £199.20 DT price = £199.20
Transdermal patch
CAUTIONARY AND ADVISORY LABELS 3
- Kentera (Orion Pharma (UK) Ltd)
  - Oxybutynin 3.9 mg per 24 hour Kentera 3.9mg/24hours patches | 8 patch (£27.20 DT price = £27.20

Solifenacin succinate

INDICATIONS AND DOSE
Urinary frequency | Urinary urgency | Urinary incontinence
- BY MOUTH
  - Adult: 5 mg once daily, increased if necessary to 10 mg once daily

Trosprim chloride

INDICATIONS AND DOSE
Urinary frequency | Urinary urgency | Urinary incontinence
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: 20 mg twice daily, to be taken before food
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 60 mg once daily

SIDE-EFFECTS
- Rare Asthenia - chest pain - dyspnoea
- Very rare Arthralgia - myalgia

PREGNANCY
Manufacturer advises caution.

BREAST FEEDING
Manufacturer advises caution.

HEPATIC IMPAIRMENT
Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

RENAI IMPAIRMENT
Reduce dose to 20 mg once daily or 20 mg on alternate days if eGFR 10–30 mL/minute/1.73m². Use with caution. Avoid Regurin® XL.

PRESCRIBING AND DISPENSING INFORMATION
The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 3
- Solifenacin succinate 5 mg Vesicare 5mg tablets | 30 tablet (£27.62 DT price = £27.62
- Solifenacin succinate 10 mg Vesicare 10mg tablets | 30 tablet (£55.91 DT price = £55.91

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2005) that Kentera® should be restricted for use in patients who benefit from oral oxybutynin but cannot tolerate its side-effects.

CAUTIONARY AND ADVISORY LABELS
- Very rare
- Rare

RENAL IMPAIRMENT
Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

HEPATIC IMPAIRMENT
Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

BREAST FEEDING
Manufacturer advises caution—present in milk in animal studies.
Propiverine hydrochloride

**INDICATIONS AND DOSE**

Urinary frequency, urgency and incontinence associated with overactive bladder

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 15 mg 1–2 times a day, increased if necessary up to 15 mg 3 times a day
  - **BY MOUTH USING MODIFIED-RELEASE CAPSULES**
  - Adult: 30 mg once daily

Urinary frequency, urgency and incontinence associated with neurogenic bladder instability

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 15 mg 3 times a day

**PREGNANCY**
Manufacturer advises avoid (restriction of skeletal development in animals).

**BREAST FEEDING**
Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Avoid in moderate to severe impairment.

**RENAL IMPAIRMENT**
Max. daily dose 30 mg if eGFR less than 30 mL/minute/1.73m². Manufacturer advises caution in mild or moderate impairment.

**PRESCRIBING AND DISPENSING INFORMATION**
The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Detrusitol**
  - **AMCo**
  - **Propiverine hydrochloride 15 mg** Detrusitnorm 15mg tablets | 56 tablet £18.00 DT price = £18.00

**Modified-release capsule**

- **AMCo**
  - **Propiverine hydrochloride 30 mg** Detrusitnorm XL 30mg capsules | 28 capsule £24.45 DT price = £24.45
  - **Propiverine hydrochloride 45 mg** Detrusitnorm XL 45mg capsules | 28 capsule £27.00 DT price = £27.00

**Tolterodine tartrate**

**INDICATIONS AND DOSE**

Urinary frequency | Urinary urgency | Urinary incontinence

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 2 mg twice daily, reduced if not tolerated to 1 mg twice daily
  - **BY MOUTH USING MODIFIED-RELEASE CAPSULES**
  - Adult: 4 mg once daily

**DOSE EQUIVALENCE AND CONVERSION**
Children stabilised on immediate-release tolterodine tartrate 2 mg twice daily may be transferred to modified-release tolterodine tartrate 4 mg once daily.

**CAUTIONS**
History of QT-interval prolongation

**INTERACTIONS**
Caution with concomitant use with other drugs known to prolong QT interval.

**SIDE-EFFECTS**
- Common or very common: Bronchitis, chest pain, fatigue, paraesthesia, peripheral oedema, sinusitis, vertigo, weight gain
- Uncommon: Memory impairment
- Frequency not known: Flushing

**PREGNANCY**
Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**
Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
Reduce dose to 1 mg twice daily. Avoid modified-release preparations.

**RENAL IMPAIRMENT**
Reduce dose to 1 mg twice daily if eGFR less than 30 mL/minute/1.73m². Avoid modified-release preparations if eGFR less than 30 mL/minute/1.73m².

**PRESCRIBING AND DISPENSING INFORMATION**
The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Tolterodine tartrate (Non-proprietary)**
  - **Tolterodine tartrate 1 mg** Tolterodine 1mg tablets | 56 tablet £25.03 DT price = £1.91
  - **Tolterodine tartrate 2 mg** Tolterodine 2mg tablets | 56 tablet £30.56 DT price = £2.08
  - **Detrusitol** (Pfizer Ltd)
    - **Tolterodine tartrate 1 mg** Detrusitol 1mg tablets | 56 tablet £29.03 DT price = £1.91
    - **Tolterodine tartrate 2 mg** Detrusitol 2mg tablets | 56 tablet £30.56 DT price = £2.08

**Modified-release capsule**

- **Tolterodine tartrate 2 mg** Tolterodine 2mg modified-release capsules | 28 capsule £25.78 DT price = £25.78
  - **Blerone XL (2entiva)**
  - **Efflosomy XL (Mylan Ltd)**
  - **Inconex XL (Sandor Ltd)**
BETA3-ADRENOCEPTOR AGONISTS

Mirabegron

INDICATIONS AND DOSE
Urinary frequency, urgency, and urge incontinence

- Adult: 50 mg once daily

CONTRA-INDICATIONS
Severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg)

CAUTIONS
History of QT-interval prolongation - stage 2 hypertension

INTERACTIONS
Appendix 1 (mirabegron). Caution with concomitant use with drugs that prolong the QT interval.

Hepatic impairment
With concomitant use of strong cytochrome P450 inhibitors such as itraconazole, ketocazole, ritonavir, or clarithromycin reduce dose to 25 mg once daily in mild impairment, and avoid in moderate impairment.

Renal impairment
With concomitant use of strong cytochrome P450 inhibitors such as itraconazole, ketocazole, ritonavir, or clarithromycin reduce dose to 25 mg once daily if eGFR 30–89 mL/minute/1.73 m², and avoid if eGFR less than 30 mL/minute/1.73 m².

SIDE-EFFECTS
- Common or very common Tachycardia - urinary-tract infection
- Uncommon Atrial fibrillation - dyspepsia - gastritis - hypertension - joint swelling - palpitation - pruritus - rash - vulvovaginal infection - vulvovaginal pruritus

CONCEPTION AND CONTRACEPTION
Contraception advised in women of child-bearing potential.

PREGNANCY
Avoid - toxicity in animal studies.

BREAST FEEDING
Avoid - present in milk in animal studies.

HEPATIC IMPAIRMENT
Reduce dose to 25 mg once daily in moderate impairment. Avoid in severe impairment - no information available.

RENAL IMPAIRMENT
Reduce dose to 25 mg once daily if eGFR 15–29 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m²—no information available.

MONITORING REQUIREMENTS
Blood pressure should be monitored before starting treatment and regularly during treatment, especially in patients with pre-existing hypertension.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (Tes)

- Mirabegron for treating symptoms of overactive bladder (June 2013) NICE TA290

Mirabegron is recommended as an option only for patients in whom antimuscarinic drugs are ineffective, contra-indicated, or not tolerated; patients currently receiving mirabegron who do not meet these criteria should have the option to continue until they and their clinician consider it appropriate to stop.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS

- Mirabegron 25 mg Betmiga (Astellas Pharma Ltd)

- Mirabegron 50 mg Betmiga 50mg modified-release tablets | 30 tablet (POM) £29.00 DT price = £29.00

1.2 Urinary retention

Drugs for urinary retention

Overview
Acute retention is painful and is treated by catheterisation. Chronic retention is painless and often long-standing. Catheterisation is unnecessary unless there is deterioration of renal function. After the cause has initially been established and treated, drugs may be required to increase detrusor muscle tone.

Benign prostatic hyperplasia is treated either surgically or medically with alpha-blockers. Dutasteride p. 720 and finasteride p. 720 are alternatives to alpha-blockers, particularly in men with a significantly enlarged prostate. Tadalafil p. 746, a phosphodiesterase type-5 inhibitor, may also be used in the management of benign prostatic hyperplasia.

Alpha-blockers

Parasympathomimetics
The parasympathomimetic bethanechol chloride p. 720 increases detrusor muscle contraction. However, it has only a limited role in the relief of urinary retention; its use has been superseded by catheterisation.

ALPHA-ADRENOCEPTOR BLOCKERS

Alfuzosin hydrochloride

INDICATIONS AND DOSE

Benign prostatic hyperplasia

- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: 2.5 mg 3 times a day; maximum 10 mg per day

- Elderly: Initially 2.5 mg twice daily, adjusted according to response; maximum 10 mg per day

- BY MOUTH USING MODIFIED-RELEASE MEDICINES

- Adult: 10 mg once daily

Acute urinary retention associated with benign prostatic hyperplasia

- BY MOUTH USING MODIFIED-RELEASE TABLETS

- Elderly: 10 mg once daily for 2–3 days during catheterisation and for one day after removal; max. 4 days
### Doxazosin

#### INDICATIONS AND DOSE

**Hypertension**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 1 mg once daily for 1–2 weeks, then increased to 2 mg once daily, then increased if necessary to 4 mg once daily; maximum 16 mg per day
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 4 mg once daily, dose can be adjusted after 4 weeks, then increased if necessary to 8 mg once daily

**Benign prostatic hyperplasia**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 1 mg daily, dose may be doubled at intervals of 1–2 weeks according to response; usual maintenance 2–4 mg daily; maximum 8 mg per day
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 4 mg once daily, dose can be adjusted after 4 weeks, then increased if necessary to 8 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required.

**DOSE EQUIVALENCE AND CONVERSION**
- Patients stabilised on immediate-release doxazosin can be transferred to the equivalent dose of modified-release doxazosin.

#### CONTRA-INDICATIONS
- History of micturition syncope (in patients with benign prostatic hypertrophy)• history of postural hypotension • monotherapy in patients with overflow bladder or anuria

#### CAUTIONS
- Care with initial dose (postural hypotension) • cataract surgery (risk of intra-operative floppy iris syndrome) • elderly • heart failure • pulmonary oedema due to aortic or mitral stenosis

#### INTERACTIONS
- **Appendix 1 (alpha-blockers).**

#### SIDE-EFFECTS
- **Very rare**
  - Angioedema • ashenha • blurred vision • depression • dizziness • drowsiness • dry mouth • erectile disorders • gastro-intestinal disturbances • headache • hypersensitivity • hypotension • intra-operative floppy iris syndrome • liver damage • oedema • palpitations • pruritus • rash • rhinitis • syncope • tachycardia

### Medicinal forms

#### There may be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**
- Alfuzosin hydrochloride (Non-proprietary)
- Alfuzosin hydrochloride 2.5 mg Alfuzosin 2.5 mg tablets | 60 tablet | £21.20 DT price = £2.40
- Xatral (Sanofi)
- Alfuzosin hydrochloride 2.5 mg Xatral 2.5 mg tablets | 60 tablet | £20.37 DT price = £2.40

**Modified-release tablet**

#### CAUTIONARY AND ADVISORY LABELS 21, 25
- Alfuzosin hydrochloride (Non-proprietary)
- Alfuzosin hydrochloride 10 mg Alfuzosin 10 mg modified-release tablets | 30 tablet | no price available DT price = £12.51
- Besavar XL (Zentiva)
- Alfuzosin hydrochloride 10 mg Besavar XL 10 mg tablets | 30 tablet | £12.51 DT price = £12.51
- Fuzatal XL (Teva UK Ltd)
- Alfuzosin hydrochloride 10 mg Fuzatal XL 10 mg tablets | 30 tablet | £12.76 DT price = £12.51
- Vasran XL (Ranbaxy (UK) Ltd)
- Alfuzosin hydrochloride 10 mg Vasran XL 10 mg tablets | 30 tablet | £11.48 DT price = £12.51
- Xatral XL (Sanofi)
- Alfuzosin hydrochloride 10 mg Xatral XL 10 mg tablets | 10 tablet | £14.17 | 30 tablet | £12.51 DT price = £12.51

**Driving and skilled tasks**
- May affect performance of skilled tasks e.g. driving.

**Hisoria of micturition syncope in patients of benign prostatic hypertrophy • history of postural hypotension • monotherapy in patients of overflow bladder or anuria

#### CAUTIONS
- Care with initial dose (postural hypotension) • cataract surgery (risk of intra-operative floppy iris syndrome) • elderly • heart failure • pulmonary oedema due to aortic or mitral stenosis

#### INTERACTIONS
- **Appendix 1 (alpha-blockers).**

#### SIDE-EFFECTS
- **Very rare**
  - Angioedema • ashenha • blurred vision • depression • dizziness • drowsiness • dry mouth • erectile disorders • gastro-intestinal disturbances • headache • hypersensitivity • hypotension • intra-operative floppy iris syndrome • liver damage • oedema • palpitations • pruritus • rash • rhinitis • syncope • tachycardia

#### Frequency not known
- Angioedema • ashenha • blurred vision • depression • dizziness • drowsiness • dry mouth • erectile disorders • gastro-intestinal disturbances • headache • hypersensitivity • hypotension • intra-operative floppy iris syndrome • liver damage • oedema • palpitations • pruritus • rash • rhinitis • syncope • tachycardia

#### Pregnancy
- No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

#### Breast feeding
- Accumulates in milk in *animal* studies—manufacturer advises avoid.

#### Hepatic impairment
- Use with caution. Manufacturer advises avoid in severe impairment—no information available.

**Patient and carer advice**
- Patient counselling is advised for doxazosin tablets (initial dose).

**Driving and skilled tasks**
- May affect performance of skilled tasks e.g. driving.
MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution.

Tablet
- **Doxazosin (Non-proprietary)**
  - Doxazosin (as Doxazosin mesilate) 1 mg: Doxazosin 1mg tablets | 28 tablet (P) £0.56 DT price = £0.72
  - Doxazosin (as Doxazosin mesilate) 2 mg: Doxazosin 2mg tablets | 28 tablet (P) £1.08 DT price = £0.74
  - Doxazosin (as Doxazosin mesilate) 4 mg: Doxazosin 4mg tablets | 28 tablet (P) £1.08 DT price = £0.83
- **Cardura**
  - Doxazosin (as Doxazosin mesilate) 1 mg: Cardura 1mg tablets | 28 tablet (P) £0.56 DT price = £0.72
  - Doxazosin (as Doxazosin mesilate) 2 mg: Cardura 2mg tablets | 28 tablet (P) £1.08 DT price = £0.74
  - **Doxadura (Discovery Pharmaceuticals)**
    - Doxazosin (as Doxazosin mesilate) 1 mg: Doxadura 1mg tablets | 28 tablet (P) £0.64 DT price = £0.72
    - Doxazosin (as Doxazosin mesilate) 2 mg: Doxadura 2mg tablets | 28 tablet (P) £0.66 DT price = £0.74
    - Doxazosin (as Doxazosin mesilate) 4 mg: Doxadura 4mg tablets | 28 tablet (P) £0.73 DT price = £0.83

Modified-release tablet
**CAUTIONARY AND ADVISORY LABELS 25**
- **Cardoxin XL** (Almus Pharmaceuticals Ltd)
  - Doxazosin (as Doxazosin mesilate) 4 mg: Cardoxin XL 4mg tablets | 28 tablet (P) £6.33 DT price = £5.00
- **Cardura XL** (Pfizer Ltd)
  - Doxazosin (as Doxazosin mesilate) 4 mg: Cardura XL 4mg tablets | 28 tablet (P) £5.00 DT price = £5.00
  - Doxazosin (as Doxazosin mesilate) 8 mg: Cardura XL 8mg tablets | 28 tablet (P) £9.98 DT price = £9.98
- **Doxadura XL** (Discovery Pharmaceuticals)
  - Doxazosin (as Doxazosin mesilate) 4 mg: Doxadura XL 4mg tablets | 28 tablet (P) £4.75 DT price = £5.00
- **LarbeXL** (Teva UK Ltd)
  - Doxazosin (as Doxazosin mesilate) 4 mg: LarbeXL 4mg tablets | 28 tablet (P) £6.08 DT price = £5.00
- **Raporsin XL** (Actavis UK Ltd)
  - Doxazosin (as Doxazosin mesilate) 4 mg: Raporsin XL 4mg tablets | 28 tablet (P) £5.70 DT price = £5.00
- **Slocinx XL** (Zentiva)
  - Doxazosin (as Doxazosin mesilate) 4 mg: Slocinx XL 4mg tablets | 28 tablet (P) £5.56 DT price = £5.00

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 25 mg twice daily, increased in steps of 25–50 mg every 2 weeks, maximum daily dose should be given in divided doses; maximum 200 mg per day

**Benign prostatic hyperplasia**
- **BY MOUTH**
  - Adult: 20 mg twice daily, increased in steps of 20 mg every 2 weeks if required, increased if necessary up to 100 mg daily in divided doses
  - Elderly: 20 mg daily may be adequate, dose to be taken at night

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required.

**CONTRA-INDICATIONS**
- Established heart failure · history micturition syncope (when used for benign prostatic hyperplasia) · history of postural hypotension (when used for benign prostatic hyperplasia)

**CAUTIONS**
- Cataract surgery (risk of intra-operative floppy iris syndrome) · control incipient heart failure before initiating indoramin · elderly · epilepsy (convulsions in

animal studies) · history of depression · Parkinson’s disease (extrapyramidal disorders reported)

**INTERACTIONS** → Appendix 1 (alpha-blockers).
Avoid alcohol (enhances rate and extent of absorption).

**SIDE-EFFECTS**
- **Common or very common** Sedation
- **Uncommon** Failure of ejaculation · fatigue · weight gain
- **Frequency not known** Angioedema · asthenia · blurred vision · depression · dizziness · drowsiness · dry mouth · erectile disorders · extrapyramidal disorders · gastrointestinal disturbances · headache · hypersensitivity reactions · hypotension · incontinence · intra-operative floppy iris syndrome · oedema · palpitations · postural hypotension · priapism · pruritus · rash · rhinitis · syncope · tachycardia · urinary frequency

**PREGNANCY** No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

**BREAST FEEDING** No information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAI IMPAIRMENT** Manufacturer advises caution.

**PATIENT AND CARER ADVICE**
Driving and skilled tasks
Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

Tablet
**CAUTIONARY AND ADVISORY LABELS 2**
- **Indoramin (Non-proprietary)**
  - **Indoramin hydrochloride 20 mg** Indoramin 20mg tablets | 60 tablet (P) £13.30 DT price = £10.15
  - **Indoramin (as indoramin hydrochloride) 25 mg** Indoramin 25mg tablets | 84 tablet (P) £60.26 DT price = £60.26
- **Doralene Tiltab** (Chemidex Pharma Ltd)
  - **Indoramin hydrochloride 20 mg** Doralene Tiltab 20mg tablets | 60 tablet (P) £11.44 DT price = £10.15

**Prazosin**

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: 500 micrograms 2–3 times a day for 3–7 days, the initial dose should be taken on retiring to bed at night to avoid collapse, increased to 1 mg 2–3 times a day for a further 3–7 days, then increased if necessary up to 20 mg daily in divided doses

**Congestive heart failure (rarely used)**
- **BY MOUTH**
  - Adult: 500 micrograms 2–4 times a day, initial dose to be taken at bedtime, then increased to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses

**Raynaud’s syndrome (but efficacy not established)**
- **BY MOUTH**
  - Adult: 500 micrograms twice daily, initial dose to be taken at bedtime, dose may be increased after 3–7 days, then increased if necessary to 1–2 mg twice daily

**Benign prostatic hyperplasia**
- **BY MOUTH**
  - Adult: Initially 500 micrograms twice daily for 3–7 days, subsequent doses should be adjusted according to response, maintenance 2 mg twice daily, initiate with lowest possible dose in elderly patients continued →
DOSE ADJUSTMENTS DUE TO INTERACTIONS
Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required.

- CONTRA-INDICATIONS History of micturition syncope, history of postural hypotension not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis)
- CAUTIONS Cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - first dose hypotension
- INTERACTIONS Appendix 1 (alpha-blockers).
- SIDE-EFFECTS Angioedema, asthenia, blurred vision, depression, dizziness, drowsiness, dry mouth, erectile disorders, gastro-intestinal disturbances, headache, hypersensitivity reactions, hypotension (notably postural hypotension), intra-operative floppy iris syndrome, oedema, palpitations, priapism, pruritus, rash, rhinitis, syncope, tachycardia
- HEPATIC IMPAIRMENT Avoid in severe impairment.
- RENAL IMPAIRMENT Use with caution if eGFR less than 10 mL/minute/1.73 m².
- PATIENT AND CARER ADVICE Driving and skilled tasks May affect performance of skilled tasks e.g. driving.
- EXCEPTIONS TO LEGAL CATEGORY Tamsulosin hydrochloride 400 microgram capsules can be sold to the public for the treatment of functional symptoms of benign prostatic hyperplasia in men aged 45–75 years to be taken for up to 6 weeks before clinical assessment by a doctor.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Modified-release tablet
  CAUTIONARY AND ADVISORY LABELS 25
  - Tamsulosin hydrochloride (Non-proprietary)
    Tamsulosin 400 microgram capsules 400 microgram modified-release tablets 30 tablet (PSt) £10.47 DT price = £10.47
    - Cositam XL (Consilient Health Ltd)
      Cositam XL 400 microgram capsules 400 microgram modified-release tablets 30 tablet (PSt) £10.47
    - Faramsil (Sandzol Ltd)
      Faramsil 400 microgram modified-release tablets 30 tablet (PSt) £8.89 DT price = £10.47
    - Flectone XL (Teva UK Ltd)
      Flectone XL 400 microgram capsules 400 microgram modified-release tablets 30 tablet (PSt) £9.55 DT price = £10.47
    - Flomaxtra XL (Astellas Pharma Ltd)
      Flomaxtra XL 400 microgram capsules 400 microgram modified-release tablets 30 tablet (PSt) £10.47 DT price = £10.47

  Modified-release capsule
  CAUTIONARY AND ADVISORY LABELS 25
  - Tamsulosin hydrochloride (Non-proprietary)
    Tamsulosin 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £5.08 DT price = £3.90
    - Contilfo XL (Ranbaxy (UK) Ltd)
      Contilfo XL 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £7.44 DT price = £3.90
    - Diffondox XL (Zentiva)
      Diffondox XL 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £9.55 DT price = £3.90
    - Flomax MR (Boehringer Ingelheim Self-Medication Division)
      Flomax MR 400 microgram capsules 400 microgram modified-release capsules 14 capsule (PSt) £5.58 DT price = £0.10
    - Galebon (Consilient Health Ltd)
      Galebon 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £3.78 DT price = £3.90
    - Losinate MR (Aspire Pharma Ltd)
      Losinate MR 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £10.14 DT price = £7.90
    - Pamsvax XL (Actavis UK Ltd, Almus Pharmaceuticals Ltd)
      Pamsvax XL 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £1.31 DT price = £3.90
    - Petyme MR (Teva UK Ltd)
      Petyme MR 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £4.06 DT price = £3.90

Tamsulosin hydrochloride

- INDICATIONS AND DOSE
  Benign prostatic hyperplasia
    - BY MOUTH USING MODIFIED-RELEASE MEDICINES
    - Adult: 400 micrograms once daily
- CONTRA-INDICATIONS History of micturition syncope, history of postural hypotension

- SIDE-EFFECTS
  - Frequency not known
    - Rare
      - Alopecia, bradycardia, flushing, gynaecomastia, hallucinations, pancreatitis, priapism, urinary incontinence, vasculitis, worsening of narcolepsy
    - Frequency not known
      - Angioedema, asthma, erectile disorders, hypersensitivity reactions, hypotension, intra-operative floppy iris syndrome, postural hypotension, rhinitis
  - PREGNANCY
    - No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.
  - BREAST FEEDING
    - Present in milk, amount probably too small to be harmful; manufacturer advises use with caution.
  - HEPATIC IMPAIRMENT
    - Initially 500 micrograms daily; increased with caution.
  - RENAL IMPAIRMENT
    - Initially 500 micrograms daily in moderate to severe impairment; increased with caution.
  - PATIENT AND CARER ADVICE
    - Driving and skilled tasks
      - May affect performance of skilled tasks e.g. driving.
      - First dose effect
        - First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patients should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  
  **Tablet**
  - Prazosin (Non-proprietary)
    - Prazosin (as Prazosin hydrochloride) 2 mg Minipress 2mg tablets
    - 100 tablet (PSt) no price available
    - Prazosin (as Prazosin hydrochloride) 5 mg Minipress 5mg tablets
    - 100 tablet (PSt) no price available
  - Hypovase (Pfizer Ltd)
    - Prazosin (as Prazosin hydrochloride) 500 microgram Hypovase 500microgram tablets
    - 60 tablet (PSt) £2.69 DT price = £2.69
    - Prazosin (as Prazosin hydrochloride) 1 microgram
    - 60 tablet (PSt) £3.46 DT price = £3.46
  - Losinate MR (Aspire Pharma Ltd)
    - Losinate MR 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £3.78 DT price = £3.90
  - Pamsvax XL (Actavis UK Ltd, Almus Pharmaceuticals Ltd)
    - Pamsvax XL 400 microgram capsules 400 microgram modified-release capsules 30 capsule (PSt) £10.14 DT price = £7.90
Tamsulosin with dutasteride

The properties listed below are those particular to the combination only. For the properties of the components please consider, tamsulosin hydrochloride p. 718, dutasteride p. 720.

- **INDICATIONS AND DOSE**
  - Benign prostatic hyperplasia
    - BY MOUTH
    - Adult (male): 1 capsule daily.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - May affect performance of skilled tasks e.g. driving.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Capsule
    - **CAUTIONARY AND ADVISORY LABELS** 25
    - **Combodart** (GlaxoSmithKline Ltd)
      - **Tamsulosin hydrochloride 400 microgram, Dutasteride 500 microgram** Combidart 0.5mg/0.4mg capsules | 30 capsule (Pom) £23.76 DT price = £23.76

Tamsulosin with solifenacin

The properties listed below are those particular to the combination only. For the properties of the components please consider, tamsulosin hydrochloride p. 718, solifenacin succinate p. 713.

- **INDICATIONS AND DOSE**
  - Moderate to severe urinary frequency, urgency, and obstructive symptoms associated with benign prostatic hyperplasia when monotherapy ineffective
    - BY MOUTH
    - Adult (male): 1 tablet daily.
  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
    - Max. 1 Vesomni® tablet daily with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole, ketoconazole, or ritonavir).

- **HEPATIC IMPAIRMENT**
  - Max. 1 Vesomni® tablet daily in moderate impairment.

- **RENAL IMPAIRMENT**
  - Max. 1 Vesomni® tablet daily if eGFR less than 30 mL/minute/1.73 m².

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Modified-release tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 3, 25
    - **Vesomni** (Astellas Pharma Ltd)
      - **Solifenacin succinate 6 mg, Tamsulosin hydrochloride 400 microgram** Vesomni 6mg/0.4mg modified-release tablets | 30 tablet (Pom) £27.62 DT price = £27.62

Terazosin

- **INDICATIONS AND DOSE**
  - Mild to moderate hypertension
    - BY MOUTH
    - Adult: 1 mg daily for 7 days, then increased if necessary to 2 mg daily, dose should be taken at bedtime; maintenance 2–10 mg once daily, doses above 20 mg rarely improve efficacy
  - Benign prostatic hyperplasia
    - BY MOUTH
    - Adult: Initially 1 mg daily, dose should be taken at bedtime, if necessary dose may be doubled at intervals of 1–2 weeks according to response; maintenance 5–10 mg daily; maximum 10 mg per day

- **CONTRA-INDICATIONS**
  - History of micturition syncope (in benign prostatic hyperplasia); history of postural hypotension (in benign prostatic hyperplasia)
  - **CAUTIONS**
    - Cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - first dose
    - **CAUTIONS, FURTHER INFORMATION**
      - First dose may cause collapse due to hypotension within 30–90 minutes, therefore should be taken on retiring to bed; may also occur with rapid dose increase.
  - **INTERACTIONS**
    - Appendix 1 (alpha-blockers).
  - **SIDE-EFFECTS**
  - **PREGNANCY**
    - No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.
  - **BREAST FEEDING**
    - No information available.
  - **PATIENT AND CARER ADVICE**
    - Patient counselling is advised for terazosin tablets (initial dose).
    - First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.
    - **Driving and skilled tasks**
    - May affect performance of skilled tasks e.g. driving.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Terazosin (Non-proprietary)**
      - **Terazosin (as Terazosin hydrochloride) 2 mg** Benph 2mg tablets | 28 tablet (Pom) £2.20 DT price = £2.15
      - **Terazosin 2mg tablets** | 28 tablet (Pom) £2.70 DT price = £2.15
      - **Terazosin (as Terazosin hydrochloride) 5 mg** Terazosin 5mg tablets | 28 tablet (Pom) £3.24 DT price = £2.31
      - **Terazosin (as Terazosin hydrochloride) 10 mg** Terazosin 10mg tablets | 28 tablet (Pom) £8.11 DT price = £7.87
Genito-urinary system

CHOLINE ESTERS

Bethanechol chloride

- **INDICATIONS AND DOSE**
  - **Urinary retention**
    - Adult: 10–25 mg 3–4 times a day, to be taken 30 minutes before food

- **CONTRA-INDICATIONS** Bradycardia, cardiovascular disorders, conditions where increased motility of the gastro-intestinal tract could be harmful, conditions where increased motility of the urinary tract could be harmful, epilepsy, heart block, hyperthyroidism, hypotension, intestinal obstruction, obstructive airways disease, parkinsonism, peptic ulcer, recent myocardial infarction, urinary obstruction

- **CAUTIONS** Autonomic neuropathy (use lower initial dose)

- **INTERACTIONS** → Appendix 1 (parasympathomimetics).

- **SIDE-EFFECTS** Abdominal pain, bradycardia, bronchoconstriction, diarrhoea, eructation, flushing, headache, hypotension, increased lacrimation, increased salivation, increased sweating, nausea, rhinorrhea, vomiting

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Manufacturer advises avoid; gastrointestinal disturbances in infant reported.

- **LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 25
  - **Avodart** (GlaxoSmithKline UK Ltd)
    - **Dutasteride 500 microgram** Avodart 500microgram capsules | 30 capsule (Pom) £14.60 DT price = £14.60
    - **Combinations available:** Hytrin with dutasteride, p. 719

5α-REDUCTASE INHIBITORS

Dutasteride

- **DRUG ACTION** A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

- **INDICATIONS AND DOSE**
  - **Benign prostatic hyperplasia**
    - Adult: 5 mg daily, review treatment at 3–6 months and then every 6–12 months (may require several months treatment before benefit is obtained)

- **INTERACTIONS** → Appendix 1 (dutasteride).

- **SIDE-EFFECTS** Breast enlargement, breast tenderness, decreased libido, ejaculation disorders, impotence

- **CONCEPTION AND CONTRACEPTION** Dutasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.

- **HEPATIC IMPAIRMENT** Avoid in severe impairment—no information available.

- **EFFECT ON LABORATORY TESTS** May decrease serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment.

- **HANDLING AND STORAGE** Women of childbearing potential should avoid handling leaking capsules of dutasteride.

- **PATIENT AND CARER ADVICE** Cases of male breast cancer have been reported. Patients or their carers should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 25
  - **Avodart** (GlaxoSmithKline UK Ltd)
    - **Dutasteride 500 microgram** Avodart 500microgram capsules | 30 capsule (Pom) £14.60 DT price = £14.60
    - **Combinations available:** Tamsulosin with dutasteride, p. 719

Finasteride

- **DRUG ACTION** A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

- **INDICATIONS AND DOSE**
  - **Benign prostatic hyperplasia**
    - Adult: 5 mg daily, review treatment at 3–6 months and then every 6–12 months (may require several months treatment before benefit is obtained)

- **SIDE-EFFECTS** Breast enlargement, breast tenderness, decreased libido, ejaculation disorders, face swelling, hypersensitivity reactions, impotence, lip swelling, male breast cancer, pruritus, rash, testicular pain

- **CONCEPTION AND CONTRACEPTION** Finasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.

- **EFFECT ON LABORATORY TESTS** Decreases serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment.

- **HANDLING AND STORAGE** Women of childbearing potential should avoid handling crushed or broken tablets of finasteride.

- **PATIENT AND CARER ADVICE** Cases of male breast cancer have been reported. Patients or their carers should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 25
  - **Avodart** (GlaxoSmithKline UK Ltd)
    - **Dutasteride 500 microgram** Avodart 500microgram capsules | 30 capsule (Pom) £14.60 DT price = £14.60
    - **Combinations available:** Tamsulosin with dutasteride, p. 719

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NHS restrictions** Finasteride is not prescribable under the NHS for the treatment of androgenetic alopecia in men.

- **CONTRA-INDICATIONS** Cases of male breast cancer have been reported. Patients or their carers should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge.

- **CAUTIONS** Obstructive uropathy

- **SIDE-EFFECTS** Breast enlargement, breast tenderness, decreased libido, ejaculation disorders, face swelling, hypersensitivity reactions, impotence, lip swelling, male breast cancer, pruritus, rash, testicular pain

- **CONCEPTION AND CONTRACEPTION** Finasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.

- **EFFECT ON LABORATORY TESTS** Decreases serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment.

- **HANDLING AND STORAGE** Women of childbearing potential should avoid handling crushed or broken tablets of finasteride.

- **PATIENT AND CARER ADVICE** Cases of male breast cancer have been reported. Patients or their carers should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 25
  - **Avodart** (GlaxoSmithKline UK Ltd)
    - **Dutasteride 500 microgram** Avodart 500microgram capsules | 30 capsule (Pom) £14.60 DT price = £14.60
    - **Combinations available:** Tamsulosin with dutasteride, p. 719

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NHS restrictions** Finasteride is not prescribable under the NHS for the treatment of androgenetic alopecia in men.
### 1.3 Urological pain

#### Urological pain

**Treatment**

The acute pain of *ureteric colic* may be relieved with pethidine hydrochloride p. 434. *Diclofenac* by injection or as suppositories is also effective and compares favourably with pethidine hydrochloride; other non-steroidal anti-inflammatory drugs are occasionally given by injection.

*Lidocaine hydrochloride* gel p. 1197 is a useful topical application in *urethral pain* or to relieve the discomfort of catheterisation.

**Alkalisation of urine**

*Alkalisation* of urine can be undertaken with potassium citrate. The alkalinising action may relieve the discomfort of *cystitis* caused by lower urinary tract infections. *Sodium bicarbonate* p. 910 is used as a urinary alkalinising agent in some metabolic and renal disorders.

### ALKALISING DRUGS

#### Citric acid with potassium citrate

**INDICATIONS AND DOSE**

**Relief of discomfort in mild urinary-tract infections**

**Alkalisation of urine**

- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 10 mL 3 times a day, diluted well with water

**CAUTIONS** Cardiac disease · elderly

**INTERACTIONS** Appendix 1 (potassium salts).

**SIDE-EFFECTS** Hyperkalaemia on prolonged high dosage · mild diuresis

**RENAAL IMPAIRMENT** Avoid in severe impairment. Close monitoring required in renal impairment—high risk of hyperkalaemia.

**PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states *Potassium Citrate Mixture* BP consists of potassium citrate 30%, citric acid monohydrate 5% in a suitable vehicle with a lemon flavour. Extemporaneous preparations should be recently prepared according to the following formula: potassium citrate 3 g, citric acid monohydrate 500 mg, syrup 2.5 mL, quillia tincture 0.1 mL, lemon spirit 0.05 mL, double-strength chloroform water 3 mL, water to 10 mL. Contains about 28 mmol K⁺/10 mL.

**EXCEPTIONS TO LEGAL CATEGORY** Proprietary brands of potassium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

*Cautionary and Advisory Labels 27*

- **Citic acid with potassium citrate (Non-proprietary)**
  - Citric acid monohydrate 50 mg per 1 mL, Potassium citrate 300 mg per 1 mL

**Price**

- 200 mL £1.33
- 400 mL £1.33

**Sodium citrate**

**INDICATIONS AND DOSE**

**Bladder washouts**

- Adult: (consult product literature)

**Relief of discomfort in mild urinary-tract infections**

- **BY MOUTH**
  - Adult: (consult product literature)

**MICOLETTE®**

**Constipation**

- **BY RECTUM**
  - Child 3-17 years: 5–10 mL for 1 dose
  - Adult: 5–10 mL for 1 dose

**MICRALAX®**

**Constipation**

- **BY RECTUM**
  - Child 3-17 years: 5 mL for 1 dose
  - Adult: 5 mL for 1 dose

**RELAXIT®**

**Constipation**

- **BY RECTUM**
  - Child 1 month-2 years: 5 mL for 1 dose, insert only half the nozzle length
  - Child 3-17 years: 5 mL for 1 dose
  - Adult: 5 mL for 1 dose

**CONTRA-INDICATIONS**

- With rectal use Acute gastro-intestinal conditions

**CAUTIONS**

- With oral use Cardiac disease · elderly · hypertension · patients on a sodium-restricted diet
- With rectal use Debilitated patients (in adults) · sodium and water retention in susceptible individuals

**INTERACTIONS**

- With oral use Appendix 1 (sodium citrate).

**SIDE-EFFECTS**

- With oral use Mild diuresis

**PREGNANCY**

- With oral use Use with caution.

**RENAAL IMPAIRMENT**

- With oral use In patients with fluid retention, avoid antacids containing large amounts of sodium.

**PRESCRIBING AND DISPENSING INFORMATION** Sodium citrate 300 mmol/litre (88.2 mg/mL) oral solution is licensed for use before general anaesthesia for caesarean section (available from Viridian).

**EXCEPTIONS TO LEGAL CATEGORY** Proprietary brands of sodium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections.
722 Bladder instillations and urological surgery

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Granules**

- Sodium citrate (Non-proprietary)
- Sodium citrate 4 gram Cystitis Relief 4g oral granules sachets | 6 sachet [SSL] £2.33
- Brands may include Cymalon (sodium citrate), Cystocalm

**Oral solution**

- Sodium citrate (Non-proprietary)
- Sodium citrate 88.23 mg per 1 ml Sodium citrate 0.3% oral solution | 30 ml [PBP] £4.50
- Sodium citrate 441.17mg/5ml oral solution | 30 ml [P] no price available

**Enema**

- Micolette Micro-enema (Pinewood Healthcare)
- Sodium citrate 90 mg per 1 ml Micolette Micro-enema 5ml | 12 enema [P] £3.40
- Micralax Micro-enema (Focus Pharmaceuticals Ltd)
- Sodium citrate 90 mg per 1 ml Micralax Micro-enema 5ml | 12 enema [P] £4.87
- Relaxit (Supra Enterprises Ltd)
- Sodium citrate 90 mg per 1 ml Relaxit Micro-enema 5ml | 12 enema £5.21

**Irrigation solution**

- Sodium citrate (Non-proprietary)
- Sodium citrate 3% irrigation solution 1 litre bags | 1 bag no price available

**Powder**

- Sodium citrate (Non-proprietary)
- Sodium citrate 1 mg per 1 mg Sodium citrate powder | 500 gram [SSL] £5.28 DT price = £5.28

**TERPENES**

**Anethol with borneol, camphene, cineole, fenchone and pinene**

**INDICATIONS AND DOSE**

**Urolithiasis for the expulsion of calculi**

- **BY MOUTH**
  - Adult: 1–2 capsules 3–4 times a day, to be taken before food

**LESS SUITABLE FOR PRESCRIBING** Preparation is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- CAUTIONARY AND ADVISORY LABELS 25
- Rowatinex (Meadow Laboratories Ltd)
  - Cineole 3 mg, Anethol 4 mg, Fenchone 4 mg, Borneol 10 mg, Camphene 15 mg, Pinene 31 mg Rowatinex capsules | 50 capsule [PBP] £7.35

2 Bladder instillations and urological surgery

**Bladder instillations and urological surgery**

**Bladder infection**

Various solutions are available as irrigations or washouts. Aqueous chlorhexidine p. 1064 can be used in the management of common infections of the bladder but it is ineffective against most *Pseudomonas spp*. Solutions containing chlorhexidine 1 in 5000 (0.02%) are used but they may irritate the mucosa and cause burning and haematuria (in which case they should be discontinued); sterile sodium chloride solution 0.9% p. 914 (physiological saline) is usually adequate and is preferred as a mechanical irritant.

Continuous bladder irrigation with amphotericin 50 micrograms/mL p. 547 may be of value in mycotic infections in adults.

**Dissolution of blood clots**

Clot retention is usually treated by irrigation with sterile sodium chloride solution 0.9% but sterile sodium citrate solution p. 721 for bladder irrigation 3% may also be helpful.

**Bladder cancer**

Bladder instillations of doxorubicin hydrochloride p. 807 and mitomycin p. 822 are used for recurrent superficial bladder tumours. Such instillations reduce systemic side-effects; adverse effects on the bladder (e.g. micturition disorders and reduction in bladder capacity) may occur.

Instillation of epirubicin hydrochloride p. 808 is used for treatment and prophylaxis of certain forms of superficial bladder cancer; instillation of doxorubicin hydrochloride is also used for some papillary tumours.

Instillation of BCG (Bacillus Calmette-Guérin p. 852), a live attenuated strain derived from *Mycobacterium bovis* is licensed for the treatment of primary or recurrent bladder carcinoma *in-situ* and for the prevention of recurrence following transurethral resection.

**Urological surgery**

Glycine irrigation solution 1.5% p. 723 is the irrigant of choice for transurethral resection of the prostate gland and bladder tumours; sterile sodium chloride solution 0.9% (physiological saline) is used for percutaneous renal surgery.

**Maintenance of indwelling urinary catheters**

The deposition which occurs in catheterised patients is usually chiefly composed of phosphate and to minimise this the catheter (if latex) should be changed at least as often as every 6 weeks. If the catheter is to be left for longer periods a silicone catheter should be used together with the appropriate use of catheter maintenance solutions. Repeated blockage usually indicates that the catheter needs to be changed.

**ANTISEPTICS AND DISINFECTANTS**

**Chlorhexidine with lidocaine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1064, lidocaine hydrochloride p. 1197.

**INDICATIONS AND DOSE**

**Urethral sounding and catheterisation**

- **BY URETHRAL APPLICATION**
  - Adult: 6–11 mL

**Cystoscopy**

- **BY URETHRAL APPLICATION**
  - Adult: 11 mL, then 6–11 mL if required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gel**

- **EXCIPIENTS:** May contain Hydroxybenzoates (parabens)
- **Instillagel (CliniMed Ltd)**
  - Chlorhexidine gluconate 500 microgram per 1 mL, Lidocaine hydrochloride 20 mg per 1 mL Instillagel gel | 60 ml [P] £14.05 DT price = £14.05 | 110 ml [P] £15.76 DT price = £15.76
IRRIGATING SOLUTIONS

Glycine

- INDICATIONS AND DOSE
  Bladder irrigation during urological surgery / Irrigation for transurethral resection of the prostate gland and bladder tumours
    - Adult: (consult product literature)

- CAUTIONS
  Urological surgery. There is a high risk of fluid absorption from the irrigant used in endoscopic surgery within the urinary tract.

- SIDE-EFFECTS
  Haemolysis - hypervolaemia - renal failure

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Irrigation solution
    - Glycine (Non-proprietary)
      Glycine 1.5% irritation solution 3 litre Easyflow bags | 1 bag no price available
      Glycine 1.5% irritation solution 1 litre Flowfusor bottles | 1 bottle no price available
      Glycine 1.5% irritation solution 1 litre Easyflow bags | 1 bag no price available
      Glycine 1.5% irritation solution 2 litre Flowfusor bottles | 1 bottle no price available

UROLOGICAL ANTI-INFLAMMATORY DRUGS

Dimethyl sulfoxide

- INDICATIONS AND DOSE
  Symptomatic relief in interstitial cystitis (Hunner’s ulcer)
    - BY INTRAVESICAL INSTILLATION
    - Adult: 50 mL every 2 weeks retained for 15 minutes then voided by the patient; 50% solution is used and instilled into the bladder

- INTERACTIONS
  → Appendix 1 (dimethyl sulfoxide).

- SIDE-EFFECTS
  Bladder spasm - hypersensitivity

- MONITORING REQUIREMENTS
  Ophthalmic, renal and hepatic assessments at intervals of 6 months are required in long-term treatment.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Liquid
    - RIMSO-50 (Thornton & Ross Ltd)
      Dimethyl sulfoxide 500 mg per 1 ml | Rimso-50 solution for instillation | 50 ml | £324.00

Catheter maintenance solutions

CATHETER MAINTENANCE SOLUTIONS

OptiFlo R citric acid 6% catheter maintenance solution (Bard Ltd) 50 mL | NHS indicative price = £3.56 | Drug Tariff (Part IXa) 100 mL | NHS indicative price = £3.56 | Drug Tariff (Part IXa)

Uro-Tainer Twin Solution R citric acid 6% catheter maintenance solution (B.Braun Medical Ltd) 60 mL | NHS indicative price = £4.81 | Drug Tariff (Part IXa)

OptiFlo S saline 0.9% catheter maintenance solution (Bard Ltd) Sodium chloride 9 mg per 1 ml 50 mL | NHS indicative price = £3.36 | Drug Tariff (Part IXa) 100 mL | NHS indicative price = £3.36 | Drug Tariff (Part IXa)

Uro-Tainer M sodium chloride 0.9% catheter maintenance solution (B.Braun Medical Ltd) Sodium chloride 9 mg per 1 mL 50 mL | No NHS indicative price available | Drug Tariff (Part IXa) 100 mL | No NHS indicative price available | Drug Tariff (Part IXa)

Uro-Tainer sodium chloride 0.9% catheter maintenance solution (B.Braun Medical Ltd) Sodium chloride 9 mg per 1 ml 50 mL | NHS indicative price = £3.51 | Drug Tariff (Part IXa) 100 mL | NHS indicative price = £3.51 | Drug Tariff (Part IXa)

3 Contraception

Contraceptives, hormonal

Overview

The Fraser Guidelines (Department of Health Guidance (July 2004)): Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health, available at www.tinyurl.com/bpg16 should be followed when prescribing contraception for women under 16 years. The UK Medical Eligibility Criteria for Contraceptive Use (available at www.fsrh.org) is published by the Faculty of Sexual and Reproductive Healthcare; it categorises the risks of using contraceptive methods with pre-existing medical conditions.

Hormonal contraception is the most effective method of fertility control, but may have major and minor side-effects, especially for certain groups of women. Hormonal contraception should only be used by adolescents after menarche.

Intra-uterine devices are a highly effective method of contraception but may produce undesirable local side-effects. They may be used in women of all ages irrespective of parity, but are less appropriate for those with an increased risk of pelvic inflammatory disease.

Barrier methods alone (condoms, diaphragms, and caps) are less effective but can be reliable for well-motivated couples if used in conjunction with a spermicide.

Occasionally sensitivity reactions occur. A female condom (Femidom®) is also available; it is pre-lubricated but does not contain a spermicide.

Combined hormonal contraceptives

Oral contraceptives containing an oestrogen and a progestogen (‘combined oral contraceptives’) are effective preparations for general use. Advantages of combined oral contraceptives include:

- reliable and reversible;
- reduced dysmenorrhoea and menorrhagia;
- reduced incidence of premenstrual tension;
- less symptomatic fibroids and functional ovarian cysts;
- less benign breast disease;
- reduced risk of ovarian and endometrial cancer;
- reduced risk of pelvic inflammatory disease.

Combined oral contraceptives containing a fixed amount of an oestrogen and a progestogen in each active tablet are termed ‘monophasic’; those with varying amounts of the two hormones are termed ‘phasic’. A transdermal patch and a vaginal ring, both containing an oestrogen with a progestogen, are also available.
### Combined Oral Contraceptives Monophasic 21-day preparations

<table>
<thead>
<tr>
<th>Oestrogen content</th>
<th>Progestogen content</th>
<th>Brand</th>
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<tbody>
<tr>
<td>Ethinylestradiol  20 micrograms</td>
<td>Desogestrel 150 micrograms</td>
<td>Gedarel® 20/150</td>
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<td>Desogestrel 150 micrograms</td>
<td>Mercilon®</td>
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<td>Femodette®</td>
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<td>Gestodene 75 micrograms</td>
<td>Millinet® 20/75</td>
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<td>Gestodene 75 micrograms</td>
<td>Sunya 20/75®</td>
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<td>Ethinylestradiol  20 micrograms</td>
<td>Norethisterone acetate 1 mg</td>
<td>Loestrin 20®</td>
</tr>
<tr>
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<td>Desogestrel 150 micrograms</td>
<td>Gedarel® 30/150</td>
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<td>Desogestrel 150 micrograms</td>
<td>Marvelon®</td>
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<td>Drospirenone 3 mg</td>
<td>Yasmin®</td>
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<td>Gestodene 75 micrograms</td>
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<td>Gestodene 75 micrograms</td>
<td>Katya 30/75®</td>
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<td>Levest®</td>
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<td>Mestranol 50 micrograms</td>
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<td>Norinyl-1®</td>
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### Combined Oral Contraceptives Phasic 21-day preparations

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<th>Oestrogen content</th>
<th>Progestogen content</th>
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</tr>
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<tbody>
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<td>Ethinylestradiol  30 micrograms</td>
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<td>Logynon ED®</td>
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<td>Norethisterone 500 micrograms</td>
<td>Logynon ED®</td>
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<td>Ethinylestradiol  30 micrograms</td>
<td>Levonorgestrel 125 micrograms</td>
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<td>Dienogest 2 mg</td>
<td>Qlaira®</td>
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<td>Qlaira®</td>
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<td>Estradiol valerate 2 mg</td>
<td>Dienogest 3 mg</td>
<td>Qlaira®</td>
</tr>
<tr>
<td>Estradiol valerate 1 mg</td>
<td>Dienogest 3 mg</td>
<td>Qlaira®</td>
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### Combined Oral Contraceptives Phasic 28-day preparations

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</tr>
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<tbody>
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<td>Levonorgestrel 50 micrograms</td>
<td>Logynon ED®</td>
</tr>
<tr>
<td>Ethinylestradiol  40 micrograms</td>
<td>Levonorgestrel 75 micrograms</td>
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<td>Levonorgestrel 125 micrograms</td>
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<tr>
<td>Estradiol valerate</td>
<td>Dienogest</td>
<td>Qlaira®</td>
</tr>
</tbody>
</table>

### Choice

The majority of combined oral contraceptives contain ethinylestradiol p. 694 as the oestrogen component; mestranol and estradiol are also used. The ethinylestradiol content of combined oral contraceptives ranges from 20 to 40 micrograms. Generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen. It is recommended that combined hormonal contraceptives are not continued beyond 50 years of age since more suitable alternatives exist.
• **Low strength preparations** (containing ethinylestradiol 20 micrograms) are particularly appropriate for women with risk factors for circulatory disease, provided a combined oral contraceptive is otherwise suitable.

• **Standard strength preparations** (containing ethinylestradiol 30 or 35 micrograms or in 30–40 microgram phase preparations) are appropriate for standard use. Phased preparations are generally reserved for women who either do not have withdrawal bleeding or who have breakthrough bleeding with monophasic products.

The progestogens ethinylestradiol with desogestrel p. 730, ethinylestradiol with drospirenone p. 736, and ethinylestradiol with gestodene p. 731 may be considered for women who have side-effects (such as acne, headache, depression, breast symptoms, and breakthrough bleeding) with other progestogens. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity; it should be used with care if an increased plasma-potassium concentration might be hazardous.

Dienogest with estradiol valerate p. 729 is in the combined oral contraceptive *Qlaira*®. Nomegestrol is the progestogen contained in the combined oral contraceptive *Zoely*, in combination with estradiol.

The progestogen norelgestromin is combined with ethinylestradiol in a transdermal patch (*Evo intrigue®*). The vaginal contraceptive ring contains the progestogen etonogestrel combined with ethinylestradiol (*NuvaRing®*).

**Surgery**

Oestrogen-containing contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb; they should normally be recommenced at the first menses occurring at least 2 weeks after full mobilisation. A progestogen-only contraceptive may be offered as an alternative and the oestrogen-containing contraceptive restarted after mobilisation. When discontinuation of an oestrogen-containing contraceptive is not possible, e.g. after trauma or if a patient admitted for an elective procedure is still on an oestrogen-containing contraceptive, thromboprophylaxis (with unfractionated or low molecular weight heparin and graduated compression hosiery) is advised. These recommendations do not apply to minor surgery with short duration of anaesthesia, e.g. laparoscopic sterilisation or tooth extraction, or to women using oestrogen-free hormonal contraceptives.

**Reason to stop immediately**

Combined hormonal contraceptives or hormone replacement therapy (HRT) should be stopped (pending investigation and treatment), if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg; (in adolescents stop if blood pressure very high);
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment.

**Progestogen-only contraceptives**

**Oral progestogen-only contraceptives**

Oral progestogen-only preparations alter cervical mucus to prevent sperm penetration and may inhibit ovulation in some women; oral desogestrel-only preparations consistently inhibit ovulation and this is their primary mechanism of action. There is insufficient clinical trial evidence to compare the efficacy of oral progestogen-only contraceptives with each other or with combined hormonal contraceptives. Progestogen-only contraceptives offer a suitable alternative to combined hormonal contraceptives when oestrogens are contra-indicated (including those with venous thrombosis or a past history or predisposition to venous thrombosis, heavy smokers, those with hypertension above systolic 160 mmHg or diastolic 95 mmHg, valvular heart disease, diabetes mellitus with complications, and migraine with aura).

**Parenteral progestogen-only contraceptives**

Medroxyprogesterone acetate (*Depo-Provera*, SAYANA PRESS®) p. 741 is a long-acting progestogen given by injection; it is at least as effective as the combined oral preparations but because of its prolonged action it should never be given without full counselling backed by the patient information leaflet. It may be used as a short-term or long-term contraceptive for women who have been counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Troublesome bleeding has been reported in patients given medroxyprogesterone acetate in the immediate puerperium; delaying the first injection until 6 weeks after birth may minimise bleeding problems. If the woman is not breast-feeding, the first injection may be given within 5 days postpartum (she should be warned that the risk of troublesome bleeding may be increased).

- In adolescents, medroxyprogesterone acetate (*Depo-Provera*, SAYANA PRESS®) should be used only when other methods of contraception are inappropriate;
- in all women, the benefits of using medroxyprogesterone acetate beyond 2 years should be evaluated against the risks;
- in women with risk factors for osteoporosis, a method of contraception other than medroxyprogesterone acetate should be considered.

**Norethisterone enantate** (*Noristerat®*) is a long-acting progestogen given as an oily injection which provides contraception for 8 weeks; it is used as short-term interim contraception e.g. before vasectomy becomes effective.

An etonogestrel-releasing implant (*Nexplanon®*) is also available. It is a highly effective long-acting contraceptive, consisting of a single flexible rod that is inserted subdermally into the lower surface of the upper arm and provides contraception for up to 3 years. The manufacturer advises that in heavier women, blood-etonogestrel concentrations are lower and therefore the implant may not provide effective contraception during the third year; they advise that earlier replacement may be considered in such patients—however, evidence to support this recommendation is lacking. Local reactions such as bruising and itching can occur at the insertion site. The contraceptive effect of etonogestrel is rapidly reversed on removal of the implant.

**Intra-uterine progestogen-only device**

The progestogen-only intra-uterine systems *Mirena®, Jaydess®* and *Levovist®, release levonorgestrel p. 737 directly into the uterine cavity. *Mirena®* is licensed for use as a contraceptive, for the treatment of primary menorrhagia and
for the prevention of endometrial hyperplasia during oestrogen replacement therapy. Jaydess® and Levosert® are licensed for contraception, and Levosert® is additionally licensed for the treatment of menorrhagia. These may therefore be a contraceptive method of choice for women who have excessively heavy menses.

The effects of the progestogen-only intra-uterine system are mainly local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus, and suppression of ovulation in some women (in some cycles). In addition to the progestogenic activity, the intra-uterine system itself may contribute slightly to the contraceptive effect. Return of fertility after removal is rapid and appears to be complete.

Advantages of the progestogen-only intra-uterine system over copper intra-uterine devices are that there may be an improvement in any dysmenorrhoea and a reduction in blood loss; there is also evidence that the frequency of pelvic inflammatory disease may be reduced (particularly in the youngest age groups who are most at risk).

In primary menorrhagia, menstrual bleeding is reduced significantly within 3–6 months of inserting the progestogen-only intra-uterine system, probably because it prevents endometrial proliferation. Another treatment should be considered if menorrhagia does not improve within this time.

Surgery
All progestogen-only contraceptives (including those given by injection) are suitable for use as an alternative to combined hormonal contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

Emergency contraception

Hormonal methods
Hormonal emergency contraceptives include levonorgestrel and ulipristal acetate p. 736; either drug should be taken as soon as possible after unprotected intercourse to increase efficacy.

Levonorgestrel is effective if taken within 72 hours (3 days) of unprotected intercourse and may also be used between 72 and 96 hours after unprotected intercourse [unlicensed use], but efficacy decreases with time. Ulipristal acetate, a progesterone receptor modulator, is effective if taken within 120 hours (5 days) of unprotected intercourse.

Levonorgestrel is less effective than insertion of an intra-uterine device. Ulipristal acetate is as effective as levonorgestrel, but its efficacy compared to an intra-uterine device is not yet known.

Intra-uterine device
Insertion of an intra-uterine device is more effective than oral levonorgestrel for emergency contraception. A copper intra-uterine contraceptive device can be inserted up to 120 hours (5 days) after unprotected intercourse; sexually transmitted infections should be tested for and insertion of the device should usually be covered by antibacterial prophylaxis (e.g. azithromycin p. 495). If intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated ovulation (i.e. within the minimum period before implantation), regardless of the number of episodes of unprotected intercourse earlier in the cycle.

Contraceptives, interactions

Combined hormonal contraceptives interactions
The effectiveness of combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, and vaginal rings can be considerably reduced by interaction with drugs that induce hepatic enzyme activity (e.g. carbamazepine p. 291, eslicarbazepine acetate p. 293, nevirapine p. 594, oxcarbazepine p. 300, phenyoitn p. 302, phenobarbital p. 313, primidone p. 313, ritonavir p. 604, St John’s Wort, topiramate p. 309 and, above all, rifabutin p. 530 and rifampicin p. 535). A condom together with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of HIV infection; advice on the possibility of interaction with antiretroviral drugs should be sought from HIV specialists.

Women taking combined hormonal contraceptives who require enzyme-inducing drugs should be advised to change to a contraceptive method that is unaffected by enzyme-inducers (e.g. some parenteral progestogen-only contraceptives, intra-uterine devices) for the duration of treatment and for 4 weeks after stopping. If a change in contraceptive method is undesirable or inappropriate the following options should be discussed:

- For a short course (2 months or less) of an enzyme-inducing drug, continue with a combined oral contraceptive providing ethinylessradiol 30 micrograms or more daily and use a ‘tricycling’ regimen (i.e. taking 3 packets of monophasic tablets without a break followed by a shortened tablet-free interval of 4 days [unlicensed use]). Additional contraceptive precautions should also be used whilst taking the enzyme-inducing drug and for 4 weeks after stopping. Another option (except for rifampicin or rifabutin) is to follow the advice for long-term courses.

- For women using combined hormonal contraceptive patches or vaginal rings, additional contraceptive precautions are also required whilst taking the enzyme-inducing drug and for 4 weeks after stopping. If concomitant administration runs beyond the 3 weeks of patch or vaginal ring use, a new treatment cycle should be started immediately, without a patch-free or ring-free break.

- For a long-term course (over 2 months) of an enzyme-inducing drug (except rifampicin or rifabutin), adjust the dose of combined oral contraceptive to provide ethinylestradiol 50 micrograms or more daily [unlicensed use] and use a ‘tricycling’ regimen; continue for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping.

- If breakthrough bleeding occurs (and all other causes are ruled out) it is recommended that the dose of ethinylestradiol is increased by increments of 10 micrograms up to a maximum of 70 micrograms daily [unlicensed use], or to use additional precautions, or to change to a method unaffected by enzyme-inducing drugs.

- Contraceptive patches and vaginal rings are not recommended for women taking enzyme-inducing drugs over a long period.

- For a long-term course (over 2 months) of rifampicin or rifabutin, an alternative method of contraception (such as an IUD) is always recommended because they are such potent enzyme-inducing drugs; the alternative method of contraception should be continued for 4 weeks after stopping the enzyme-inducing drug.

Antibacterials that do not induce liver enzymes
Latest recommendations are that no additional contraceptive precautions are required when combined oral contraceptives are used with antibacterials that do not induce liver enzymes, unless diarrhoea or vomiting occur. These recommendations should be discussed with the woman, who should also be advised that guidance in patient information leaflets may differ.

It is also currently recommended that no additional contraceptive precautions are required when contraceptive patches or vaginal rings are used with antibacterials that do not induce liver enzymes. There have been concerns that some antibacterials that do not induce liver enzymes (e.g. ampicillin p. 507, doxycycline p. 521) reduce the efficacy of
combined oral contraceptives by impairing the bacterial flora responsible for recycling ethinylestradiol from the large bowel. However, there is a lack of evidence to support this interaction.

**Oral progestogen-only contraceptives interactions**

Effectiveness of oral progestogen-only preparations is not affected by antibacterials that do not induce liver enzymes. The efficacy of oral progestogen-only preparations is, however, reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with an enzyme-inducing drug and for at least 4 weeks afterwards. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the progestogen-only oral method may be continued in combination with additional contraceptive precautions (e.g. barrier methods) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping.

**Parenteral progestogen-only contraceptives interactions**

Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. The effectiveness of norethisterone intramuscular injection p. 699 and medroxyprogesterone acetate intramuscular and subcutaneous injections p. 741 is not affected by enzyme-inducing drugs and they may be continued as normal during courses of these drugs. However, effectiveness of the etonogestrel-releasing implant p. 740 may be reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with the enzyme-inducing drug and for at least 4 weeks after stopping. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the implant may be continued in combination with additional contraceptive precautions (e.g. condom) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.

**Hormonal emergency contraception interactions**

The effectiveness of levonorgestrel p. 737, and possibly ulipristal acetate p. 736, is reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose (unlicensed dose—advise women accordingly). There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

**Contraceptives, non-hormonal**

**Spermicidal contraceptives**

Spermicidal contraceptives are useful additional safeguards but do not give adequate protection if used alone unless fertility is already significantly diminished. They have two components: a spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. They are suitable for use with barrier methods, such as diaphragms or caps; however, spermicidal contraceptives are not generally recommended for use with condoms, as there is no evidence of any additional protection compared with non-spermicidal lubricants.

Spermicidal contraceptives are not suitable for use in those with or at high risk of sexually transmitted infections (including HIV); high frequency use of the spermicide nonoxinol ‘9’ p. 743 has been associated with genital lesions, which may increase the risk of acquiring these infections.

**Contraceptive devices**

**Intra-uterine devices**

The intra-uterine device (IUD) is a suitable contraceptive for women of all ages irrespective of parity; however, it is less appropriate for those with an increased risk of pelvic inflammatory disease e.g. women under 25 years.

The most effective intra-uterine devices have at least 380 mm² of copper and have banded copper on the arms. Smaller devices have been introduced to minimise side-effects; these consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper.

Fertility declines with age and therefore a copper intra-uterine device which is fitted in a woman over the age of 40, may remain in the uterus until menopause.

A frameless, copper-bearing intra-uterine device (Gyne Fix®) is also available. It consists of a knotted, polypropylene thread with 6 copper sleeves; the device is anchored in the uterus by inserting the knot into the uterine fundus.

**Caution with oil-based lubricants**

Products such as petroleum jelly (Vaseline®), baby oil and oil-based vaginal and rectal preparations are likely to damage condoms and contraceptive diaphragms made from latex rubber, and may render them less effective as a barrier method of contraception and as a protection from sexually transmitted infections (including HIV).

### 3.1 Contraception, combined

**OESTROGENS COMBINED WITH PROGESTOGENS**

**Combined hormonal contraceptives**

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 - gallstones - heart disease associated with pulmonary hypertension or risk of embolus - history during pregnancy of cholestatic jaundice - history during pregnancy of chorea - history during pregnancy of phephoid gestationis - history during pregnancy of pruritus - history of breast cancer (but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable) - history of haemolytic uraemic syndrome - migraine with aura - personal history of venous or arterial thrombosis - sclerosing treatment for varicose veins - severe or multiple risk factors for arterial disease - severe or multiple risk factors for venous thromboembolism - systemic lupus erythematosus with (or unknown) antiphospholipid antibodies - transient cerebral ischaemic attacks without headaches - undiagnosed vaginal bleeding

- **CAUTIONS** Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - Crohn’s disease - gene mutations associated with breast cancer (e.g. BRCA 1) - history of severe depression especially if induced by hormonal contraceptive - hyperprolactinaemia (seek specialist advice) - inflammatory bowel disease - migraine - personal or family history of hypertriglyceridaemia (increased risk of pancreatitis) - risk factors for arterial disease - risk factors for venous thromboembolism - sickle-cell disease - undiagnosed breast mass

**CAUTIONS, FURTHER INFORMATION**

- Risk of venous thromboembolism There is an increased risk of venous thromboembolic disease in users of combined...
hormonal contraceptives particularly during the first year and possibly after restarting combined hormonal contraceptives following a break of four weeks or more. This risk is considerably smaller than that associated with pregnancy (about 60 cases of venous thromboembolic disease per 100,000 pregnancies). In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors, such as obesity. The risk also varies depending on the type of progestogen.

Provided that women are informed of the relative risks of venous thromboembolism and accept them, the choice of oral contraceptive is for the woman together with the prescriber jointly to make in light of her individual medical history and any contra-indications.

Combined hormonal contraceptives also slightly increase the risk of arterial thromboembolism; however, there is no evidence to suggest that this risk varies between different preparations.

- **Risk factors for venous thromboembolism** Use with caution if any of following factors present but avoid if two or more factors present:
  - family history of venous thromboembolism in first-degree relatives aged under 45 years (avoid contraceptive containing desogestrel or gestodene, or avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
  - obesity; body mass index $\geq 30$ kg/m$^2$ (avoid if body mass index $\geq 35$ kg/m$^2$ unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
  - long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
  - history of superficial thrombophlebitis;
  - age over 35 years (avoid if over 50 years);
  - smoking.

### Combined Hormonal Contraception and Risk of Venous Thromboembolism

<table>
<thead>
<tr>
<th>Progestogen in Combined Hormonal Contraceptive</th>
<th>Estimated incidence per 10,000 women per year of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant, not using combined hormonal contraception</td>
<td>2</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>5-7</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>5-7</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>5-7</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>6-12</td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>6-12</td>
</tr>
<tr>
<td>Gestodene</td>
<td>9-12</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>9-12</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>9-12</td>
</tr>
<tr>
<td>Dienogest</td>
<td>Not known–insufficient data</td>
</tr>
<tr>
<td>Nomegestrol</td>
<td>Not known–insufficient data</td>
</tr>
</tbody>
</table>

Combined with ethinylestradiol Combined with estradiol

- **Risk factors for arterial disease** Use with caution if any one of following factors present but avoid if two or more factors present:
  - family history of arterial disease in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
  - diabetes mellitus (avoid if diabetes complications present);
  - hypertension; blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (in adolescents, avoid if blood pressure very high);
  - smoking (avoid if smoking 40 or more cigarettes daily);
  - age over 35 years (avoid if over 50 years);
  - obesity (avoid if body mass index $\geq 35$ kg/m$^2$ unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
  - migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

Migraine Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).

Combined hormonal contraceptives should be stopped (pending investigation and treatment), if serious neurological effects occur, including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body.

- **INTERACTIONS** Appendix 1 (oestrogens, progestogens).
- **SIDE-EFFECTS**
  - Rare Gallstones · systemic lupus erythematosus · Frequency not known Abdominal cramps · absence of withdrawal bleeding · amenorrhoea after discontinuation · breast enlargement · breast secretion · breast tenderness · cervical erosion · changes in libido · changes in lipid metabolism · changes in vaginal discharge · chloasma · chloasma · contact lenses may irritate · depression · fluid retention · headache · hepatic tumours · hypertension · irritability · leg cramps · liver impairment · nausea · nervousness · photosensitivity · reduced menstrual loss · skin reactions · thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB) · visual disturbances · vomiting · ‘spotting’ in early cycles
  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women taking the combined oral contraceptive pill; this relative risk may be due to an earlier diagnosis. In users of combined oral contraceptive pills the cancers are more likely to be localised to the breast. The most important factor for diagnosing breast cancer appears to be the age at which the contraceptive is stopped rather than the duration of use; any increase in the rate of diagnosis diminishes gradually during the 10 years after stopping and disappears by 10 years.
    - Cervical cancer Use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years.

The possible small increase in the risk of breast cancer and cervical cancer should be weighed against the protective effect against cancers of the ovary and endometrium.

- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Avoid until weaning or for 6 months after birth (adverse effects on lactation).
- **HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), liver tumours.
- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use Each tablet should be taken at approximately same time each day; if delayed, contraceptive protection...
may be lost. 21-day combined preparations, 1 tablet daily for 21 days; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs); if reasonably certain a woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days. Every day (ED) combined preparations, 1 active tablet daily for 21 days, followed by 1 inactive tablet daily for 7 days; subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets being taken); if reasonably certain a woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days.

Changing to combined preparation containing different progestogen If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start the first active tablet of new brand immediately. See individual monographs for requirements of specific preparations. Changing from progestogen-only tablet If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start new brand immediately, additional precautions (barrier methods) necessary for first 7 days. Secondary amenorrhoea (exclude pregnancy) Start any day, additional precautions (barrier methods) necessary during first 7 days (9 days for Qlaira®).

After childbirth (not breast-feeding) Start 3 weeks after birth (increased risk of thrombosis if started earlier); later than 3 weeks postpartum additional precautions (barrier methods) necessary for first 7 days (9 days for Qlaira®).

After abortion or miscarriage Start same day.

### PATIENT AND CARER ADVICE

#### Missed pill

The critical time for loss of contraceptive protection is when a pill is omitted at the beginning or end of a cycle (which lengthens the pill-free interval).

If a woman forgets to take a pill, it should be taken as soon as she remembers, and the next one taken at the normal time (even if this means taking 2 pills together). A missed pill is one that is 24 or more hours late. If a woman misses only one pill, she should take an active pill as soon as she remembers and then resume normal pill-taking. No additional precautions are necessary.

If a woman misses 2 or more pills (especially from the first 7 in a packet), she may not be protected. She should take an active pill as soon as she remembers and then resume normal pill-taking. In addition, she must either abstain from sex or use an additional method of contraception such as a condom for the next 7 days. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of everyday (ED) pills, omitting the 7 inactive tablets).

Emergency contraception is recommended if 2 or more combined oral contraceptive tablets are missed from the first 7 tablets in a packet and unprotected intercourse has occurred since finishing the last packet.

Travel Women taking oral contraceptives are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of combined oral contraceptives. If vomiting occurs within 2 hours of taking a combined oral contraceptive another pill should be taken as soon as possible. In cases of persistent vomiting or severe diarrhoea lasting more than 24 hours, additional precautions should be used during and for 7 days after recovery. If the vomiting and diarrhoea occurs during the last 7 tablets, the next pill-free interval should be omitted (in the case of ED tablets the inactive ones should be omitted).

### Dienogest with estradiol valerate

#### INDICATIONS AND DOSE

Contraception with 28-day combined preparations

Menstrual symptoms with 28-day combined preparations

- BY MOUTH
- Females of childbearing potential: 1 active tablet once daily for 26 days, followed by 1 inactive tablet daily for 2 days, withdrawal bleeding may occur during the 2-day interval of inactive tablets, tablets should be taken at approximately the same time each day

#### DIRECTIONS FOR ADMINISTRATION

Changing to Qlaira®: start the first active Qlaira® tablet on the day after taking the last active tablet of the previous brand

#### PATIENT AND CARER ADVICE

Missed dose A missed pill for a patient taking Qlaira® is one that is 12 hours or more late; for information on how to manage missed pills in women taking Qlaira®, refer to product literature.

Diarrhoea and vomiting In cases of persistent vomiting or severe diarrhoea lasting more than 12 hours in women taking Qlaira®, refer to product literature.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Dienogest with estradiol valerate (Non-proprietary)
  - Dienogest 2 mg, Estradiol valerate 2 mg
  - Dienogest 2 mg tablets | 15 tablet [POM] no price available
  - Estradiol valerate 2 mg, Dienogest 3 mg
  - Estradiol valerate 2 mg | Dienogest 3 mg tablets | 51 tablet [POM] no price available
  - Qlaira (Bayer Plc)
  - Qlaira tablets | 84 tablet [POM] £25.18

### Estradiol with nomegestrol

#### INDICATIONS AND DOSE

Contraception

- BY MOUTH
- Females of childbearing potential: 1 active tablet daily for 24 days, followed by 1 inactive tablet daily for 4 days, to be started on day 1 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval

#### PREGNANCY

Toxicity in animal studies.

#### DIRECTIONS FOR ADMINISTRATION

Changing to Zoely®, start the first active Zoely® tablet on the day after taking the last active tablet of the previous brand or, at the latest, the day after the tablet-free or inactive tablet interval of the previous brand.

#### PATIENT AND CARER ADVICE

Missed doses A missed pill for a patient taking Zoely® is one that is 12 hours or more late; for information on how to manage missed pills in women taking Zoely®, refer to product literature.

Diarrhoea and vomiting In cases of persistent vomiting or severe diarrhoea lasting more than 12 hours in women taking Zoely®, refer to product literature.
Ethinylestradiol with desogestrel

### INDICATIONS AND DOSE

Contraception with 21-day combined preparations | Menstrual symptoms with 21-day combined preparations

- **BY MOUTH**
  - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **Ethinylestradiol with desogestrel (Non-proprietary)**
  - Ethinylestradiol 20 microgram, Desogestrel
    - 150 microgram Ethinylestradiol 20microgram / Desogestrel 150microgram tablets | 63 tablet £6.13
    - Ethinylestradiol 30 microgram, Desogestrel
      - 150 microgram Ethinylestradiol 30microgram / Desogestrel 150microgram tablets | 63 tablet £5.04

- **Alenini (Actavis UK Ltd)**
  - Ethinylestradiol 20 microgram, Desogestrel
    - 150 microgram Alenini 150microgram/20microgram tablets | 63 tablet £8.44

- **Alenima (Teva Uk Ltd)**
  - Ethinylestradiol 30 microgram, Desogestrel
    - 150 microgram Alenima 150microgram/30microgram tablets | 63 tablet £6.13
  - Bimizza (Morningside Healthcare Ltd)
    - Ethinylestradiol 20 microgram, Desogestrel
      - 150 microgram Bimizza 150microgram/20microgram tablets | 63 tablet £5.04

- **Cimizt (Morningside Healthcare Ltd)**
  - Ethinylestradiol 30 microgram, Desogestrel
    - 150 microgram Cimizt 150microgram/30microgram tablets | 63 tablet £8.44

- **Gedarel (Consilient Health Ltd)**
  - Ethinylestradiol 20 microgram, Desogestrel
    - 150 microgram Gedarel 20microgram/150microgram tablets | 63 tablet £5.08

- **Lestramyl (Mylan Ltd)**
  - Ethinylestradiol 20 microgram, Desogestrel
    - 150 microgram Lestramyl 20microgram/150microgram tablets | 63 tablet £4.19

- **Marvelon (Merck Sharp & Dohme Ltd)**
  - Ethinylestradiol 30 microgram, Desogestrel
    - 150 microgram Marvelon 150microgram/30microgram tablets | 63 tablet £7.10

### Ethinylestradiol with drospirenone

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **Ethinylestradiol with drospirenone (Non-proprietary)**
  - Drospirenone 3 mg, Ethinylestradiol 30 microgram
    - Ethinylestradiol 30microgram / Drospirenone 3mg tablets | 63 tablet £8.35 DT price = £14.70
  - Acondro (Mylan Ltd)
    - Drospirenone 3 mg, Ethinylestradiol 30 microgram Acondro 0.03mg/3mg tablets | 63 tablet £14.70 DT price = £14.70
  - Cleosensa (Actavis UK Ltd)
    - Drospirenone 3 mg, Ethinylestradiol 30 microgram Cleosensa 0.03mg/3mg tablets | 63 tablet £14.70 DT price = £14.70
  - Daylette (Consilient Health Ltd)
    - Drospirenone 3 mg, Ethinylestradiol 20 microgram Daylette 0.02mg/3mg tablets | 84 tablet £10.50 DT price = £14.70
  - Dretine (Teva Uk Ltd)
    - Drospirenone 3 mg, Ethinylestradiol 30 microgram Dretine 0.02mg/3mg tablets | 63 tablet £8.30 DT price = £14.70
  - Eloine (Bayer Plc)
    - Drospirenone 3 mg, Ethinylestradiol 20 microgram Eloine 0.02mg/3mg tablets | 84 tablet £14.70 DT price = £14.70
  - Lucette (Consilient Health Ltd)
    - Drospirenone 3 mg, Ethinylestradiol 30 microgram Lucette 0.03mg/3mg tablets | 63 tablet £9.35 DT price = £14.70
  - Yacella (Morningside Healthcare Ltd)
    - Drospirenone 3 mg, Ethinylestradiol 30 microgram Yacella 0.03mg/3mg tablets | 63 tablet £8.30 DT price = £14.70

### Ethinylestradiol with etonogestrel

### INDICATIONS AND DOSE

Contraception | Menstrual symptoms

- **BY VAGINA**
  - Females of childbearing potential: 1 unit, insert the ring into the vagina on day 1 of cycle and leave in for 3 weeks; remove ring on day 22; subsequent courses repeated after 7-day ring free interval (during which withdrawal bleeding occurs)

### DIRECTIONS FOR ADMINISTRATION

Changing method of contraception to vaginal ring
Changing from combined hormonal contraception
Insert ring at the latest on the day after the usual tablet-free, patch-free, or inactive-tablet interval. If previous contraceptive used
correctly, or pregnancy can reasonably be excluded, can switch to ring on any day of cycle.
Changing from progestogen-only method From an implant or intra-uterine progestogen-only device, insert ring on the day implant or intra-uterine progestogen-only device removed; from an injection, insert ring when next injection due; from oral preparation, first ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days.

- **PATIENT AND CARER ADVICE**
  Patients or carers should be given advice on how to administer vaginal ring.
  Counselling: The presence of the ring should be checked regularly.
  **Missed doses**
  Expulsion, delayed insertion or removal, or broken vaginal ring: If the vaginal ring is expelled for less than 3 hours, rinse the ring with cool water and reinsert immediately; no additional contraception is needed.
  If the ring remains outside the vagina for more than 3 hours or if the user does not know when the ring was expelled, contraceptive protection may be reduced:
  - If ring expelled during week 1 or 2 of cycle, rinse ring with cool water and reinsert; use additional precautions (barrier methods) for next 7 days;
  - If ring expelled during week 3 of cycle, either insert a new ring to start a new cycle or allow a withdrawal bleed and insert a new ring no later than 7 days after ring was expelled; latter option only available if ring was used continuously for at least 7 days before expulsion.

If insertion of a new ring at the start of a new cycle is delayed, contraceptive protection is lost. A new ring should be inserted as soon as possible; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. If intercourse occurred during the extended ring-free interval, pregnancy should be considered.

No additional contraception is required if removal of the ring is delayed by up to 1 week (4 weeks of continuous use). The 7-day ring-free interval should be observed and subsequently a new ring should be inserted. Contraceptive protection may be reduced with continuous use of the ring for more than 4 weeks—pregnancy should be ruled out before inserting a new ring.

If the ring breaks during use, remove it and insert a new ring immediately; additional precautions (barrier methods) should be used for the first 7 days of the new cycle.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Vaginal delivery system**
  - Ethinylestradiol with etonogestrel (Non-proprietary)
    Ethinylestradiol 2.7 mg, Etonogestrel 11.7 mg  
    Ethinylestradiol 2.7 mg / Etonogestrel 11.7 mg vaginal delivery system | 3 system [POM] no price available
  - NuvaRing (Merck Sharp & Dohme Ltd)
    Ethinylestradiol 2.7 mg, Etonogestrel 11.7 mg  
    NuvaRing 0.12 mg/0.015 mg per day vaginal delivery system | 3 system [POM] £28.70

- **INDICATIONS AND DOSE**
  Contraception with 21-day combined preparations | Menstrual symptoms with 21-day combined preparations
  - **BY MOUTH**
    - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.
  Contraception with 28-day combined preparations | Menstrual symptoms with 28-day combined preparations
  - **BY MOUTH**
    - Females of childbearing potential: 1 active tablet once daily for 21 days, followed by 1 inactive tablet daily for 7 days; subsequent courses repeated without interval, withdrawal bleeding occurs during the 7-day interval of inactive tablets being taken, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.
Genito-urinary system

Ethinylestradiol with levonorgestrel

- **INDICATIONS AND DOSE**
  - **Contraception with 21-day combined preparations**
    - **Menstrual symptoms with 21-day combined preparations**
      - **BY MOUTH**
        - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.
  - **Contraception with 28-day combined preparations**
    - **Menstrual symptoms with 28-day combined preparations**
      - **BY MOUTH**
        - Females of childbearing potential: 1 active tablet once daily for 21 days, followed by 1 inactive tablet once daily for 7 days, withdrawal bleeding occurs during the 7-day interval of inactive tablets being taken, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day. Subsequent courses repeated without interval.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Ethinylestradiol with levonorgestrel (Non-proprietary)**
      - Ethinylestradiol 30 microgram, Levonorgestrel
        - 50 microgram: Ethinylestradiol 30 microgram / Levonorgestrel 50 microgram tablets | 6 tablet (POM) no price available | 18 tablet (POM) no price available
        - Ethinylestradiol 40 microgram, Levonorgestrel
          - 75 microgram: Ethinylestradiol 40 microgram / Levonorgestrel 75 microgram tablets | 5 tablet (POM) no price available | 15 tablet (POM) no price available
          - Ethinylestradiol 30 microgram, Levonorgestrel
            - 125 microgram: Ethinylestradiol 30 microgram / Levonorgestrel 125 microgram tablets | 10 tablet (POM) no price available | 30 tablet (POM) no price available
    - **Eleven (MedRx Healthcare LLP)**
      - Ethinylestradiol 30 microgram, Levonorgestrel
        - 150 microgram: Eleven 150 microgram/30 microgram tablets | 63 tablet (POM) £29.25 DT price = £2.82
    - **Erlibelle (Actavis UK Ltd)**
      - Ethinylestradiol 30 microgram, Levonorgestrel
        - 150 microgram: Erlibelle 30 microgram/150 microgram tablets | 63 tablet (POM) £2.82 DT price = £2.82

- **Levest (Morningside Healthcare Ltd)**
  - Ethinylestradiol 30 microgram, Levonorgestrel
    - 150 microgram: Levest 150/30 tablets | 21 tablet (POM) £0.85 (Hospital only) | 63 tablet (POM) £1.80 DT price = £2.82

- **Maxen (Lupin (Europe) Ltd)**
  - Ethinylestradiol 30 microgram, Levonorgestrel
    - 150 microgram: Maxen 150 microgram/30 microgram tablets | 63 tablet (POM) £1.88 DT price = £2.82
  - **Microgynon 30 (Bayer Plc)**
    - Ethinylestradiol 30 microgram, Levonorgestrel
      - 150 microgram: Microgynon 30 tablets | 63 tablet (POM) £2.82 DT price = £2.82

- **Ovranette (Pfizer Ltd)**
  - Ethinylestradiol 30 microgram, Levonorgestrel
    - 150 microgram: Ovranette 150 microgram/30 microgram tablets | 63 tablet (POM) £2.20 DT price = £2.82

- **Rigevidon (Consilient Health Ltd)**
  - Ethinylestradiol 30 microgram, Levonorgestrel
    - 150 microgram: Rigevidon tablets | 63 tablet (POM) £1.89 DT price = £2.82

Ethinylestradiol with norelgestromin

- **INDICATIONS AND DOSE**
  - **Contraception**
    - **Menstrual symptoms**
      - **BY TRANSDERMAL APPLICATION**
        - Females of childbearing potential: Apply 1 patch once weekly for 3 weeks, apply first patch on day 1 of cycle, change patch on days 8 and 15; remove third patch on day 22 and apply new patch after 7-day patch-free interval to start subsequent contraceptive cycle, subsequent courses repeated after a 7-day patch free interval (during which withdrawal bleeding occurs)

- **DIRECTIONS FOR ADMINISTRATION**
  - Adhesives or bandages should not be used to hold patch in place. If no longer sticky do not reapply but use a new patch.
  - Changing to a transdermal combined hormonal contraceptive Changing from combined oral contraception Apply patch on the first day of withdrawal bleeding; if no withdrawal bleeding within 5 days of taking last active tablet, rule out pregnancy before applying first patch. Unless patch is applied on first day of withdrawal bleeding, additional precautions (barrier methods) should be used concurrently for first 7 days.
  - Changing from progestogen-only method
    - from an implant, apply first patch on the day implant removed
    - from an injection, apply first patch when next injection due
    - from oral progestogen, first patch may be applied on any day after stopping pill
  - For all methods additional precautions (barrier methods) should be used concurrently for first 7 days.

After childbirth (not breast-feeding)

- Start 4 weeks after birth; if started later than 4 weeks after birth additional precautions (barrier methods) should be used for first 7 days.

After abortion or miscarriage

- Before 20 weeks’ gestation start immediately; no additional contraception required if started immediately. After 20 weeks’ gestation on day 21 after abortion or on the first day of first spontaneous menstruation; additional precautions (barrier methods) should be used for first 7 days after applying the patch.

**PATIENT AND CARER ADVICE**

- Patients and carers should be given advice on how to administer patches.

Missed doses

- Delayed application or detached patch If a patch is partly detached for less than 24 hours, reapply to the same site or replace with a new patch immediately; no additional
contraception is needed and the next patch should be applied on the usual ‘change day’. If a patch remains detached for more than 24 hours or if the user is not aware when the patch became detached, then stop the current contraceptive cycle and start a new cycle by applying a new patch, giving a new ‘Day 1’; an additional non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle.

If application of a new patch at the start of a new cycle is delayed, contraceptive protection is lost. A new patch should be applied as soon as remembered giving a new ‘Day 1’; additional non-hormonal methods of contraception should be used for the first 7 days of the new cycle. If application of a patch in the middle of the cycle is delayed (i.e. the patch is not changed on day 8 or day 15):

- for up to 48 hours, apply a new patch immediately; next patch ‘change day’ remains the same and no additional contraception is required;
- for more than 48 hours, contraceptive protection may have been lost. Stop the current cycle and start a new 4-week cycle immediately by applying a new patch giving a new ‘Day 1’; additional non-hormonal contraception should be used for the first 7 days of the new cycle.

If the patch is not removed at the end of the cycle (day 22), remove it as soon as possible and start the next cycle on the usual ‘change day’, the day after day 28; no additional contraception is required.

Travel
Women using patches are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

### NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (September 2003) that Evra® patches should be restricted for use in women who are likely to comply poorly with combined oral contraceptives.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Transdermal patch**
- **Evra** (Janssen-Cilag Ltd)
  - Ethinylestradiol 3.9 microgram per 24 hour, Norelgestromin 203 microgram per 24 hour Evra transdermal patches | 9 patches
  - DT price = £19.51

### Ethinylestradiol with norethisterone

**INDICATIONS AND DOSE**

Contraception with 21-day combined preparations

Menstrual symptoms with 21-day combined preparations

- **BY MOUTH**
- Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Ethinylestradiol with norethisterone (Non-proprietary)**
  - Ethinylestradiol 35 microgram, Norethisterone 500 microgram Ethinylestradiol 35 microgram / Norethisterone 500 microgram tablets | 5 tablet (Pom) no price available | 7 tablet (Pom) no price available | 21 tablet (Pom) no price available
  - Ethinylestradiol 35 microgram, Norethisterone 750 microgram Ethinylestradiol 35 microgram / Norethisterone 750 microgram tablets | 21 tablet (Pom) no price available
  - Ethinylestradiol 35 microgram, Norethisterone 1 mg Ethinylestradiol 35 microgram / Norethisterone 1 mg tablets | 9 tablet (Pom) no price available | 21 tablet (Pom) no price available | 42 tablet (Pom) no price available
  - **Brevina** (Pfizer Ltd)
    - Ethinylestradiol 35 microgram, Norethisterone 500 microgram Brevina 500 microgram tablets | 63 tablet (Pom) £1.99 DT price = £1.99
  - Ethinylestradiol 20 microgram, Norethisterone acetate 1 mg Ethinylestradiol 20 microgram / Norethisterone acetate 1 mg tablets | 63 tablet (Pom) £2.30 DT price = £2.30
  - **Loestrin** 20 (Galen Ltd)
    - Ethinylestradiol 30 microgram, Norethisterone acetate 1.5 mg Ethinylestradiol 30 microgram / Norethisterone acetate 1.5 mg tablets | 63 tablet (Pom) £3.32 DT price = £3.32
  - **Norina** (Pfizer Ltd)
    - Ethinylestradiol 35 microgram, Norethisterone 1 mg Norina 1 mg tablets | 63 tablet (Pom) £2.28 DT price = £2.28

**Evra transdermal patches**

- **Lizinna** (Janssen-Cilag Ltd)
  - Ethinylestradiol 3.9 microgram, Norelgestromin 203 microgram Ethinylestradiol 3.9 microgram / Norelgestromin 203 microgram patches | 9 patch (Pom) £19.51

**Cilique** (Janssen-Cilag Ltd)
- Ethinylestradiol 3.9 microgram, Norelgestromin 203 microgram Ethinylestradiol 3.9 microgram / Norelgestromin 203 microgram patches | 9 patch (Pom) £19.51

**Cilest** (Janssen-Cilag Ltd)
- Ethinylestradiol 3.9 microgram, Norelgestromin 203 microgram Ethinylestradiol 3.9 microgram / Norelgestromin 203 microgram patches | 9 patch (Pom) £19.51

**Loestrin** 20 (Galen Ltd)
- Ethinylestradiol 30 microgram, Norelgestromin 1.5 mg Ethinylestradiol 30 microgram / Norelgestromin 1.5 mg tablets | 63 tablet (Pom) £3.32

**Clique** (Consilient Health Ltd)
- Ethinylestradiol 35 microgram, Norelgestromin 500 microgram Ethinylestradiol 35 microgram / Norelgestromin 500 microgram tablets | 63 tablet (Pom) £4.65 DT price = £4.65

**Lizinna** (Morningside Healthcare Ltd)
- Ethinylestradiol 35 microgram, Norelgestromin 500 microgram Ethinylestradiol 35 microgram / Norelgestromin 500 microgram tablets | 63 tablet (Pom) £5.37 DT price = £5.37
Norethisterone with mestranol

**INDICATIONS AND Dose**

**Contraception | Menstrual symptoms**

- **By mouth**
- Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval; withdrawal bleeding can occur during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at the same time each day.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Norinyl-1 (Pfizer Ltd)
  - Mestranol 50 microgram, Norethisterone 1 mg Norinyl-1 tablets | 63 tablet | £2.19 DT price = £2.19

3.2 Contraception, devices

Contraception devices not listed below Levonorgestrel, p. 737

CONTRACEPTIVE DEVICES

Intra-uterine contraceptive devices (copper)

**INDICATIONS AND Dose**

**Contraception**

- **By intra-uterine administration**
- Females of childbearing potential: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (JUNE 2015) INTRA-UTERINE CONTRACEPTION: UTERINE PERFORATION—UPDATED INFORMATION ON RISK FACTORS

Uterine perforation most often occurs during insertion, but might not be detected until sometime later. The risk of uterine perforation is increased when the device is inserted up to 36 weeks postpartum or in patients who are breastfeeding. Before inserting an intra-uterine contraceptive device, inform patients that perforation occurs in approximately 1 in every 1000 insertions and signs and symptoms include:

- severe pelvic pain after insertion (worse than period cramps);
- pain or increased bleeding after insertion which continues for more than a few weeks;
- sudden changes in periods;
- pain during intercourse;
- unable to feel the threads.

Patients should be informed on how to check their threads and to arrange a check-up if threads cannot be felt, especially if they also have significant pain. Partial perforation may occur even if the threads can be seen; consider this if there is severe pain following insertion and perform an ultrasound.

**CONTRA-INDICATIONS**

Active trophoblastic disease (until return to normal of urine and plasma·gonadotrophin concentration) - distorted uterine cavity - established or marked immunosuppression - genital malignancy - medical diathesis - pelvic inflammatory disease - recent sexually transmitted infection (if not fully investigated and treated) - severe anaemia - small uterine cavity - unexplained uterine bleeding - Wilson’s disease.

**CAUTIONS**

Anaemia - anticoagulant therapy (avoid if possible) - diabetes - disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression) - drug-induced immunosuppression (risk of infection—avoid if marked immunosuppression) - endometriosis - epilepsy (risk of seizure at time of insertion) - fertility problems - history of pelvic inflammatory disease - increased risk of expulsion if inserted before uterine involution - menorrhagia (progestogen intra-uterine system might be preferable) - nulliparity - severe cervical stenosis - severe primary dysmenorrhea - severely scarred uterus (including after endometrial resection) - young age

**CAUTIONS, FURTHER INFORMATION**

An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential post-coital contraception should be considered.

- **Risk of infection** The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:
  - they are under 25 years old or
  - they are over 25 years old and have a new partner or have had more than one partner in the past year or their regular partner has other partners.

  In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, Neisseria gonorrhoeae) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days.

- **SIDE-EFFECTS**

  Allergy - bleeding (on insertion) - cervical perforation - displacement - dysmenorrhea - expulsion - menorrhagia - occasionally epileptic seizure (on insertion) - pain (on insertion, alleviated by NSAID such as ibuprofen 30 minutes before insertion) - pelvic infection may be exacerbated - uterine perforation - vasovagal attack (on insertion)

- **SIDE-EFFECTS, FURTHER INFORMATION**

  Presence of significant symptoms (especially pain). Advise the patient to seek medical attention promptly in case of significant symptoms.

  - **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if patient has a copper allergy.
  - **PREGNANCY** If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Remove device; if pregnancy occurs, increased likelihood that it may be ectopic.
  - **BREAST FEEDING** Not known to be harmful.
  - **MONITORING REQUIREMENTS** Gynaecological examination before insertion, 6–8 weeks after insertion, then annually.
  - **DIRECTIONS FOR ADMINISTRATION** The timing and technique of fitting an intra-uterine device are critical for its subsequent performance. The healthcare professional inserting (or removing) the device should be fully trained in the technique and should provide full counselling backed, where available, by the patient information leaflet. Devices should not be fitted during the heavy days of the period; they are best fitted after the end of menstruation and before the calculated time of implantation.
### Vaginal contraceptives

#### SILICONE CONTRACEPTIVE DIAPHRAGMS

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#### SILICONE CONTRACEPTIVE PESSARIES

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### Other drugs used for Contraception, emergency

Intra-uterine contraceptive devices (copper), p. 734 Levonorgestrel, p. 737
**Ulipristal acetate**

**DRUG ACTION** Ulipristal acetate is a progesterone receptor modulator with a partial progesterone antagonist effect.

**INDICATIONS AND DOSE**

**Pre-operative and intermitent treatment of moderate to severe symptoms of uterine fibroids**
- **BY MOUTH**
- Adult: 5 mg once daily for up to 3 months starting during the first week of menstruation, courses may be repeated if necessary, re-treatment should start no sooner than during the first week of the second menstruation following completion of the first course; max. 4 courses

**Emergency contraception**
- **BY MOUTH**
- Females of childbearing potential: 30 mg for 1 dose, to be taken as soon as possible after coitus, but no later than after 120 hours

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**
Repeated use as an emergency contraceptive within a menstrual cycle

**SPECIFIC CONTRA-INDICATIONS**
- When used for uterine fibroids: Breast cancer | cervical cancer | ovarian cancer | undiagnosed vaginal bleeding | uterine cancer | vaginal bleeding not caused by uterine fibroids

**CAUTIONS** Uncontrolled severe asthma

**INTERACTIONS** → Appendix 1 (ulipristal).

The effectiveness of ulipristal as an emergency contraceptive is possibly reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

**SIDE-EFFECTS**

- **Common or very common**
  - When used for emergency contraception: Abdominal pain | back pain | diarrhoea | dizziness | fatigue | gastrointestinal disturbances | headache | menstrual irregularities | muscle spasms | nausea | vomiting
  - When used for uterine fibroids: Abdominal pain | acne | breast pain | dizziness | endometrial thickening | headache | hot flushes | hyperhidrosis | malaise | menstrual disturbances | myalgia | nausea | oedema | ovarian cyst (including rupture) | pelvic pain | uterine haemorrhage

- **Uncommon**
  - When used for emergency contraception: Blurred vision | breast tenderness | dry mouth | hot flushes | pruritus | rash | tremor | uterine spasm
  - When used for uterine fibroids: Anxiety | constipation | dry mouth | dyspepsia | epistaxis | flatulence | urinary incontinence

**CONCEPTION AND CONTRACEPTION** When ulipristal is given as an emergency contraceptive the effectiveness of combined hormonal and progestogen-only contraceptives may be reduced—additional precautions (barrier methods) required for 14 days for combined and parenteral progestogen-only hormonal contraceptives (16 days for Quaira®) and 9 days for oral progestogen-only contraceptives. When ulipristal is given for uterine fibroids non-hormonal contraceptive methods (barrier methods or intra-uterine device) should be used both during treatment and for 12 days after stopping, if required.

**PREGNANCY** Limited information available when used as an emergency contraceptive. Manufacturer advises avoid for uterine fibroids—no information available.

**BREAST FEEDING** In emergency contraception manufacturer advises avoid for 1 week after administration—present in milk. When used for uterine fibroids, manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
- When used for Emergency contraception: Manufacturer advises avoid in severe impairment—no information available.
- When used for Uterine fibroids: Manufacturer advises avoid in moderate to severe impairment unless patient is closely monitored—no information available.

**RENAL IMPAIRMENT**
- When used for Uterine fibroids: Manufacturer advises avoid in severe impairment unless patient is closely monitored—no information available.

**MONITORING REQUIREMENTS**
- When used for Uterine fibroids: Periodic monitoring of the endometrium is recommended following repeated intermittent treatment.

**PATIENT AND CARER ADVICE**

**Missed doses**
- When used for Uterine fibroids: If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. Treatment free intervals
- When used for Uterine fibroids: The prescriber should explain the requirement for treatment free intervals.
- When used for Emergency contraception: If vomiting occurs within 3 hours of taking a dose, a replacement dose should be given. When prescribing or supplying hormonal emergency contraception, women should be advised:
  - that their next period may be early or late;
  - that a barrier method of contraception needs to be used until the next period;
  - to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy;
  - to return in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned (if there is any doubt as to whether menstruation has occurred, a pregnancy test should be performed at least 3 weeks after unprotected intercourse).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **EllaOne** (HRA Pharma UK Ltd) Ulipristal acetate 30 mg EllaOne 30mg tablets | 1 tablet | £14.05
- **Esmya** (Gedeon Richter (UK) Ltd) Ulipristal acetate 5 mg Esmya 5mg tablets | 28 tablet | £114.13

### 3.4 Contraception, oral progestogen-only

Other drugs used for Contraception, oral progestogen-only Nor ethisterone, p. 699
Desogestrel

- **INDICATIONS AND DOSE**
  - **Contraception**
    - **BY MOUTH**
    - Females of childbearing potential: 75 micrograms daily, dose to be taken at the same time each day, starting on day 1 of cycle then continuously, if administration delayed for 12 hours or more it should be regarded as a ‘missed pill’

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 930 · history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable · severe arterial disease · undiagnosed vaginal bleeding

- **CAUTIONS**
  - Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice · arterial disease · functional ovarian cysts · history of jaundice in pregnancy · malabsorption syndromes · past ectopic pregnancy · sex-steroid dependent cancer · systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

- **SIDE-EFFECTS**
  - Breast cancer · There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

- **PREGNANCY**
  - Not known to be harmful.

- **BREAST FEEDING**
  - Progestogen-only contraceptives do not affect lactation.

- **HEPATIC IMPAIRMENT**
  - Caution in severe liver disease and recurrent cholestatic jaundice. Avoid in liver tumour.

- **PATIENT AND CARER ADVICE**
  - **Missed pill** The following advice is recommended: ‘If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 12 hours overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days’.

  The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more tablets are missed or taken more than 12 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

  Surgery · All progestogen-only contraceptives are suitable for use as an alternative to combined hormonal contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

  Starting routine · One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 12 hours contraceptive protection may be lost). Additional contraceptive precautions are not required if desogestrel is started up to and including day 5 of the menstrual cycle; if started after this time, additional contraceptive precautions are required for 2 days.

  Changing from a combined oral contraceptive · Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

  After childbirth · Oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

  Diarrhoea and vomiting · Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking desogestrel, another pill should be taken as soon as possible. If a replacement pill is not taken within 12 hours of the normal time for taking desogestrel, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium has advised (September 2003) that Cerazette® should be restricted for use in women who cannot tolerate oestrogen-containing contraceptives or in whom such preparations are contraindicated.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Desogestrel (Non-proprietary)
    - Desogestrel 75 microgram tablets 84 [POM] £9.55 DTP price = £1.93
    - Aizea (Besins Healthcare (UK) Ltd) Desogestrel 75 microgram tablets 84 [POM] £5.21 DTP price = £1.93
    - Cerazette (Merck Sharp & Dohme Ltd) Desogestrel 75 microgram tablets 84 [POM] £9.55 DTP price = £1.93
    - Cerelle (Consilient Health Ltd) Desogestrel 75 microgram tablets 84 [POM] £3.50 DTP price = £1.93
    - Desomono (Smedix Developments Ltd) Desogestrel 75 microgram tablets 84 [POM] £7.49 DTP price = £1.93
    - Desorex (Somex Pharma) Desogestrel 75 microgram tablets 84 [POM] £6.70 DTP price = £1.93
    - Desorex (Smedix Developments Ltd) Desogestrel 75 microgram tablets 84 [POM] £3.49 DTP price = £1.93
    - Nacrez (Teva UK Ltd) Desogestrel 75 microgram tablets 84 [POM] £3.50 DTP price = £1.93
    - Zelleta (Morningside Healthcare Ltd) Desogestrel 75 microgram tablets 84 [POM] £3.35 DTP price = £1.93
Contraception

- **BY MOUTH**
- Females of childbearing potential: 1 tablet daily starting on day 1 of the cycle then continuously, dose is to be taken at the same time each day, if administration delayed for 3 hours or more it should be regarded as a ‘missed pill’

**JAYDESS®, 13.5MG INTRA-UTERINE DEVICE**

Contraception

- **BY VAGINA**
- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement, or immediately after first-trimester termination; postpartum insertions should be delayed until at least 6 weeks after delivery (12 weeks if uterus involution is substantially delayed); effective for 3 years

**LEVOSERT®, 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE**

Contraception | Menorrhagia

- **BY INTRA-UTERINE ADMINISTRATION**
- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement, or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately after first-trimester abortion; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years

**MIRENA®, 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE**

Contraception | Menorrhagia

- **BY INTRA-UTERINE ADMINISTRATION**
- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement, or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately after first-trimester abortion; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years

**Prevention of endometrial hyperplasia during oestrogen replacement therapy**

- **BY INTRA-UTERINE ADMINISTRATION**
- Females of childbearing potential: Insert during last days of menstruation or withdrawal bleeding at any time if amenorrhoeic; effective for 4 years

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

When used orally as an emergency contraceptive, the effectiveness of levonorgestrel is reduced in women taking enzyme-inducing drugs (and for up to 4 weeks after stopping); a copper intra-uterine device should preferably be used instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose [unlicensed dose—advise women accordingly]; pregnancy should be excluded following use, and medical advice sought if pregnancy occurs. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

With the progestogen—only intra-uterine device, levonorgestrel is released close to the site of the main contraceptive action (on cervical mucus and endometrium) and therefore progestogenic side-effects and interactions are less likely; in particular, enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effect of the progestogen—only intra-uterine system and additional contraceptive precautions are not required.

**UNLICENSED USE**

- With oral use in children: Consult product literature for licensing status of individual preparations.
- With vaginal use in children: Not licensed for use in women under 18 years.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (JUNE 2015) INTRA-UTERINE CONTRACEPTION: UTERINE PERFORATION—UPDATED INFORMATION ON RISK FACTORS**

Uterine perforation most often occurs during insertion, but might not be detected until sometime later. The risk of uterine perforation is increased when the device is inserted up to 36 weeks postpartum or in patients who are breastfeeding. Before inserting an intra-uterine contraceptive device, inform patients that perforation occurs in approximately 1 in every 1000 insertions and signs and symptoms include:

- severe pelvic pain after insertion (worse than period cramps);
- pain or increased bleeding after insertion which continues for more than a few weeks;
- sudden changes in periods;
- pain during intercourse;
- unable to feel the threads.

Patients should be informed on how to check their threads and to arrange a check-up if threads cannot be felt, especially if they also have significant pain. Partial perforation may occur even if the threads can be seen; consider this if there is severe pain following insertion and perform an ultrasound.

**CONTRA-INDICATIONS**

- With intra-uterine use: Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration — acute cervicitis — acute vaginitis — distorted uterine cavity — established immunosuppression — genital malignancy — history of breast cancer but can be considered for a woman in long-term remission who has menorrhagia and requires effective contraception — infected abortion during the previous three months — marked immunosuppression — not suitable for emergency contraception — pelvic inflammatory disease — postpartum endometritis — recent sexually transmitted infection (if not fully investigated and treated) — severe anaemia — small uterine cavity — unexplained uterine bleeding
- With oral use: Acute porphyrias p. 930
- With oral use for contraception: History of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable — severe arterial disease — undiagnosed vaginal bleeding

**CAUTIONS**

- With intra-uterine use: Disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression) — anaemia — anticoagulant therapy (avoid if possible) — diabetes — drug-induced immunosuppression (risk of infection—avoid if marked immunosuppression) — endometriosis — epilepsy (risk of seizure at time of insertion) — fertility problems — history of pelvic inflammatory disease — increased risk of expulsion if inserted before uterine involution — menorrhagia (progestogen intra-uterine system might be preferable) — nulliparity — severe cervical stenosis — severe primary dysmenorrhoea — severely scarred uterus (including after endometrial resection) — young age
- With oral use for contraception: Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice — arterial disease — functional ovarian cysts — history of jaundice in pregnancy — malabsorption syndromes — past ectopic pregnancy — sex-steroid dependent cancer —
systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

- With oral use for emergency contraception. Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - past ectopic pregnancy - severe malabsorption syndromes

**CAUTIONS, FURTHER INFORMATION**

An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential post-coital contraception should be considered.

- Risk of infection with intra-uterine devices. The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:
  - they are under 25 years old
  - they are over 25 years old and
  - have a new partner or
  - have had more than one partner in the past year or
  - their regular partner has other partners.

In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, Neisseria gonorrhoeae) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days.

- Use as a contraceptive in co-morbidities
- With oral use The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory.

**MIRENA® 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE** Advanced uterine atrophy

**INTERACTIONS** → Appendix 1 (progestogens).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Depresssion (sometimes severe) - headache - nausea
- Frequency not known Vomiting

**SPECIFIC SIDE-EFFECTS**

- Common or very common
  - With intra-uterine use Changes in the pattern and duration of menstrual bleeding (spotting or prolonged bleeding) - abdominal pain - acne - alopecia - back pain - breast pain - expulsion - hirsutism - migraine - nervousness - pelvic pain - peripheral oedema - salpingitis

- Uncommon
  - With intra-uterine use Abdominal distension - cervicitis - eczema - pelvic inflammatory disease - pruritus - skin hyperpigmentation
- Rare
  - With intra-uterine use Rash - uterine perforation
- Frequency not known
  - With intra-uterine use Functional ovarian cysts (usually asymptomatic and usually resolve spontaneously—ultrasound monitoring recommended) - allergy - bleeding (on insertion) - cervical perforation - displacement - dysmenorrhoea - epileptic seizures (on insertion) - menorrhagia - pain (on insertion, alleviated by NSAID such as ibuprofen 30 minutes before insertion) - pelvic infection may be exacerbated - vasovagal attack (on insertion)
  - With oral use Breast discomfort - breast tenderness - changes in libido - disturbances of appetite - dizziness - fatigue - menstrual irregularities - skin disorders

**SIDE-EFFECTS, FURTHER INFORMATION**

- Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

- Although the progestogen-only intra-uterine system produces little systemic progestogenic activity, it is usually avoided for 5 years after any evidence of breast cancer. However, the system can be considered for a woman in long-term remission from breast cancer who has menorrhagia and requires effective contraception.

- With intra-uterine use Endometrial disorders should be ruled out before insertion and the patient should be fully counselled (and provided with a patient information leaflet). Improvement in progestogenic side-effects, such as mastalgia and in the bleeding pattern may often become very light or absent. Removal of the intra-uterine system should be considered if the patient experiences migraine or severe headache, jaundice, marked increase of blood pressure, or severe arterial disease.

**PREGNANCY**

- With oral use Not known to be harmful.

- With vaginal use If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Avoid; if pregnancy occurs remove intra-uterine system.

**BREAST FEEDING** Progestogen-only contraceptives do not affect lactation.

**HEPATIC IMPAIRMENT** Caution in severe liver disease and recurrent cholestatic jaundice. Avoid in liver tumour.

**MONITORING REQUIREMENTS**

- With intra-uterine use Gynaecological examination before insertion, 4–6 weeks after insertion, then annually.

**DIRECTIONS FOR ADMINISTRATION**

- With intra-uterine use The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.

**PRESCRIBING AND DISPENSING INFORMATION**

- With intra-uterine use Levonorgestrel-releasing intra-uterine devices vary in licensed indication, duration of use and insertion technique—the MHRA recommends to prescribe and dispense by brand name to avoid inadvertent switching.

**MIRENA® 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE** When system is removed (and not immediately replaced) and pregnancy is not desired, remove during the first few days of menstruation, otherwise additional precautions (e.g. barrier methods) should be used for at least 7 days before removal.

**JAYDESS® 13.5MG INTRA-UTERINE DEVICE** When system is removed (and not immediately replaced) and pregnancy is not desired, remove within 7 days of the onset of menstruation; additional precautions (e.g. barrier methods) should be used if the system is removed at some other time during the cycle and there is intercourse within 7 days.

**LEVONELLE® ONE STEP** Can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society.

**PATIENT AND CARER ADVICE**

**Missed doses**

When used as an oral contraceptive, the following advice is recommended ‘If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours overdue you are not protected. Continue normal pill-taking but you must also
use another method, such as the condom, for the next 2 days’.

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

Diarrhoea and vomiting with use as an oral contraceptive

Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

Starting routine

▶ With oral use for Contraception One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not required if levonorgestrel is started up to and including day 5 of the menstrual cycle; if started after this time, additional contraceptive precautions are required for 2 days.

▶ With intra-uterine use Counsel women to seek medical attention promptly in case of significant symptoms, especially pain. Patient counselling advised. Patient information leaflet to be provided.

After childbirth

Oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

▶ With oral use for Emergency contraception If vomiting occurs within 2 hours of taking levonorgestrel, a replacement dose should be given.

When prescribing or supplying hormonal emergency contraception, women should be advised:

● that their next period may be early or late;

● that a barrier method of contraception needs to be used until the next period;

● to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy;

● to return in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned (if there is any doubt as to whether menstruation has occurred, a pregnancy test should be performed at least 3 weeks after unprotected intercourse).

EXCEPTIONS TO LEGAL CATEGORYLEVONELLE® One Step can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ LEVONORGESTREL (NON-proprietary) Levonorgestrel 1.5mg tablets | 1 tablet P £13.83 DT price = £5.20 | 1 tablet POM £3.74–£5.20 DT price = £5.20

▶ EMERRES (Morningside Healthcare Ltd) Levonorgestrel 1.5 mg Emerves Una 1.5 mg tablets | 1 tablet POM £13.83 DT price = £5.20 | 1 tablet P £13.74–£5.20 DT price = £5.20

▶ ISTERANDA (Sandoz Ltd) Levonorgestrel 1.5 mg Isteranda 1.5 mg tablets | 1 tablet POM £5.20 DT price = £5.20

▶ LEVONELLE (Bayer Plc) Levonorgestrel 1.5 mg Levonelle 1500 microgram tablets | 1 tablet POM £5.20 DT price = £5.20

Intra-uterine device

▶ JAYDESS (Bayer Plc) | LEVONORGESTREL 30 microgram Jaydess 13.5 mg intra-uterine device | 1 device POM £69.22 | Levovert 20 micrograms/24 hours intra-uterine device | 1 device POM £66.00

▶ UPOSTELLE (Consilient Health Ltd) Levonorgestrel 1.5 mg Upostelle 1500 microgram tablets | 1 tablet POM £5.75 DT price = £5.20

▶ NORGESTON (Bayer Plc) | NORGESTON 30 microgram Norgeston 30 microgram tablets | 35 tablet POM £0.92 DT price = £0.92

3.5 Contraception, parenteral progestogen-only

PROGESTOGENS

ETONOGESTREL 27-Sep-2016

INDICATIONS AND DOSE

Contraception (no hormonal contraceptive use in previous month)

▶ BY SUBDERMAL IMPLANTATION

Females of childbearing potential: 1 implant inserted during first 5 days of cycle, implant should be removed within 3 years of insertion

Contraception (postpartum)

▶ BY SUBDERMAL IMPLANTATION

Females of childbearing potential: 1 implant to be inserted 21–28 days after delivery, 1 implant to be inserted after 28 days postpartum in breast-feeding mothers, implant should be removed within 3 years of insertion

Contraception following abortion or miscarriage in the second trimester

▶ BY SUBDERMAL IMPLANTATION

Females of childbearing potential: 1 implant to be inserted 21–28 days after abortion or miscarriage, implant should be removed within 3 years of insertion

Contraception following abortion or miscarriage in the first trimester

▶ BY SUBDERMAL IMPLANTATION

Females of childbearing potential: 1 implant to be inserted within 5 days, implant should be removed within 3 years of insertion

Other drugs used for Contraception, parenteral progestogen-only Norethisterone, p. 699
Medroxyprogesterone acetate

### INDICATIONS AND DOSE

**Dysfunctional uterine bleeding**

- **By mouth**
  - Adult: 2.5–10 mg daily for 5–10 days, repeated for 2 cycles, begin treatment on day 16–21 of cycle

**Secondary amenorrhoea**

- **By mouth**
  - Adult: 2.5–10 mg daily for 5–10 days, repeated for 3 cycles, begin treatment on day 16–21 of cycle

**Mild to moderate endometriosis**

- **By mouth**
  - Adult: 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle

**Progestogenic opposition of oestrogen HRT**

- **By mouth**
  - Adult: 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle

**Endometrial cancer | Renal cell cancer**

- **By mouth**
  - Adult: 200–600 mg daily

**Breast cancer**

- **By mouth**
  - Adult: 0.4–1.5 g daily

**Contraception**

- **By deep intramuscular injection**
  - Females of childbearing potential: 150 mg, to be administered within the first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding)
  - **By subcutaneous injection**
  - Females of childbearing potential: 104 mg, to be administered within first 5 days of cycle or within 5 days postpartum (delay until 6 weeks postpartum if breast-feeding), injected into anterior thigh or abdomen, dose only suitable if no hormonal contraceptive use in previous month

**Long-term contraception**

- **By deep intramuscular injection**
  - Females of childbearing potential: 150 mg every 12 weeks, to be administered within the first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding)
  - **By subcutaneous injection**
  - Females of childbearing potential: 104 mg every 13 weeks, to be administered within first 5 days of cycle or within 5 days postpartum (delay until 6 weeks postpartum if breast-feeding), injected

• **PREGNANCY** Not known to be harmful, remove implant if pregnancy occurs.

• **CONTRA-INDICATIONS** Acute porphyria p. 930 · history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable · severe arterial disease · undiagnosed vaginal bleeding

• **CAUTIONS** Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice · arterial disease · disturbances of lipid metabolism · history during pregnancy of deterioration of otosclerosis · history during pregnancy of pruritus · history of jaundice in pregnancy · malabsorption syndromes · possible risk of breast cancer · sex-steroid dependent cancer · systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

• **INTERACTIONS** Appendix 1 (progestogens). Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. Effectiveness of the etonogestrel-releasing implant may be reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with the enzyme-inducing drug and for at least 4 weeks after stopping. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the implant may be continued in combination with additional contraceptive precautions (e.g. condom) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.

• **SIDE-EFFECTS** Breast discomfort · changes in libido · depression · disturbance of appetite · dizziness · headache · injection-site reactions · menstrual irregularities · nausea · vomiting

• **SIDE-EFFECTS, FURTHER INFORMATION**
  - **Cervical cancer** Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives. The risk of cervical cancer with other progestogen-only contraceptives is not yet known.
  - **Breast cancer** There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

• **BREAST FEEDING** Progestogen-only contraceptives do not affect lactation.

• **DIRECTIONS FOR ADMINISTRATION** The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.

• **PATIENT AND CARER ADVICE** Full counselling backed by patient information leaflet required before administration.
CONTRA-INDICATIONS

GENERAL CONTRA-INDICATIONS
- Acute porphyrias p. 930.
- Severe arterial disease.
- Undiagnosed vaginal bleeding.

SPECIFIC CONTRA-INDICATIONS
- With intramuscular use or subcutaneous use.
  - History of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable.
- With oral use.
  - Breast cancer (unless progestogens are being used in the management of this condition).
  - Genital cancer (unless progestogens are being used in the management of this condition).
  - History of liver tumours.

CAUTIONS

GENERAL CAUTIONS
- Possible risk of breast cancer.

SPECIFIC CAUTIONS
- With intramuscular use or subcutaneous use.
  - History during pregnancy in disturbances of lipid metabolism.
  - History during pregnancy of deterioration of otsosclerosis.
  - History during pregnancy of pruritus.
- With oral use.
  - Asthma.
  - Cardiac dysfunction.
  - Conditions that may worsen with fluid retention (diabetes [progestogens can decrease glucose tolerance—monitor patient closely]).
  - Epilepsy.
  - History of depression.
  - Hypertension.
  - Migraine.
  - Susceptibility to thromboembolism (particular caution with high dose).

INTERACTIONS → Appendix 1 (progestogens).
- With intramuscular use or subcutaneous use.
  - Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes.
  - The effectiveness of medroxyprogesterone acetate intramuscular and subcutaneous injections is not affected by enzyme-inducing drugs and they may be continued as normal during courses of these drugs.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Breast discomfort.
- Changes in libido.
- Depression.
- Dizziness.
- Headache.
- Indigestion.
- (Discontinue treatment if papilloedema or retinal vascular lesions). 
- Menstrual irregularities.
- Nausea.
- Pruritus.
- Vomiting.
- Weight gain.

SPECIFIC SIDE-EFFECTS
- Rare
  - With intramuscular use or subcutaneous use.
    - Osteoporosis.
    - Osteoporotic fractures.
- Frequency not known
  - With intramuscular use or subcutaneous use.
    - Disturbance of appetite.
    - Injection site-reactions.
    - Reduced bone mineral density.
    - Skin disorders.
  - With oral use:
    - Acne.
    - Adrenergic-like effects (when used for malignant disease).
    - Alopecia.
    - Anaphylactoid reactions.
    - Bloating.
    - Breast tenderness.
    - Cervical erosions (when used for malignant disease).
    - Confusion (when used for malignant disease).
    - Congestive heart failure (when used for malignant disease).
    - Constipation (when used for malignant disease).
    - Diarrhoea (when used for malignant disease).
    - Drowsiness.
    - Dry mouth (when used for malignant disease).
    - Euphoria (when used for malignant disease).
    - Fluid retention.
    - Galactorrhoea (when used for malignant disease).
    - Glucocorticoid effects may lead to a cushingoid syndrome (with high doses for malignant disease).
  - Hyperparathyroidism.
  - Hypercalcaemia.
  - Hyperpyrexia.
  - Hypertension.
  - Insomnia.
  - Jaundice.
  - Loss of concentration (when used for malignant disease).
  - Nervousness (when used for malignant disease).
  - Palpitation (when used for malignant disease).
  - Premenstrual-like syndrome.
  - Raised platelet count (when used for malignant disease).
  - Raised white blood cell count (when used for malignant disease).
  - Rash.
  - Retinal thrombosis (when used for malignant disease).
  - Skin reactions.
  - Tachycardia (when used for malignant disease).
  - Urticaria.
  - Vision disorders (when used for malignant disease).

SIDE-EFFECTS, FURTHER INFORMATION
- With intramuscular use or subcutaneous use.
  - Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives.

CONCEPTION AND CONTRACEPTION
- With intramuscular use.
  - If interval between dose is greater than 12 weeks and 5 days (in long-term contraception), rule out pregnancy before next injection and advise patient to use additional contraceptive measures (e.g. barrier) for 14 days after the injection.
- With subcutaneous use.
  - If interval between dose is greater than 13 weeks and 7 days (in long-term contraception), rule out pregnancy before next injection.

PREGNANCY
- With oral use.
  - Avoid—genital malformations and cardiac defects reported.
- With intramuscular use or subcutaneous use.
  - Not known to be harmful.

BREAST FEEDING
- Present in milk—no adverse effects reported. Progestogen-only contraceptives do not affect lactation.
- With intramuscular use or subcutaneous use.
  - The manufacturers advise that in women who are breast-feeding, the first dose should be delayed until 6 weeks after birth; however, evidence suggests no harmful effect to infant if given earlier. The benefits of using medroxyprogesterone acetate in breast-feeding women outweigh any risks.

HEPATIC IMPAIRMENT
- Avoid in liver tumour.
- With oral use.
  - Avoid in hepatic impairment.
- With intramuscular use or subcutaneous use.
  - Caution in severe liver disease and recurrent cholestatic jaundice.

RENAL IMPAIRMENT
- When used for mild to moderate endometriosis or Progestogenic opposition of oestrogen HRT or Dysfunctional uterine bleeding or Secondary amenorrhea.
  - Use with caution.

PATIENT AND CARER ADVICE
- With intramuscular use or subcutaneous use.
  - Full counselling backed by patient information leaflet required before administration—likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility.
3.6 Contraception, spermicidal

SPERMICIDALS

Nonoxinol

- INDICATIONS AND DOSE
  Spermicidal contraceptive in conjunction with barrier methods of contraception such as diaphragms or caps
  - BY VAGINA
  - Females of childbearing potential: consult product literature

- SIDE-EFFECTS
  Genital lesions

SIDE-EFFECTS, FURTHER INFORMATION
High frequency use of the spermicide nonoxinol '9' has been associated with genital lesions, which may increase the risk of acquiring these infections.

- CONCEPTION AND CONTRACEPTION
  No evidence of harm to latex condoms and diaphragms.

- PREGNANCY
  Toxicity in animal studies.

- BREAST FEEDING
  Present in milk in animal studies.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Gel
  EXCIPIENTS: May contain Hydroxybenzoates (parabens), propylene glycol, sorbic acid
  - Gygel (Marlborough Pharmaceuticals Ltd)
  Nonoxinol-9 20 mg per 1 ml Gygel 2% contraceptive jelly: 30 gram £4.25; 81 gram £11.00

4 Erectile and ejaculatory conditions

4.1 Erectile dysfunction

Erectile dysfunction

Overview
Reasons for failure to produce a satisfactory erection include psychogenic, vascular, neurogenic, and endocrine abnormalities; impotence can also be drug-induced.

Intracavernosal, urethral or topical application of vasoactive drugs under careful medical supervision are used for the management of erectile dysfunction. Intracavernosal or intraurethral preparations can also be used in the diagnosis of erectile dysfunction.

Erectile disorders may also be treated with drugs given by mouth which increase the blood flow to the penis. Drugs should be used with caution if the penis is deformed (e.g. in angulation, cavernous fibrosis, and Peyronie's disease).

Priapism

If priapism occurs with alprostadil p. 748, treatment should not be delayed more than 6 hours and is as follows:

- Initial therapy by penile aspiration—using aseptic technique a 19–21 gauge butterfly needle inserted into the corpus cavernosum and 20–50 mL of blood aspirated; if necessary the procedure may be repeated on the opposite side.
- If initial aspiration is unsuccessful a second 19–21 gauge butterfly needle can be inserted into the opposite corpus cavernosum and sterile physiological saline introduced through the first needle and drained through the second.
- If aspiration and lavage of corpora are unsuccessful, cautious intracavernosal injection of a sympathomimetic with action on alpha-adrenergic receptors, continuously monitoring blood pressure and pulse (extreme caution: coronary heart disease, hypertension, cerebral ischaemia or if taking antidepressant) can be given.
- If necessary the sympathomimetic injections can be followed by further aspiration of blood through the same butterfly needle.
- If sympathomimetics unsuccessful, urgent surgical referral for management (possibly including shunt procedure).

Prescribing on the NHS
Some drug treatments for erectile dysfunction may only be prescribed on the NHS under certain circumstances; for details see the criteria listed in part XVIIIIB of the Drug Tariff (Part Xlb of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The Drug Tariffs can be accessed online at: National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm

Health and Personal Social Services for Northern Ireland Drug Tariff: www.hscbusiness.hscni.net/services/2034.htm
Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

Alprostadil

Alprostadil, (prostaglandin E1) is given by intracavernosal injection, intraurethral application, or topical application for the management of erectile dysfunction (after exclusion of treatable medical causes). Intracavernosal or intraurethral preparations can also be used in the diagnosis of erectile dysfunction.

Phosphodiesterase type-5 inhibitors

Avanafil p. 744, sildenafil p. 744, tadalafil p. 746 and vardenafil p. 747 are phosphodiesterase type-5
inhibitors licensed for the treatment of erectile dysfunction; they are not recommended for use with other treatments for erectile dysfunction. The patient should be assessed appropriately before prescribing avanafil, sildenafil, tadalaflı or vardenafil. Since these drugs are given by mouth there is a potential for drug interactions.

Papaverine and phentolamine
Although not licensed the smooth muscle relaxant papaverine has also been given by intracavernosal injection for erectile dysfunction. Patients with neurological or psychogenic impotence are more sensitive to the effect of papaverine than those with vascular abnormalities. Phentolamine mesilate p. 173 is added if the response is inadequate [unlicensed indication]. Persistence of the erection for longer than 4 hours is an emergency.

PHOSPHODIESTERASE TYPE-5 INHIBITORS

Avanafil

- **INDICATIONS AND DOSE**
  - **Erectile dysfunction**
    - **BY MOUTH**
    - Adult: Initially 100 mg, to be taken approximately 15–30 minutes before sexual activity, then adjusted according to response to 50–200 mg (max. per dose 200 mg), to be taken as a single dose as needed; maximum 1 dose per day
  - **Erectile dysfunction in patients on alpha-blocker therapy**
    - **BY MOUTH**
    - Adult: Initially 50 mg, to be taken approximately 15–30 minutes before sexual activity, then adjusted according to response to 50–200 mg (max. per dose 200 mg), to be taken as a single dose as needed; maximum 1 dose per day

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  Max. 100 mg once every 48 hours with concomitant moderate inhibitors of cytochrome P450 enzyme CYP3A4 e.g. aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, or verapamil. Concomitant treatment with a phosphodiesterase type-5 inhibitor and an alpha-blocker can increase the risk of postural hypotension—initiate treatment with a phosphodiesterase type-5 inhibitor (at a low dose) only once the patient is stable on the alpha-blocker.

- **CONTRA-INDICATIONS**
  Avoid if systolic blood pressure below 90 mmHg (no information available) · blood pressure > 170/100 mmHg · hereditary degenerative retinal disorders · history of non-articteric anterior ischaemic optic neuropathy · life-threatening arrhythmia in previous 6 months · mild to severe heart failure · patients in whom vasodilatation or sexual activity are inadvisable · recent history of myocardial infarction · recent history of stroke · recent unstable angina

- **CAUTIONS**
  Active peptic ulceration · anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) · bleeding disorders · cardiovascular disease · left ventricular outflow obstruction · predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)

- **INTERACTIONS**
  ➔ Appendix I (avanafil).

- **SIDE-EFFECTS**
  ➔ Common or very common Back pain · dizziness · dyspepsia · flushing · headache · migraine · myalgia · nasal congestion · nausea · visual disturbances · vomiting

- **Uncommon**
  Drowsiness · epistaxis · hypertension · hypotension · malaise · painful red eyes · palpitation · tachycardia

- **Rare**
  Abdominal pain · diarrhoea · dry mouth · facial oedema · gastritis · genital irritation · gout · haematuria · hyperactivity · hyperbilirubinaemia · hypersensitivity reactions · increased serum creatinine · insomnia · muscle spasms · peripheral oedema · pollakiuria · priapism · rash · Stevens-Johnson syndrome · syncope · weight gain

- **Frequency not known**
  Arrhythmia · myocardial infarction · non-articteric anterior ischaemic optic neuropathy (stop drug if sudden visual impairment occurs) · retinal vascular occlusion · seizures · serious cardiovascular events · sudden hearing loss (discontinue drug and seek medical advice) · unstable angina

- **HEPATIC IMPAIRMENT**
  Use lowest effective initial dose in mild to moderate impairment, adjusted according to response. Manufacturer advises avoid in severe impairment—no information available.

- **RENAL IMPAIRMENT**
  Avoid if eGFR less than 30 mL/minute/1.73 m².

- **PATIENT AND CARER ADVICE**
  Onset of effect may be delayed if taken with food.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  NHS restrictions Spedra™ is not prescribable under the NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’.


- **MEDITIC FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Spedra (A. Menarini Farmaceutica Internazionale SRL) ➔ Avanafil 50 mg Spedra 50mg tablets | 4 tablet [DT] £10.94 DT price + £10.94 8 tablet [DT] £19.70 DT price + £19.70
  - Avanafil 100 mg Spedra 100mg tablets | 4 tablet [DT] £14.08 DT price + £14.08 8 tablet [DT] £26.26 DT price + £26.26

Sildenafil

- **INDICATIONS AND DOSE**
  - **Pulmonary arterial hypertension (initiated under specialist supervision)**
    - **BY MOUTH**
    - Adult: 20 mg 3 times a day
    - **BY INTRAVENOUS INJECTION**
    - Adult: 10 mg 3 times a day, use intravenous route when the oral route is not appropriate

  - **Erectile dysfunction**
    - **BY MOUTH**
    - Adult: Initially 50 mg, to be taken approximately 1 hour before sexual activity, adjusted according to response to 25–100 mg (max. per dose 100 mg) as required, to be taken as a single dose; maximum 1 dose per day

- **CONTRA-INDICATIONS**
  - **GENERAL CONTRA-INDICATIONS**
    - Hereditary degenerative retinal disorders · history of non-articteric anterior ischaemic optic neuropathy · recent history of myocardial infarction · recent history of stroke
SPECIFIC CONTRA-INDICATIONS

- When used for erectile dysfunction: Avoid if systolic blood pressure below 90 mmHg (no information available). Patients in whom vasodilation or sexual activity are inadvisable. Recent unstable angina is a contraindication.
- When used for pulmonary arterial hypertension: Sickle-cell anaemia.

CAUTIONS

GENERAL CAUTIONS
Active peptic ulceration - bleeding disorders - cardiovascular disease - left ventricular outflow obstruction.

SPECIFIC CAUTIONS

- When used for erectile dysfunction: Anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, Peyronie's disease) - predisposition to priapism (e.g., in sickle-cell disease, multiple myeloma, or leukaemia).
- When used for pulmonary arterial hypertension: Anatomical deformation of the penis - autonomic dysfunction - hypotension (avoid if systolic blood pressure below 90 mmHg) - intravascular volume depletion - predisposition to priapism - pulmonary veno-occlusive disease.

INTERACTIONS → Appendix 1 (sildenafil).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Common or very common: Back pain - dyspepsia - flushing - migraine - myalgia - nasal congestion - visual disturbances.
- Frequency not known: Non-articulating anterior ischaemic optic neuropathy (discontinue if sudden visual impairment occurs) - sudden hearing loss (advise patient to seek medical help).

SPECIFIC SIDE-EFFECTS

- Common or very common: Nausea - dizziness - vomiting.
- When used for pulmonary arterial hypertension: Gynaecomastia - haematuria - penile haemorrhage - priapism.
- Rare: When used for erectile dysfunction: Atrial fibrillation - cerebrovascular accident - facial oedema - hypersensitivity reactions - priapism - rash - Stevens-Johnson syndrome - syncope.
- Frequency not known: When used for erectile dysfunction: Arrhythmia - myocardial infarction - seizures - unstable angina.
- When used for pulmonary arterial hypertension: Rash - retinal vascular occlusion.

PREGNANCY
Use only if potential benefit outweighs risk — no evidence of harm in animal studies.

BREAST FEEDING
Manufacturer advises avoid — no information available.

HEPATIC IMPAIRMENT
In pulmonary arterial hypertension, if usual dose not tolerated, reduce oral dose to 20 mg twice daily and intravenous dose to 10 mg twice daily. For erectile dysfunction, use initial dose of 25 mg. Manufacturer advises avoid in severe impairment.

RENAL IMPAIRMENT
Use initial dose of 25 mg in erectile dysfunction if eGFR less than 30 mL/minute/1.73 m².

In pulmonary hypertension, if usual dose not tolerated, reduce oral dose to 20 mg twice daily and intravenous dose to 10 mg twice daily.

TREATMENT CESSATION

- When used for Pulmonary arterial hypertension: Consider gradual withdrawal.

PATIENT AND CARER ADVICE

- When used for Erectile dysfunction: Onset of effect may be delayed if taken with food.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2010 and February 2011) that sildenafil tablets (Revatio®) should be initiated for patients with pulmonary arterial hypertension only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists and that sildenafil injection (Revatio®) should be prescribed only on the advice of specialists in the Scottish Pulmonary Vascular Unit or the Scottish Adult Congenital Cardiac Service.

NHS restrictions
Viagra® is not prescribable under NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XIb of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution containing the same drug.

Tablet

- Sildenafil (Non-proprietary)
  - Sildenafil (as Sildenafil citrate) 20 mg: Sildenafil 20 mg tablets | 90 tablet (Pom) £42.01
  - Sildenafil (as Sildenafil citrate) 25 mg: Sildenafil 25 mg tablets | 4 tablet (Pom) £16.59 DT price = £0.82 | 8 tablet (Pom) £33.19
  - Sildenafil (as Sildenafil citrate) 50 mg: Sildenafil 50 mg tablets | 4 tablet (Pom) £21.27 DT price = £0.99 | 8 tablet (Pom) £42.54
  - Sildenafil (as Sildenafil citrate) 100 mg: Sildenafil 100 mg tablets | 4 tablet (Pom) £23.50 DT price = £0.99 | 8 tablet (Pom) £46.99 | 12 tablet (Pom) £3.69
- Revatio (Pfizer Ltd)
  - Sildenafil (as Sildenafil citrate) 20 mg: Sildenafil 20 mg tablets | 90 tablet (Pom) £44.33
- Viagra (Pfizer Ltd)
  - Sildenafil (as Sildenafil citrate) 25 mg: Viagra 25 mg tablets | 4 tablet (Pom) £16.59 DT price = £0.82 | 8 tablet (Pom) £33.19
  - Sildenafil (as Sildenafil citrate) 50 mg: Viagra 50 mg tablets | 4 tablet (Pom) £21.27 DT price = £0.99 | 8 tablet (Pom) £42.54
  - Sildenafil (as Sildenafil citrate) 100 mg: Viagra 100 mg tablets | 4 tablet (Pom) £23.50 DT price = £0.99 | 8 tablet (Pom) £46.99
- Vizarsin (Consilient Health Ltd)
  - Sildenafil (as Sildenafil citrate) 25 mg: Vizarsin 25 mg tablets | 4 tablet (Pom) £14.10 DT price = £0.82
  - Sildenafil (as Sildenafil citrate) 50 mg: Vizarsin 50 mg tablets | 4 tablet (Pom) £18.07 DT price = £0.99
  - Sildenafil (as Sildenafil citrate) 100 mg: Vizarsin 100 mg tablets | 4 tablet (Pom) £19.57 DT price = £0.99

Chewable tablet

CAUTIONARY AND ADVISORY LABELS: 24 EXCIPIENTS: May contain Aspartame.

- Nipatra (AMCo)
  - Sildenafil (as Sildenafil citrate) 25 mg: Nipatra 25 mg chewable tablets sugar-free | 4 tablet (Pom) £1.05 sugar-free | 8 tablet (Pom) £2.10
  - Sildenafil (as Sildenafil citrate) 50 mg: Nipatra 50 mg chewable tablets sugar-free | 4 tablet (Pom) £1.03 sugar-free | 8 tablet (Pom) £2.06
  - Sildenafil (as Sildenafil citrate) 100 mg: Nipatra 100 mg chewable tablets sugar-free | 4 tablet (Pom) £1.11 sugar-free | 8 tablet (Pom) £2.22
Tadalafil

**INDICATIONS AND DOSE**

**Pulmonary arterial hypertension (initiated under specialist supervision)**

- **BY MOUTH**
  - Adult: 40 mg once daily

**Erectile dysfunction**

- **BY MOUTH**
  - Adult: Initially 10 mg once daily (max. per dose 20 mg), to be taken at least 30 minutes before sexual activity, subsequent doses adjusted according to response, the effect of intermittent dosing may persist for longer than 24 hours, daily dose of 10–20 mg not recommended; maximum 1 dose per day

**Erectile dysfunction; for patients who anticipate sexual activity at least twice a week**

- **BY MOUTH**
  - Adult: 5 mg once daily, reduced to 2.5 mg once daily, adjusted according to response, the effect of intermittent dosing may persist for longer than 24 hours

**Benign prostatic hyperplasia**

- **BY MOUTH**
  - Adult: 5 mg once daily

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**

History of non-articrterial anterior ischaemic optic neuropathy

**SPECIFIC CONTRA-INDICATIONS**

- When used for benign prostatic hyperplasia or erectile dysfunction Hypotension (avoid if systolic blood pressure below 90 mmHg) · mild to severe heart failure · myocardial infarction · patients in whom vasodilation or sexual activity are inadvisable · recent stroke · uncontrolled arrhythmias · uncontrolled hypertension · unstable angina

- When used for pulmonary arterial hypertension Acute myocardial infarction in past 90 days

**CAUTIONS**

- When used for benign prostatic hyperplasia or erectile dysfunction Anatomical deformation of the penis (e.g. angulation, cavernous fibrosis, Peyronie’s disease) · cardiovascular disease · left ventricular outflow obstruction · predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)

- When used for pulmonary arterial hypertension Anatomical deformation of the penis · aortic and mitral valve disease · congestive cardiomyopathy · coronary artery disease · hereditary degenerative retinal disorders · hypotension (avoid if systolic blood pressure below 90 mmHg) · left ventricular dysfunction · life-threatening arrhythmias · pericardial constriction · predisposition to priapism · pulmonary veno-occlusive disease · uncontrolled hypertension

**INTERACTIONS**

- Appendix 1 (tadalafil).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Back pain · dyspepsia · flushing · headache · myalgia · nausea · vomiting

- **Uncommon** Hypertension · tachycardia

- **Frequency not known** Arrhythmia · myocardial infarction · non-artericterial anterior ischaemic optic neuropathy (stop drug if sudden visual impairment occurs) · retinal vascular occlusion · sudden hearing loss (discontinue drug and seek medical advice) · unstable angina

**SPECIFIC SIDE-EFFECTS**

- **Common or very common**
  - When used for benign prostatic hyperplasia or erectile dysfunction Dizziness · migraine · nasal congestion · visual disturbances

- When used for pulmonary arterial hypertension Blurred vision · chest pain · epistaxis · facial oedema · gastro-oesophageal reflux · hypotension · increased uterine bleeding · limb pain · nasopharyngitis · palpitation · rash

- **Uncommon**
  - When used for benign prostatic hyperplasia or erectile dysfunction Epistaxis · hypotension · painful red eyes · palpitation

- When used for pulmonary arterial hypertension Amnesia · hyperhidrosis · priapism · seizures

- **Rare**
  - When used for benign prostatic hyperplasia or erectile dysfunction Facial oedema · hypersensitivity reactions · priapism · rash · Stevens-Johnson syndrome · syncope

- **Frequency not known**
  - When used for benign prostatic hyperplasia or erectile dysfunction Abdominal pain · increased sweating · seizures · serious cardiovascular events · transient annemia

- When used for pulmonary arterial hypertension Stevens-Johnson syndrome · stroke · visual field defect

**PREGNANCY**

Manufacturer advises avoid.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

For pulmonary arterial hypertension use initial dose of 20 mg once daily in mild to moderate impairment. Use maximum dose of 10 mg in erectile dysfunction and benign prostatic hyperplasia. When used for pulmonary arterial hypertension, avoid in severe impairment. Manufacturer advises caution in severe impairment and for regular once-daily dosing in erectile dysfunction and benign prostatic hyperplasia—no information available.

**RENAL IMPAIRMENT**

In pulmonary arterial hypertension for patients with mild to moderate impairment, initially use 20 mg once daily, increased to 40 mg once daily if tolerated. For erectile dysfunction and benign prostatic hyperplasia, maximum dose 10 mg if eGFR less than 30 mL/minute/1.73 m² (avoid regular once-daily dosing). In pulmonary arterial hypertension, avoid in severe impairment.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (June 2012) that tadalafil (Adcirca®) should be initiated only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

**NHS restrictions**

Cialis® is not prescribable under the NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII of the Drug Tariff (Part XIB of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use the BNF.
Vardenafil

**INDICATIONS AND DOSE**

**Erectile dysfunction**

- **BY MOUTH USING TABLETS**
  - Adult: Initially 10 mg (max. per dose 20 mg), to be taken approximately 25–60 minutes before sexual activity, subsequent doses adjusted according to response, onset of effect may be delayed if taken with high-fat meal; maximum 1 dose per day

- **BY MOUTH USING ORODISPERSE TABLET**
  - Adult: 10 mg, to be taken approximately 25–60 minutes before sexual activity; maximum 10 mg per day

**Erectile dysfunction (patients on alpha-blocker therapy)**

- **BY MOUTH USING TABLETS**
  - Adult: Initially 5 mg (max. per dose 20 mg), to be taken approximately 25–60 minutes before sexual activity, subsequent doses adjusted according to response, onset of effect may be delayed if taken with high-fat meal; maximum 1 dose per day

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Concomitant treatment with phosphodiesterase type-5 inhibitor and an alpha-blocker can increase the risk of postural hypotension—initiate treatment with a phosphodiesterase type-5 inhibitor (at a low dose) only once the patient is stable on the alpha-blocker.

**DOSE EQUIVALENT AND CONVERSION**

- Levitra® 10 mg orodispersible tablets and Levitra® 10 mg film coated tablets are not bioequivalent.

**CONTRA-INDICATIONS**

Avoid if systolic blood pressure below 90 mmHg · hereditary degenerative retinal disorders · myocardial infarction · patients in whom vasodilation or sexual activity are inadvisable · previous history of non-arteritic anterior ischaemic optic neuropathy · recent stroke · unstable angina

**CAUTIONS**

Active peptic ulceration · anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) · bleeding disorders · cardiovascular disease · elderly · left ventricular outflow obstruction · predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukemia) · susceptibility to prolongation of QT interval

**INTERACTIONS**

Appendix 1 (vardenafil)

Caution with concomitant use of drugs which prolong QT interval. Avoid concomitant use of nitrates.

**SIDE-EFFECTS**

- Back pain · dizziness · dyspepsia · flushing · headache · migraine · myalgia · nasal congestion · nausea · visual disturbances · vomiting

- Drowsiness · dyspnoea · epistaxis · hypertension · hypotension · increased lacrimation · painful red eyes · palpitation · photosensitivity · tachycardia

**RARE**

Anxiety · facial oedema · hypersensitivity reactions · hypertension · priapism · raised intra-ocular pressure · rash · Stevens-Johnson syndrome · syncope · transient amnesia

**FREQUENCY NOT KNOWN**

Arrhythmia · myocardial infarction · non-arteritic anterior ischaemic optic neuropathy (stop drug if sudden visual impairment occurs) · retinal vascular occlusion · seizures · serious cardiovascular events · sudden hearing loss (discontinue drug and seek medical advice) · unstable angina

**HEPATIC IMPAIRMENT**

Initial dose 5 mg in mild to moderate impairment, increased subsequently according to response (max. 10 mg in moderate impairment). Manufacturer advises avoid in severe impairment. Orodispersible tablets not suitable for patients with moderate hepatic impairment.

**RENAL IMPAIRMENT**

Initial dose 5 mg if eGFR less than 30 mL/minute/1.73 m². Orodispersible tablets not suitable if eGFR less than 30 mL/minute/1.73 m².

**PRESCRIBING AND DISPENSING INFORMATION**

Orodispersible tablets not suitable for initiation of therapy in patients taking alpha-blockers.

**NATIONAL FUNDING/ACCESS DECISIONS**

The Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (September 2011) that vardenafil orodispersible tablets (Levitra®) are accepted for restricted use within NHS Scotland for men for whom an orodispersible tablet is an appropriate formulation.

**NHS restrictions**

Levitra® is not prescribable under the NHS for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIB of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use the BNF.

**LEVITRA® ORODISPERSIBLE TABLETS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (September 2011) that vardenafil orodispersible tablets (Levitra®) are accepted for restricted use within NHS Scotland for men for whom an orodispersible tablet is an appropriate formulation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Levitra® (Bayer Plc)
  - Vardenafil (as Vardenafil hydrochloride trihydrate) 5 mg Levitra 5mg tablets | 4 tablet POM £7.56 DT price = £7.56 | 8 tablet POM £15.12
  - Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra 10mg tablets | 4 tablet POM £14.08 DT price = £14.08 | 8 tablet POM £28.16
  - Vardenafil (as Vardenafil hydrochloride trihydrate) 20 mg Levitra 20mg tablets | 4 tablet POM £23.48 DT price = £23.48 | 8 tablet POM £46.96

**Orodispersible tablet**

EXCIPIENTS: May contain Aspartame

- Levitra® (Bayer Plc)
  - Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra 10mg orodispersible tablets sugar-free | 4 tablet POM £17.88 DT price = £17.88
**Prostaglandin Analogues and Prostamides**

Prostaglandins, erectile dysfunction

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**Alprostadil**

- **Indications and Dose**
  - Erectile dysfunction (initiated under specialist supervision)
    - By urethral application
      - Adult: Initially 250 micrograms, adjusted according to response; usual dose 0.125–1 mg; maximum 2 doses per day; maximum 7 doses per week
  - Aid to diagnosis of erectile dysfunction
    - By urethral application
      - Adult: 500 micrograms for 1 dose
  - Erectile dysfunction
    - To the skin
      - Adult: Apply 300 micrograms, to the tip of the penis, 5–30 minutes before sexual activity; max 1 dose in 24 hours not more than 2–3 times per week

**Caverject**

- Erectile dysfunction
  - By intracavernosal injection
    - Adult: Initially 2.5 micrograms for 1 dose (first dose), followed by 5 micrograms for 1 dose (second dose), to be given if some response to first dose, alternatively 7.5 micrograms for 1 dose (second dose), to be given if no response to first dose, then increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection lasting not more than 1 hour; if no response to dose then next higher dose can be given within 1 hour, if there is a response the next dose should not be given for at least 24 hours; usual dose 5–20 micrograms (max. per dose 60 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections

**Erectile dysfunction associated with neurological dysfunction**

- By intracavernosal injection
  - Adult: Initially 1.25 micrograms for 1 dose (first dose), then 2.5 micrograms for 1 dose (second dose), then 5 micrograms for 1 dose (third dose), increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection lasting not more than 1 hour; if no response to dose then next higher dose can be given within 1 hour, if there is a response the next dose should not be given for at least 24 hours; usual dose 5–20 micrograms (max. per dose 60 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections

**Aid to diagnosis**

- By intracavernosal injection
  - Adult: 10–20 micrograms for 1 dose (consult product literature)

**Aid to diagnosis where evidence of neurological dysfunction**

- By intracavernosal injection
  - Adult: Initially 5 micrograms (max. per dose 10 micrograms) for 1 dose, (consult product literature)

**Viridal® DUO Continuation Pack**

- Erectile dysfunction
  - By intracavernosal injection
    - Adult: Initially 5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**Neurogenic erectile dysfunction**

- By intracavernosal injection
  - Adult: Initially 2.5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**Viridal® DUO Starter Pack**

- Erectile dysfunction
  - By intracavernosal injection
    - Adult: Initially 5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours
producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

● CONTRA-INDICATIONS

GENERAL CONTRA-INDICATIONS
Not for use in patients with penile implants or when sexual activity medically inadvisable (e.g. orthostatic hypotension, myocardial infarction, and syncope) - not for use with other agents for erectile dysfunction - predisposition to prolonged erection (as in thrombocythemia, polycythemia, sickle cell anaemia, multiple myeloma or leukaemia) - urethral application contra-indicated in balanitis - urethral application contra-indicated in severe curvature - urethral application contra-indicated in severe hypospadia - urethral application contra-indicated in urethral stricture - urethral application contra-indicated in urethritis

SPECIFIC CONTRA-INDICATIONS
> With topical use Balanitis - severe curvature - severe hypospadia - urethral stricture - urethritis

● CAUTIONS
Anatomical deformations of penis (painful erection more likely) - follow up regularly to detect signs of penile fibrosis (consider discontinuation if angulation, cavernosal fibrosis or Peyronie’s disease develop) - priapism (patients should be instructed to report any erection lasting 4 hours or longer)

● INTERACTIONS  ➔ Appendix 1 (alprostadil).

● SIDE-EFFECTS
> Common or very common Dizziness - haematoma - haemosiderin deposits - headache - hypertension - hypotension - influenza-like syndrome - injection site reactions - other localised pain (buttocks, leg, testicular, abdominal) - penile fibrosis - penile oedema - penile pain - penile rash - urethral bleeding - urethral burning


> Rare Anaphylaxis - erythema - hypersensitivity reactions - rash - urinary-tract infection - urticaria - vertigo

● CONCEPTION AND CONTRACEPTION
> With urethral use If partner is pregnant, barrier contraception should be used. No evidence of harm to latex condoms and diaphragms.

> With topical use Condoms should be used to avoid exposure to women of child-bearing age, pregnant or lactating women. No evidence of harm to latex condoms.

● DIRECTIONS FOR ADMINISTRATION
> With intracavernosal use The first dose of the intracavernosal injection must be given by medically trained personnel; self-administration may only be undertaken after proper training.

> With urethral use During initiation of treatment the urethral application should be used under medical supervision; self-administration may only be undertaken after proper training.

● PATIENT AND CARER ADVICE
Patients should be instructed to report any erection lasting 4 hours or longer.

With topical use Counsel patients that condoms should be used to avoid local reactions and exposure of alprostadil to women of childbearing age, pregnant, or lactating women.

● NATIONAL FUNDING/ACCESS DECISIONS
NHS restrictions Caverject®, Viridil® Duo, Vitaros® and MUSE® are not prescribable under the NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIIB of the Drug Tariff (Part XIIb of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use BNF Publications.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
> Caverject (Pfizer Ltd) Alprostadil 250 microgram Caverject 5microgram powder and solvent for solution for injection vials | 1 vial (Pom) £7.73 DT price = £7.73 Alprostadil 10 microgram Caverject 10microgram powder and solvent for solution for injection vials | 1 vial (Pom) £9.24 DT price = £9.24 Alprostadil 20 microgram Caverject 20microgram powder and solvent for solution for injection vials | 1 vial (Pom) £11.94 DT price = £11.94 Alprostadil 40 microgram Caverject 40microgram powder and solvent for solution for injection vials | 1 vial (Pom) £21.58 DT price = £21.58

> Caverject Dual Chamber (Pfizer Ltd) Alprostadil 10 microgram Caverject Dual Chamber 10microgram powder and solvent for solution for injection | 2 pre-filled disposable injection (Pom) £14.70 Alprostadil 20 microgram Caverject Dual Chamber 20microgram powder and solvent for solution for injection | 2 pre-filled disposable injection (Pom) £19.00

> Viridal (UCB Pharma Ltd) Alprostadil 10 microgram Viridal Duo Starter Pack 10microgram powder and solvent for solution for injection cartridges with device | 2 cartridge (Pom) £20.13 (Hospital only) Viridal Duo Continuation Pack 10microgram powder and solvent for solution for injection cartridges | 2 cartridge (Pom) £16.55 Alprostadil 20 microgram Viridal Duo Starter Pack 20microgram powder and solvent for solution for injection cartridges with device | 2 cartridge (Pom) £24.54 (Hospital only) Viridal Duo Continuation Pack 20microgram powder and solvent for solution for injection cartridges | 2 cartridge (Pom) £21.39 Alprostadil 40 microgram Viridal Duo Starter Pack 40microgram powder and solvent for solution for injection cartridges with device | 2 cartridge (Pom) £29.83 (Hospital only) Viridal Duo Continuation Pack 40microgram powder and solvent for solution for injection cartridges | 2 cartridge (Pom) £27.22

Cream
> Vitaros (Ferring Pharmaceuticals Ltd) Alprostadil 3 mg per 1 gram Vitaros 3mg/g cream | 4 applicator (Pom) £40.00

Stick
> Muse (Meda Pharmaceuticals Ltd) Alprostadil 500 microgram Muse 500microgram urethral sticks | 1 applicator (Pom) £11.30 DT price = £11.30 | 6 applicator (Pom) £67.79 Alprostadil 1 mg Muse 1000microgram urethral sticks | 1 applicator (Pom) £11.56 DT price = £11.56 | 6 applicator (Pom) £65.67 Alprostadil 250 microgram Muse 250microgram urethral sticks | 1 applicator (Pom) £11.30 DT price = £11.30 | 6 applicator (Pom) £67.79
**SYMPATHOMIMETICS \ VASOCONSTRICTOR**

### Adrenaline/epinephrine

**DRUG ACTION** Acts on both alpha and beta receptors and increases both heart rate and contractility (beta₂ effects); it can cause peripheral vasodilatation (a beta₁ effect) or vasoconstriction (an alpha effect).

### INDICATIONS AND DOSE

**Priapism associated with alprostadil, if aspiration and lavage of corpora are unsuccessful (alternative to phenylephrine or metaraminol)**

- **BY INTRACAVERNOSAL INJECTION**

  - **Adult:** 10–20 micrograms every 5–10 minutes, using a 20 microgram/mL solution. **Important:** If suitable strength of adrenaline not available may be specially prepared by diluting 0.1 mL of the adrenaline 1 in 1000 (1 mg/mL) injection to 5 mL with sodium chloride 0.9%, continuously monitor blood pressure and pulse; maximum 100 micrograms per course

### UNLICENSED USE

The use of adrenaline for the treatment of priapism is an unlicensed indication.

### CAUTIONS

- Arteriosclerosis
- arrhythmias
- cerebrovascular disease
- cor pulmonale
- diabetes mellitus
- elderly
- hypercalcaemia
- hyperreflexia
- hypertension
- hyperthyroidism
- hypokalaemia
- ischaemic heart disease
- obstructive cardiomyopathy
- oculuseive vascular disease
- organic brain damage
- phaeochromocytoma
- prostate disorders
- psychoneurosis
- severe angina
- susceptibility to angle-closure glaucoma

### INTERACTIONS

→ Appendix 1 (sympathomimetics)

### SIDE-EFFECTS

- Angina
- angle-closure glaucoma
- anorexia
- anxiety
- arrhythmias
- cold extremities
- confusion
- difficulty in micturition
- dizziness
- dry mouth
- dyspnoea
- headache
- hyperglycaemia
- hypersalivation
- hypertension (risk of cerebral haemorrhage)
- hypokalaemia
- insulinoma
- metabolic acidosis
- mydriasis
- myocardial infarction
- nausea
- pallor
- palpitation
- psychosis
- pulmonary oedema (on excessive dosage or extreme sensitivity)
- restlessness
- sweating
- tachycardia
- tissue necrosis at injection site
- tissue necrosis of bowel
- tissue necrosis of extremities
- tissue necrosis of kidneys
- tissue necrosis of liver
- tremor
- urinary retention
- vomiting
- weakness

### RENAL IMPAIRMENT

Manufacturers advise use with caution in severe impairment.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

**EXCIPIENTS:** May contain Sulfites

- **Adrenaline/epinephrine (Non-proprietary)**
  - Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 ml Adrenaline (base) 5mg/5ml (1 in 1,000) solution for injection ampoules | 10 ampoule [POD] £73.66
  - Adrenaline (base) 500micrograms/0.5ml (1 in 1,000) solution for injection ampoules | 10 ampoule [POD] £58.40–£58.41 DT price = £58.41
  - Adrenaline (base) 1mg/1ml (1 in 1,000) solution for injection ampoules | 10 ampoule [POD] £6.03 DT price = £6.01

### Metaraminol

**INDICATIONS AND DOSE**

**Priapism (alternative to intracavernosal injections of phenylephrine and adrenaline)**

- **BY INTRACAVERNOSAL INJECTION**

  - **Adult:** 1 mg every 15 minutes

### UNLICENSED USE

Use for priapism is an unlicensed indication.

### CONTRA-INDICATIONS

Hypertension

### CAUTIONS

- Associated with fatal hypertensive crises
- cirrhosis
- coronary vascular thrombosis
- diabetes mellitus
- elderly
- extravasation at injection site may cause necrosis
- following myocardial infarction
- hypercapnia
- hyperthyroidism
- hypoxia
- mesenteric vascular thrombosis
- peripheral vascular thrombosis
- Prinzmetal’s variant angina
- uncorrected hypovolaemia

### INTERACTIONS

→ Appendix 1 (sympathomimetics)

### SIDE-EFFECTS

- Angle-closure glaucoma
- anorexia
- anxiety
- arrhythmias
- bradycardia
- confusion
- dyspnoea
- fatal ventricular arrhythmia reported in Laennec’s cirrhosis
- headache
- hypertension
- hypoxia
- insomnia
- nausea
- palpitation
- peripheral ischaemia
- psychosis
- tachycardia
- tremor
- urinary retention
- vomiting
- weakness

### MONITORING REQUIREMENTS

Monitor blood pressure and rate of flow frequently.

### DIRECTIONS FOR ADMINISTRATION

For intracavernosal injection, dilute 1 mg (0.1 mL of 10 mg/mL) metaraminol injection to 50 mL with Sodium chloride 0.9% and give carefully by slow injection into the corpora in 5 mL injections.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- **Metaraminol (Non-proprietary)**
  - Metaraminol (as Metaraminol tartrate) 10 mg per 1 ml Metaraminol 10mg/1ml solution for injection ampoules | 10 ampoule [POD] £31.97

### Phenylephrine hydrochloride

**INDICATIONS AND DOSE**

**Priapism associated with alprostadil, if aspiration and lavage of the corpora are unsuccessful (alternative to adrenaline or metaraminol)**

- **BY INTRACAVERNOSAL INJECTION**

  - **Adult:** 100–200 micrograms every 5–10 minutes, dose to be administered using a 200 micrograms/mL solution; maximum 1 mg per course

### UNLICENSED USE

Use of phenylephrine hydrochloride injection in priapism is an unlicensed indication.

### CONTRA-INDICATIONS

Hypertension

### INTERACTIONS

→ Appendix 1 (sympathomimetics)

Phenylephrine may interact with systemically administered monoamine-oxidase inhibitors.

### SIDE-EFFECTS

- Arrhythmias
- hypertension
- palpitation
- tachycardia

### DIRECTIONS FOR ADMINISTRATION

For intracavernosal injection, if suitable strength of phenylephrine injection is not available, it may be specially prepared by diluting 0.1 mL of the phenylephrine 1% (10 mg/mL) injection to 5 mL with sodium chloride 0.9%.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- **Phenylephrine hydrochloride (Non-proprietary)**
  - Phenylephrine hydrochloride 10 mg per 1 ml Phenylephrine 10mg/1ml solution for injection ampoules | 10 ampoule [POD] £99.12
4.2 Premature ejaculation

**SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS**

**Dapoxetine**

- **DRUG ACTION** Dapoxetine is a short-acting selective serotonin re-uptake inhibitor.

- **INDICATIONS AND DOSE**
  
  Premature ejaculation in men who meet all the following criteria: poor control over ejaculation, a history of premature ejaculation over the past 6 months, marked distress or interpersonal difficulty as a consequence of premature ejaculation, and an intravaginal ejaculatory latency time of less than two minutes
  
  - **BY MOUTH**
  
    - **Adult:** Initially 30 mg, to be taken approximately 1–3 hours before sexual activity, subsequent doses adjusted according to response; review treatment after 4 weeks (or 6 doses) and at least every 6 months thereafter, not recommended for adults 65 years and over; maximum 1 dose per day; maximum 60 mg per day

  Premature ejaculation in men who meet all the following criteria: poor control over ejaculation, a history of premature ejaculation over the past 6 months, marked distress or interpersonal difficulty as a consequence of premature ejaculation, and an intravaginal ejaculatory latency time of less than two minutes (with concomitant apreptin, clarithromycin, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil)
  
  - **BY MOUTH**
  
    - **Adult:** Up to 30 mg, to be taken approximately 1–3 hours before sexual activity; review treatment after 4 weeks (or 6 doses) and at least every 6 months thereafter, not recommended for adults 65 years and over; maximum 1 dose per day

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  
  Max. single dose 30 mg with concomitant apreptin, clarithromycin, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil.

  Use 60–mg dose with caution with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4.

- **CONTRA-INDICATIONS** History of bipolar disorder • history of mania • history of severe depression • history of syncope • significant cardiac disease • uncontrolled epilepsy

- **CAUTIONS** Bleeding disorders • epilepsy (discontinue if convulsions develop) • susceptibility to angle-closure glaucoma

- **INTERACTIONS** → Appendix 1 (dapoxetine).

  Caution with concomitant use of drugs that increase risk of bleeding.

- **SIDE-EFFECTS**
  
  - **Common or very common** Abdominal distension • abdominal pain • abnormal dreams • agitation • anxiety • constipation • diarrhea • dizziness • drowsiness • dry mouth • dyspepsia • flushing • headache • hypertension • impaired attention • irritability • malaise • nausea • paraesthesia • sexual dysfunction • sleep disturbances • sweating • tinnitus • tremor • visual disturbances • vomiting

  - **Uncommon** Abnormal thoughts • bradycardia • bruxism • confusion • depression • eye pain • hypotension • mood disturbances • mydriasis • postural hypotension • pruritus • restlessness • sinus arrest • syncope • tachycardia • taste disturbances • vertigo

  - **Rare** Defaecation urgency • sudden onset of sleep

**SIDE-EFFECTS, FURTHER INFORMATION**

Discontinue if psychiatric disorder develops.

Avoid if postural hypotension occurs during test dose.

- **HEPATIC IMPAIRMENT** Avoid in moderate to severe impairment.

- **RENAL IMPAIRMENT** Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

- **PRE-TREATMENT SCREENING** Test for postural hypotension before starting treatment.

- **PATIENT AND CARER ADVICE**

  Postural hypotension and syncope Patients should be advised to maintain hydration and to sit or lie down until prodromal symptoms such as nausea, dizziness, and sweating abate.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  **CAUTIONARY AND ADVISORY LABELS 2, 25**

  - **Dapoxetine (Non-proprietary)**
    
    Dapoxetine 30 mg Dapoxetine 30mg tablets | 6 tablet £42.68

    Priligy (A. Menarini Farmaceutica Internazionale SRL)

    Dapoxetine 30 mg Priligy 30mg tablets | 3 tablet £14.71 | 6 tablet £26.48

    Dapoxetine 60 mg Priligy 60mg tablets | 3 tablet £19.12 | 6 tablet £34.42

5 **Obstetrics**

**Obstetrics**

**Prostaglandins and oxytocics**

Prostaglandins and oxytocics are used to induce abortion or induce or augment labour and to minimise blood loss from the placental site. They include oxytocin p. 753, carbetocin p. 754, ergometrine maleate p. 754, and the prostaglandins. All induce uterine contractions with varying degrees of pain according to the strength of contractions induced.

**Induction of abortion**

Gemeprost p. 756, a prostaglandin administered vaginally as pessaries, is suitable for the medical induction of late therapeutic abortion; gemeprost is also used to ripen the cervix before surgical abortion, particularly in primigravidas. The prostaglandin misoprostol p. 756 is given by mouth, buccally, sublingually, or vaginally, to induce medical abortion [unlicensed indication]; intravaginal use ripens the cervix before surgical abortion [unlicensed indication].

Extra-amniotic dinoprostone is rarely used nowadays.

Pre-treatment with mifepristone p. 755 can facilitate the process of medical abortion. It sensitises the uterus to subsequent administration of a prostaglandin and, therefore, abortion occurs in a shorter time and with a lower dose of prostaglandin.

**Induction and augmentation of labour**

Dinoprostone is available as vaginal tablets, pessaries and vaginal gels for the induction of labour. The intravenous solution is rarely used; it is associated with more side-effects.

Oxytocin (Syntocinon®) is administered by slow intravenous infusion, using an infusion pump, to induce or augment labour, usually in conjunction with amniotomy. Uterine activity must be monitored carefully and hyperstimulation avoided. Large doses of oxytocin may result in excessive fluid retention.

Misoprostol is given orally or vaginally for the induction of
labour [unlicensed indication].

Prevention and treatment of haemorrhage
Bleeding due to incomplete miscarriage or abortion can be controlled with ergometrine maleate and oxytocin (Syntometrine®) given intramuscularly, the dose is adjusted according to the patient's condition and blood loss. This is commonly used before surgical evacuation of the uterus, particularly when surgery is delayed. Oxytocin and ergometrine maleate combined are more effective in early pregnancy than either drug alone.

Active management of the third stage of labour reduces the risk of postpartum haemorrhage; oxytocin is given by intramuscular injection [unlicensed] on delivery of the anterior shoulder or, at the latest, immediately after the baby is delivered. Alternatively, ergometrine maleate with oxytocin (Syntometrine®) can be given by intramuscular injection in the absence of hypertension; oxytocin alone causes less nausea, vomiting, and hypertension than when given with ergometrine maleate.

In excessive uterine bleeding, any placental products remaining in the uterus should be removed. Oxytocic drugs are used to treat postpartum haemorrhage caused by uterine atony; treatment options are as follows:

- oxytocin by slow intravenous injection, followed in severe cases by intravenous infusion of oxytocin at a rate that controls uterine atony or
- ergometrine by intramuscular injection or
- ergometrine by slow intravenous injection (use with caution—risk of hypertension) or
- ergometrine with oxytocin (Syntometrine®) by intramuscular injection

Carboprost p. 754 has an important role in severe postpartum haemorrhage unresponsive to ergometrine maleate and oxytocin.

Mifepristone
For termination of pregnancy, a single dose of mifepristone is followed by administration of a prostaglandin (gemeprost or misoprostol [unlicensed]).

Guidelines of the Royal College of Obstetricians and Gynaecologists (November 2011) include [unlicensed] regimens for inducing medical abortion.

Myometrial relaxants
Tocolytic drugs postpone premature labour and they are used with the aim of reducing harm to the child. However, there is no satisfactory evidence that the use of these drugs reduces mortality. The greatest benefit is gained by using the delay to administer corticosteroid therapy or to implement other measures which improve perinatal health (including transfer to a unit with neonatal intensive care facility).

The oxytocin receptor antagonist, atosiban p. 755, is licensed for the inhibition of uncomplicated premature labour between 24 and 33 weeks of gestation. Atosiban may be preferable to a beta, agonist because it has fewer side effects. The dihydropyridine calcium-channel blocker nifedipine p. 153 also has fewer side-effects than a beta, agonist.

The beta, agonists salbutamol p. 239 and terbutaline sulfate p. 241 are licensed for inhibiting uncomplicated premature labour between 22 and 37 weeks of gestation to permit a delay in delivery of up to 48 hours. Use of high-dose short acting beta, agonists in obstetric indications has been associated with serious, sometimes fatal cardiovascular events in the mother and fetus, particularly when used for a prolonged period of time. Oral therapy is no longer recommended and parenteral therapy should be restricted to a maximum duration of 48 hours, given under the supervision of a specialist, and with close monitoring.

Indometacin p. 1001, a cyclo-oxygenase inhibitor, also inhibits labour [unlicensed indication] and it can be useful in situations where a beta, agonist is not appropriate; however, there are concerns about neonatal complications such as transient impairment of renal function and premature closure of ductus arteriosus.

5.1 Induction of labour

PROSTAGLANDINS AND OXYTOCICS

Dinoprostone

- INDICATIONS AND DOSE

PROPESS®

Cervical ripening and induction of labour at term
- BY VAGINA
  - Adult: 1 pessary, insert pessary (in retrieval device) high into posterior fornix and remove when cervical ripening adequate; if oxytocin necessary, remove 30 minutes before oxytocin infusion; remove if cervical ripening inadequate after 24 hours (dose not to be repeated)

PROSTIN E2® VAGINAL GEL

Induction of labour
- BY VAGINA
  - Adult: 1 mg, inserted high into the posterior fornix (avoid administration into the cervical canal), followed by 1–2 mg after 6 hours if required; maximum 3 mg per course

Induction of labour (unfavourable primigravida)
- BY VAGINA
  - Adult: 2 mg, inserted high into the posterior fornix (avoid administration into the cervical canal), followed by 1–2 mg if required, after 6 hours; maximum 4 mg per course

PROSTIN E2® VAGINAL TABLETS

Induction of labour
- BY VAGINA
  - Adult: 3 mg, inserted high into the posterior fornix, followed by 3 mg after 6–8 hours, to be given if labour not established; maximum 6 mg per course

DOSE EQUIVALENCE AND CONVERSION
- Prostin E2 Vaginal tablets and Vaginal Gel are not bioequivalent.

- CONTRA-INDICATIONS

Active cardiac disease • active pulmonary disease • avoid extra-amniotic route in cervicitis or vaginitis • fetal distress • fetal malpresentation • grand multiparas • history of caesarean section • history of difficult or traumatic delivery • history of major uterine surgery • major cephalopelvic disproportion • multiple pregnancy • placenta praevia or unexplained vaginal bleeding during pregnancy • ruptured membranes • untreated pelvic infection

- CAUTIONS

Effect of oxytocin enhanced • history of asthma • history of epilepsy • history of glaucoma and raised intraocular pressure • hypertension • risk factors for disseminated intravascular coagulation • uterine rupture • uterine scarring

- INTERACTIONS

- Appendix 1 (prostaglandins).

- SIDE-EFFECTS

Abruptio placenta • amniotic fluid embolism • backache • bronchospasm • cardiac arrest • diarrhoea • disseminated intravascular coagulation • fetal distress • fever • low Apgar scores • maternal hypertension • nausea • pulmonary embolism • rapid cervical dilation • severe
Oxytocin

**INDICATIONS AND DOSE**

**Induction of labour for medical reasons | Stimulation of labour in hypotonic uterine inertia**

- **BY INTRAVENOUS INFUSION**
- **Adult:** Initially 0.001–0.004 unit/minute, not to be started for at least 6 hours after administration of vaginal prostaglandin, dose increased at intervals of at least 30 minutes until a maximum of 3–4 contractions occur every 10 minutes (0.01 units/minute is often adequate) up to max. 0.02 units/minute, if regular contractions not established after a total 5 units, stop induction attempt (may be repeated next day starting again at 0.001–0.004 units/minute)

**Caesarean section**

- **BY SLOW INTRAVENOUS INJECTION**
- **Adult:** 5 units immediately after delivery

**Prevention of postpartum haemorrhage after delivery of placenta**

- **BY SLOW INTRAVENOUS INJECTION**
- **Adult:** 5 units, if infusion previously used for induction or enhancement of labour, increase rate during third stage and for next few hours

**BY INTRAMUSCULAR INJECTION**

- **Adult:** 10 units, can be used instead of oxytocin with ergometrine (Syntometrine®).

**Treatment of postpartum haemorrhage**

- **BY SLOW INTRAVENOUS INJECTION**
- **Adult:** 5 units, repeated if necessary

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**Treatment of severe cases of postpartum haemorrhage (following intravenous injection)**

- **BY INTRAVENOUS INFUSION**
- **Adult:** 40 units, given in 500 mL infusion fluid given at a rate sufficient to control uterine atony

**Incomplete, inevitable, or missed miscarriage**

- **INITIALLY BY SLOW INTRAVENOUS INJECTION**
- **Adult:** 5 units, followed by (by intravenous infusion) 0.02–0.04 unit/minute if required, the rate of infusion can be faster if necessary

**UNLICENSED USE** Oxytocin doses in the BNF may differ from those in the product literature. Administration by Intramuscular injection is an unlicensed use.

**IMPORTANT SAFETY INFORMATION**

Prolonged intravenous administration at high doses with large volume of fluid (which is possible in inevitable or missed miscarriage or postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid: use electrolyte-containing diluent (i.e. not glucose), increase oxytocin concentration to reduce fluid, restrict fluid intake by mouth; monitor fluid and electrolytes.

**CONTRA-INDICATIONS** Any condition where spontaneous labour inadvisable • any condition where vaginal delivery inadvisable • avoid intravenous injection during labour • avoid prolonged administration in oxytocin–resistant uterine inertia • avoid rapid intravenous injection (may transiently reduce blood pressure) • fetal distress (discontinue immediately if this occurs) • hypertonic uterine contractions (discontinue immediately if this occurs) • severe cardiovascular disease • severe pre-eclamptic toxaemia

**CAUTIONS** Avoid large infusion volumes and restrict fluid intake by mouth (risk of hyponatraemia and water-intoxication) • enhancement of labour—presence of borderline cephalopelvic disproportion (avoid if significant) • history of lower-uterine segment caesarean section • induction of labour—presence of borderline cephalopelvic disproportion (avoid if significant) • mild pregnancy-induced cardiac disease • mild pregnancy-induced hypertension • moderate pregnancy-induced cardiac disease • moderate pregnancy-induced hypertension • risk factors for disseminated intravascular coagulation • secondary uterine inertia • women over 35 years

**INTERACTIONS** • Appendix 1 (oxytocin). Effects enhanced by concomitant prostaglandins (very careful monitoring of uterine activity). Caudal block anaesthesia (may enhance hypertensive effects of sympathomimetic vasopressors).

**SIDE-EFFECTS**

- **Common or very common** Arrhythmia • headache • nausea • vomiting
- **Rare** Anaphylactoid reactions (with dyspnoea, hypotension, or shock) • disseminated intravascular coagulation • hyponatraemia associated with high doses with large infusion volumes of electrolyte-free fluid • rash • uterine hyperstimulation (usually with excessive doses—may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture) • uterine spasm (may occur at low doses) • water intoxication associated with high doses with large infusion volumes of electrolyte-free fluid

**SIDE-EFFECTS, FURTHER INFORMATION**

Avoid rapid intravenous injection (may transiently reduce blood pressure).

**Overdose**

Placental abruption and amniotic fluid embolism reported on overdose.
5.2 Postpartum haemorrhage

Other drugs used for Postpartum haemorrhage Oxytocin, p. 753

PROSTAGLANDINS AND OXYTOCICS

Carbetocin

- INDICATIONS AND DOSE
  - Prevention of uterine atony after caesarean section
    - By slow intravenous injection
      - Adult: 100 micrograms for 1 dose, to be given over 1 minute, administer as soon as possible after delivery, preferably before removal of placenta

- CONTRA-INDICATIONS
  - Eclampsia, epilepsy, pre-eclampsia

- CAUTIONS
  - Asthma, cardiovascular disease (avoid if severe), hypotenraemia, migraine

- SIDE-EFFECTS
  - Abdominal pain, anaemia, back pain, chest pain, chills, dizziness, dyspnoea, feeling of warmth, flushing, headache, hypotension, metallic taste, nausea, pruritus, sweating, tachycardia, tremor, vomiting

- HEPATIC IMPAIRMENT
  - Manufacturer advises avoid.

- RENAL IMPAIRMENT
  - Manufacturer advises avoid.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - Pabal (Ferring Pharmaceuticals Ltd)
      - Carbetocin 100 microgram per 1 ml Pabal 100micrograms/1ml solution for injection ampoules | 5 ampoule £88.20 (Hospital only)

Carboprost

- INDICATIONS AND DOSE
  - Postpartum haemorrhage due to uterine atony in patients unresponsive to ergometrine and oxytocin
    - By deep intramuscular injection
      - Adult: 250 micrograms at least every 15 minutes, repeated if necessary, total dose should not exceed 2 mg (8 doses)

- CONTRA-INDICATIONS
  - Cardiac disease, pulmonary disease, untreated pelvic infection

- CAUTIONS
  - Excessive dosage may cause uterine rupture, history of anaemia, history of asthma, history of diabetes, history of epilepsy, history of glaucoma, history of hypertension, history of hypotension, history of jaundice, history of raised intraocular pressure, uterine scars

- INTERACTIONS
  - Appendix 1 (prostaglandins)

- SIDE-EFFECTS
  - Bronchospasm, cardiovascular collapse, chills, diaphoresis, diarrhoea, dizziness, dyspnoea, erythema at injection site, flushing, headache, hyperthermia, nausea, pain at injection site, pulmonary oedema, raised blood pressure, vomiting

- HEPATIC IMPAIRMENT
  - Manufacturer advises avoid.

- RENAL IMPAIRMENT
  - Manufacturer advises avoid.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - Hemabate (Pfizer Ltd)
      - Carboprost (as Carboprost trometamol) 250 microgram per 1 ml Hemabate 250micrograms/1ml solution for injection ampoules | 1 ampoule £182.01 (Hospital only)

Ergometrine maleate

- INDICATIONS AND DOSE
  - Postpartum haemorrhage caused by uterine atony
    - By intramuscular injection, or by slow intravenous injection
      - Adult: 250–500 micrograms

- CONTRA-INDICATIONS
  - Eclampsia, first stage of labour, induction of labour, second stage of labour, septis, severe cardiac disease, severe hypertension, vascular disease

- CAUTIONS
  - Acute porphyrias, p. 930, cardiac disease, hypertension, multiple pregnancy, risk of hypertension associated with intravenous administration

- INTERACTIONS
  - Appendix 1 (ergot alkaloids)

- SIDE-EFFECTS
  - Common or very common
    - Abdominal pain, arrhythmias, bradycardia, chest pain, dizziness, dyspnoea, headache, hypertension, nausea, palpitation, pulmonary oedema, rash, tinnitus, vasoconstriction, vomiting

  - Very rare
    - Myocardial infarction

- HEPATIC IMPAIRMENT
  - Manufacturer advises caution in mild or moderate impairment. Manufacturer advises avoid in severe impairment.

- RENAL IMPAIRMENT
  - Manufacturer advises caution in mild or moderate impairment. Manufacturer advises avoid in severe impairment.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - Ergometrine maleate (Non-proprietary)
      - Ergometrine maleate 500 microgram per 1 ml Ergometrine 500micrograms/1ml solution for injection ampoules | 10 ampoule £12.00–£15.00
Ergometrine with oxytocin

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergometrine maleate p. 754, oxytocin p. 753.

**INDICATIONS AND DOSE**

Active management of the third stage of labour

Postpartum haemorrhage caused by uterine atony

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 1 mL for one dose
  - Adult: No longer recommended

Bleeding due to incomplete miscarriage or abortion

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Adjusted according to response to, the patient’s condition and blood loss

**SIDE-EFFECTS**

- nausea.
- vomiting.
- rash.
- For intravenous infusion (Tractocile® concentrate for intravenous infusion), give continuously in Glucose 5% or Sodium chloride 0.9%.

**CONTRA-INDICATIONS**

Abruptio placenta · antepartum haemorrhage (requiring immediate delivery) · eclampsia · intra-uterine fetal death · intra-uterine infection · intra-uterine growth restriction with abnormal fetal heart rate · placenta praevia · premature rupture of membranes after 30 weeks’ gestation · severe pre-eclampsia

**CAUTIONS**

Abnormal placental site · intra-uterine growth restriction

**SIDE-EFFECTS**

- Common or very common Dizziness · headache · hot flushes · hyperglycaemia · hypotension · injection-site reaction · nausea · tachycardia · vomiting
- Uncommon Fever · insomnia · pruritus · rash

**HEPATIC IMPAIRMENT**

No information available.

**RENAL IMPAIRMENT**

No information available.

**MONITORING REQUIREMENTS**

Monitor blood loss after delivery.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Tractocile® concentrate for intravenous infusion), give continuously in Glucose 5% or Sodium chloride 0.9%.

Withdraw 10 mL infusion fluid from 100-mL bag and replace with 10 mL atosiban concentrate (7.5 mg/mL) to produce a final concentration of 750 micrograms/mL.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Atosiban (Non-proprietary)**
  - Atosiban (as Atosiban acetate) 7.5 mg per 1 mL Atosiban
    - Adult: 6.75mg/0.9ml solution for injection vials | 1 vial (Hospital only)
  - **Tractocile** (Ferring Pharmaceuticals Ltd)
    - Atosiban (as Atosiban acetate) 7.5 mg per 1 mL Tractocile
      - Adult: 6.75mg/0.9ml solution for injection vials | 1 vial (Hospital only)

**Solution for infusion**

- **Atosiban (Non-proprietary)**
  - Atosiban (as Atosiban acetate) 7.5 mg per 1 mL Atosiban
    - Adult: 37.5mg/5ml concentrate for solution for infusion vials | 1 vial (Hospital only)
    - Adult: 37.5mg/5ml concentrate for solution for infusion vials | 1 vial (Hospital only)
  - **Tractocile** (Ferring Pharmaceuticals Ltd)
    - Atosiban (as Atosiban acetate) 7.5 mg per 1 mL Tractocile
      - Adult: 37.5mg/5ml solution for infusion vials | 1 vial (Hospital only)

5.3 Premature labour

Other drugs used for Premature labour

- Nifedipine, p. 153
- Salbutamol, p. 239
- Terbutaline sulfate, p. 241

**OXYTOCIN RECEPTOR ANTAGONISTS**

**Atosiban**

**INDICATIONS AND DOSE**

Uncomplicated premature labour between 24 and 33 weeks of gestation

- Initially by intravenous injection
- Adult: Initially 6.75 mg over 1 minute, then (by intravenous infusion) 18 mg/hour for 3 hours, then (by intravenous infusion) reduced to 6 mg/hour for up to 45 hours. Maximum duration of treatment is 48 hours

**CONTRA-INDICATIONS**

Abruptio placenta · antepartum haemorrhage (requiring immediate delivery) · eclampsia · intra-uterine fetal death · intra-uterine infection · intra-uterine growth restriction with abnormal fetal heart rate · placenta praevia · premature rupture of membranes after 30 weeks’ gestation · severe pre-eclampsia

**CAUTIONS**

Abnormal placental site · intra-uterine growth restriction

**SIDE-EFFECTS**

- Common or very common Dizziness · headache · hot flushes · hyperglycaemia · hypotension · injection-site reaction · nausea · tachycardia · vomiting
- Uncommon Fever · insomnia · pruritus · rash

**HEPATIC IMPAIRMENT**

No information available.

**RENAL IMPAIRMENT**

No information available.

**MONITORING REQUIREMENTS**

Monitor blood loss after delivery.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Tractocile® concentrate for intravenous infusion), give continuously in Glucose 5% or Sodium chloride 0.9%.

Withdraw 10 mL infusion fluid from 100-mL bag and replace with 10 mL atosiban concentrate (7.5 mg/mL) to produce a final concentration of 750 micrograms/mL.

**5.4 Termination of pregnancy**

PROGESTERONE RECEPTOR MODULATORS

**Mifepristone**

**INDICATIONS AND DOSE**

Cervical ripening before mechanical cervical dilatation for termination of pregnancy of up to 84 days gestation (under close medical supervision)

- **BY MOUTH**
  - Adult: 200 mg for 1 dose, to be taken 36–48 hours before procedure

Labour induction in fetal death in utero where prostaglandin or oxytocin inappropriate (under close medical supervision)

- **BY MOUTH**
  - Adult: 600 mg once daily for 2 days, if labour not started within 72 hours of first dose, another method should be used

Medical termination of intra-uterine pregnancy of up to 49 days gestation (under close medical supervision)

- **BY MOUTH**
  - Adult: 600 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina or misoprostol 400 micrograms by mouth, alternatively 200 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding

Medical termination of intra-uterine pregnancy of 50–63 days gestation (under close medical supervision)

- **BY MOUTH**
  - Adult: 600 mg for 1 dose, alternatively 200 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding
**Termination of pregnancy of 13–24 weeks gestation (in combination with a prostaglandin) (under close medical supervision)**

- **BY MOUTH**
  - Adult: 600 mg for 1 dose, alternatively 200 mg for 1 dose, dose followed 36–48 hours later by gemeprost 1 mg by vagina every 3 hours up to max. 5 mg or misoprostol; if abortion does not occur, 24 hours after start of treatment repeat course of gemeprost 1 mg by vagina up to max. 5 mg; follow-up visit after appropriate interval to assess vaginal bleeding recommended.

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 · chronic adrenal failure · suspected ectopic pregnancy (use other specific means of termination) · uncontrolled severe asthma

- **CAUTIONS** Adrenal suppression (may require corticosteroid) · anticoagulant therapy · asthma (avoid if severe and uncontrolled) · existing cardiovascular disease · haemorrhagic disorders · history of endocarditis · prosthetic heart valve · risk factors for cardiovascular disease

- **INTERACTIONS** → Appendix 1 (mifepristone).

- **SIDE-EFFECTS**
  - Common or very common Gastro-intestinal cramps · uterine contractions · vaginal bleeding (sometimes severe) may occur between administration of misoprostol and surgery (and rarely abortion may occur before surgery)
  - Uncommon Hypersensitivity reactions · rash · urticaria
  - Rare Chills · dizziness · fever · headache · hot flushes · hypotension · malaise
  - Frequency not known Infections · toxic shock syndrome

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid.

- **RENAL IMPAIRMENT** Manufacturer advises avoid.

- **MONITORING REQUIREMENTS** Careful monitoring of blood pressure and pulse essential for 3 hours after administration of gemeprost pessary (risk of profound hypotension).

- **PRESCRIBING AND DISPENSING INFORMATION** Supplied to NHS hospitals and premises approved under Abortion Act 1967.

- **PATIENT AND CARER ADVICE** Patient information leaflet to be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 10
  - **Mifepristone (Non-proprietary)** Mifepristone 200 mg Mifepristone 200mg tablets | 1 tablet [POM] no price available (Hospital only)
  - **Mifegyne (Nordic Pharma Ltd)** Mifepristone 200 mg Mifegyne 200mg tablets | 3 tablet [POM] £52.66 (Hospital only)

**PROSTAGLANDINS AND OXYTOCICS**

**Gemeprost**

- **INDICATIONS AND DOSE**
  - **Cervical ripening prior to first trimester surgical abortion**
    - **BY VAGINA**
    - Adult: 1 mg, dose to be inserted into posterior fornix 3 hours before surgery
  - **Second trimester abortion**
    - **BY VAGINA**
    - Adult: 1 mg every 3 hours for maximum 5 administrations, to be inserted into posterior fornix

- **CONTRA-INDICATIONS** Placenta praevia · unexplained vaginal bleeding · uterine scarring

- **CAUTIONS** Cardiovascular insufficiency · cervicitis · obstructive airways disease · raised intra-ocular pressure · vaginitis

- **INTERACTIONS** → Appendix 1 (prostaglandins).

- **SIDE-EFFECTS** Backache · chest pain · chills · coronary artery spasm · diarrhoea · dizziness · dyspnoea · flushing · headache · mild pyrexia · muscle weakness · myocardial infarction · nausea · palpitation · severe hypotension · uterine pain · uterine rupture (most commonly in multiparas or if history of uterine surgery or if given with intravenous oxytocics) · vaginal bleeding · vomiting

- **MONITORING REQUIREMENTS**
  - If used in combination with mifepristone, carefully monitor blood pressure and pulse for 3 hours.
  - When used for second trimester intra-uterine death, monitor for coagulopathy during treatment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Pessary**
    - **Gemeprost (Non-proprietary)**
    - Gemeprost 1 mg Gemeprost 1mg pessaries | 5 pessary [POM] no price available

**Misoprostol**

- **DRUG ACTION** Misoprostol acts as a potent uterine stimulant.

- **INDICATIONS AND DOSE**
  - **Termination of pregnancy following mifepristone (gestation up to 49 days)**
    - **BY MOUTH**
    - Adult: 400 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone
Termination of pregnancy following mifepristone (gestation 50 to 63 days)

- **INITIALLY BY VAGINA, OR BY BUCCAL ADMINISTRATION, OR BY SUBLINGUAL ADMINISTRATION**
- Adult: 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, if abortion has not occurred 4 hours after first misoprostol dose a further dose may be given, (by mouth or by vagina) 400 micrograms for 1 dose

Termination of pregnancy following mifepristone (gestation of 9 to 13 weeks)

- **INITIALLY BY VAGINA**
- Adult: 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses

Termination of pregnancy following mifepristone (gestation of 13 to 24 weeks)

- **INITIALLY BY VAGINA**
- Adult: 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses, if abortion has not occurred 3 hours after the last dose of misoprostol, a further dose of mifepristone may be given, and misoprostol may be recommenced 12 hours later

- **UNLICENSED USE** Use of misoprostol for termination of pregnancy is an unlicensed use.
- **CAUTIONS** Conditions where hypotension might precipitate severe complications (e.g. cerebrovascular disease, cardiovascular disease) - inflammatory bowel disease
- **INTERACTIONS** → Appendix 1 (misoprostol)
- **SIDE-EFFECTS**
  - Common or very common Diarrhoea
  - Frequency not known Abdominal pain - abnormal vaginal bleeding - dizziness - dyspesia - flatulence - intermenstrual bleeding - menorrhagia - nausea - postmenopausal bleeding - rashes - vomiting
- **BREAST FEEDING** Present in milk, but amount probably too small to be harmful.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misoprostol 200 microgram</td>
<td>Misoprostol 200 microgram vaginal tablets</td>
</tr>
<tr>
<td>Cytotec (Pfizer Ltd)</td>
<td>Misoprostol 200 microgram</td>
</tr>
<tr>
<td>Topogyne (Nordic Pharma Ltd)</td>
<td>Misoprostol 400 microgram</td>
</tr>
</tbody>
</table>

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### Vaginal and vulval conditions

#### Vaginal and vulval conditions

##### Management

Symptoms are often restricted to the vulva, but infections almost invariably involve the vagina which should also be treated. Applications to the vulva alone are likely to give only symptomatic relief without cure. *Aqueous medicated douches* may disturb normal vaginal acidity and bacterial flora.

**Topical anaesthetic agents** give only symptomatic relief and may cause sensitivity reactions. They are indicated only in cases of pruritus where specific local causes have been excluded.

**Systemic drugs** are required in the treatment of infections such as gonorrhoea and syphilis.

#### Preparations for vaginal and vulval changes

**Topical HRT for vaginal atrophy**

A cream containing an oestrogen may be applied on a short-term basis to improve the vaginal epithelium in *menopausal atrophic vaginitis*. It is important to bear in mind that topical oestrogens should be used in the **smallest effective** amount to minimise systemic effects. Modified-release vaginal tablets and an impregnated vaginal ring are now also available.

The risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods. The endometrial safety of long-term or repeated use of *topical* vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Topical oestrogens are also used in postmenopausal women before vaginal surgery for prolapse when there is epithelial atrophy.

**Non-hormonal preparations for vaginal atrophy**

Several non-hormonal vaginal moisturisers are available and some are prescribable on the NHS (consult Drug Tariff).

#### Vaginal and vulval infections

Effective specific treatments are available for the common vaginal infections.

**Fungal infections**

*Candidal vulvitis* can be treated locally with cream, but is almost invariably associated with vaginal infection which should also be treated. *Vaginal candidiasis* is treated primarily with antifungal pessaries or cream inserted high into the vagina (including during menstruation). Single-dose preparations offer an advantage when compliance is a problem. Local irritation may occur on application of vaginal antifungal products.

**Imidazole** drugs (clotrimazole p. 758, econazole nitrate p. 759, fenticonazole nitrate p. 759, and miconazole p. 760) are effective against candida in short courses of 1 to 14 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur. Vaginal applications may be supplemented with antifungal cream for vulvitis and to treat other superficial sites of infection.

Oral treatment of vaginal infection with *fluconazole* p. 548 or *itraconazole* p. 550 is also effective.

**Vulvovaginal candidiasis in pregnancy**

Vulvovaginal candidiasis is common during pregnancy and can be treated with vaginal application of an imidazole (such as clotrimazole), and a topical imidazole cream for vulvitis. Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

**Recurrent vulvovaginal candidiasis**

Recurrence of vulvovaginal candidiasis is particularly likely if there are predisposing factors, such as antibacterial therapy, pregnancy, diabetes mellitus, or possibly oral contraceptive use. Reservoirs of infection may also lead to recontamination and should be treated; these include other skin sites such as the digits, nail beds, and umbilicus as well as the gastro-intestinal tract and the bladder. The partner
may also be the source of reinfection and, if symptomatic, should be treated with a topical imidazole cream at the same time.

Treatment against candida may need to be extended for 6 months in recurrent vulvovaginal candidiasis.

Other infections
Trichomonal infections commonly involve the lower urinary tract as well as the genital system and need systemic treatment with metronidazole p. 499 or tinidazole p. 501. Bacterial infections with Gram-negative organisms are particularly common in association with gynaecological operations and trauma. Metronidazole is effective against certain Gram-negative organisms, especially Bacteroides spp. and can be used prophylactically in gynaecological surgery. Clindamycin, cream below and metronidazole gel are indicated for bacterial vaginosis.

Vaginal preparations intended to restore normal acidity may prevent recurrence of vaginal infections and permit the re-establishment of the normal vaginal flora.

The antiviral drugs aciclovir, famciclovir and valaciclovir p. 587, and famciclovir p. 587, and valaciclovir p. 587 can be used in the treatment of genital infection due to herpes simplex virus, the HSV type 2 being a major cause of genital ulceration; they have a beneficial effect on virus shedding and healing, generally giving relief from pain and other symptoms.

6.1 Vaginal and vulval infections

6.1a Vaginal and vulval bacterial infections

Other drugs used for Vaginal and vulval bacterial infections Metronidazole, p. 499

6.1b Vaginal and vulval fungal infections

Other drugs used for Vaginal and vulval fungal infections Fluconazole, p. 548 · Itraconazole, p. 550

CARBOXYLIC ACIDS

Lactic acid

- INDICATIONS AND DOSE
  - BALANCE ACTIV RX® GEL
    - Prevention of bacterial vaginosis
      - BY VAGINA
        - Adult: 5 mL 1–2 times a week, insert the content of 1 tube (5 mL)
    - RELACTAGEL® GEL
      - Prevention of bacterial vaginosis
        - BY VAGINA
        - Adult: 5 mL daily for 2–3 nights after menstruation, insert the contents of one tube

- SIDE-EFFECTS
  - RELACTAGEL® GEL Mild irritation
  - CONCEPTION AND CONCEPTION
    - RELACTAGEL® GEL Not recommended if trying to conceive.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Gel EXCIPIENTS: May contain Propylene glycol
    - Balance Activ (BBI Healthcare Ltd)
      - Balance Activa BV vaginal pH correction gel | 7 device £5.25
    - Relactagel (KoRa Healthcare)
      - Relactagel vaginal pH correction gel | 7 device £5.25

- ANTIFUNGALS ➤ IMIDAZOLE ANTIFUNGALS

Clotrimazole

- INDICATIONS AND DOSE
  - Superficial sites of infection in vaginal and vulval candidiasis (dose for 1% or 2% cream)
    - BY VAGINA USING CREAM
      - Adult: Apply 2–3 times a day, to be applied to anogenital area
  - Vaginal candidiasis (dose for 10% intravaginal cream)
    - BY VAGINA USING VAGINAL CREAM
      - Adult: 5 g for 1 dose, one applicatorful to be inserted into the vagina at night, dose can be repeated once if necessary
  - Vaginal candidiasis
    - BY VAGINA USING PESSARIES
      - Adult: 200 mg for 3 nights, course can be repeated once if necessary, alternatively 100 mg for 6 nights, course can be repeated once if necessary, alternatively 500 mg for 1 night, dose can be repeated once if necessary
  - Recurrent vulvovaginal candidiasis
    - BY VAGINA USING PESSARIES
      - Adult: 500 mg every week for 6 months, dose to be administered following topical imidazole for 10–14 days

- SIDE-EFFECTS Local irritation
- CONCEPTION AND CONCEPTION
  - Cream and pessaries may damage latex condoms and diaphragms.
Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

Brands for sale to the public include Canesten® Internal Cream.

There can be variation in the licensing of different medicines containing the same drug.

**Pessary**

- Canesten (Janssen-Cilag Ltd)
  - Econazole nitrate 150 mg | 1 pessary £3.69
  - Canesten 150mg vaginal pessaries | 3 pessary £4.17

**Cream**

- Canesten (Janssen-Cilag Ltd)
  - Econazole nitrate 10 mg per 1 gram | 15 gram £2.11 | 30 gram £3.78

**Fenticonazole nitrate**

**INDICATIONS AND DOSE**

**Vaginal and vulva candidiasis**

- Adult: 200 mg daily for 3 days, alternatively 600 mg daily for 1 dose, to be inserted at night
- BY VAGINA USING CREAM
  - Adult: 1 applicatorful twice daily for 3 days

**DOSE EQUIVALENT AND CONVERSION**

- With topical use: 1 applicatorful delivers a 5 g dose of fenticonazole 2 %.

**SIDE-EFFECTS** Local irritation

**CONCEPTION AND CONTRACEPTION** Intravaginal cream and vaginal capsules damage latex condoms and diaphragms.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Gynoxin (Recordati Pharmaceuticals Ltd)
  - Fenticonazole nitrate 200 mg | 3 capsule £2.42

**Cream**

- Gynoxin (Recordati Pharmaceuticals Ltd)
  - Fenticonazole nitrate 20 mg per 1 gram | 1 capsule £3.74

**Ketoconazole**

**INDICATIONS AND DOSE**

**Vaginal and vulva candidiasis**

- Adult: Apply 1–2 times a day, to be applied to the anogenital area

**SIDE-EFFECTS** Occasional local irritation

**CONCEPTION AND CONTRACEPTION** Effects on latex condoms and diaphragms not yet known.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

- Nizoral (Janssen-Cilag Ltd)
  - Ketoconazole 20 mg per 1 gram | 30 gram £4.24 DT price = £4.24
Miconazole

**INDICATIONS AND DOSE**

**Vaginal and vulval candidiasis**
- By vagina using cream or capsule
- Child: 1 capsule daily, ovule to be inserted at night as a single dose, dose can be repeated once if necessary
- Adult: 1 capsule daily, ovule to be inserted at night as a single dose, dose can be repeated once if necessary
- By vagina using cream
  - Adult: Apply 1 applicatorful daily for 10 to 14 days, alternatively apply 1 applicatorful twice daily for 7 days, course can be repeated once if necessary

Superficial sites of infection in vaginal and vulval candidiasis | Vulvitis
- By vagina using cream
- Adult: Apply twice daily, apply to the anogenital area

**INTERACTIONS**
- Common or very common: Nausea, rash, vomiting
- Frequency not known: Occasional local irritation
- CONCEPTION AND CONTRACEPTION: Gyno-Daktarin® damages latex condoms and diaphragms.
- Pregnancy: Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection.
- Breast feeding: Manufacturer advises caution—no information available.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- Capsule: **EXCIPIENTS:** May contain hydroxybenzoates (parabens)
  - Gyno-Daktarin (Janssen-Cilag Ltd)
  - Miconazole nitrate 1.2 gram Gyno-Daktarin 1200 mg vaginal capsules 1 capsule (Pom) £2.94 OT price £2.94
- Cream: **EXCIPIENTS:** May contain butylated hydroxyanisole
  - Gyno-Daktarin (Janssen-Cilag Ltd)
  - Miconazole nitrate 20 mg per 1 gram Gyno-Daktarin 2% vaginal cream 1 tube (Pom) £4.33

6.2 Vaginal atrophy

**OESTROGENS**

**Estradiol**

**INDICATIONS AND DOSE**

**ESTRING®**
- Postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis)
- By vagina
- Adult: To be inserted into upper third of vagina and worn continuously; replace after 3 months; max. duration of continuous treatment 2 years

**VAGIFEM®**
- Improve the vaginal epithelium in menopausal atrophic vaginitis
  - By vagina
  - Adult: 1 tablet daily for 2 weeks, then reduced to 1 tablet twice weekly

**CONTRA-INDICATIONS**
- Active arterial thromboembolic disease (e.g. angina or myocardial infarction)

thrombophlebitis · Dubin-Johnson syndrome (or monitor closely) · history of breast cancer · history of recurrent venous thromboembolism (unless already on anticoagulant treatment) · oestrogen-dependent cancer · recent arterial thromboembolic disease (e.g. angina or myocardial infarction) · Rotor syndrome (or monitor closely) · thrombophiolic disorder · undiagnosed vaginal bleeding · untreated endometrial hyperplasia · venous thromboembolism

**CAUTIONS**
- Avoid in acute porphyrias p. 930 · avoid intravaginal preparations (particularly those that require use of an applicator) in young girls who are not sexually active, unless there is no alternative
- **SIDE-EFFECTS**
  - Common or very common: Nausea, rash, vomiting
  - Frequency not known: Occasional local irritation

• Risk of breast cancer: It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.

Radiological detection of breast cancer can be made more difficult by mammographic density increase with HRT use.

• Risk of endometrial cancer: The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.

In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

• Risk of ovarian cancer: Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

• Risk of venous thromboembolism: Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.

In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

• Risk of stroke: Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

• Risk of coronary heart disease: HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause,
studies suggest a lower relative risk compared with older women.

- **Other conditions** The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **INTERACTIONS** → Appendix 1 (oestrogens).

- **SIDE-EFFECTS** Abdominal bloating - abdominal cramps - altered blood lipids (may lead to pancreatitis, rashes and chloasma) - breast enlargement - breast tenderness - changes in libido - chloasma - glucose intolerance - headache - headache (on vigorous exercise) - leg cramps (rule out venous thrombosis) - local irritation - migraine - mood changes - nausea - premenstrual-like syndrome - sodium retention - vaginal candidiasis - vomiting - weight changes

- **SIDE-EFFECTS, FURTHER INFORMATION**

  - **Withdrawal bleeding** Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

- **CONCEPTION AND CONTRACEPTION** HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly if not repeated under 50 years) do not necessarily preclude the possibility of becoming pregnant.

**VAGIFEM®** No evidence of damage to latex condoms and diaphragms.

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Avoid; adverse effects on lactation.

- **HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

- **MONITORING REQUIREMENTS**

  - History of breast nodules or fibrocystic disease—closely monitor breast status (risk of breast cancer).
  - The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Pessary**

- **Vagifem** (Novo Nordisk Ltd)
  - Estradiol 10 microgram vaginal tablets | 24 pessary £16.72 0T price = £16.72

**Vaginal delivery system**

**CAUTIONARY AND ADVISORY LABELS 10**

- **Estring** (Pfizer Ltd)
  - Estradiol (as Estradiol hemihydrate) 7.5 microgram per 24 hour
    - Estring 7.5micrograms/24hours vaginal delivery system | 1 device £31.42

**Estriol**

- **INDICATIONS AND DOSE**

  **OVESTIN®**

  - **Improve the vaginal epithelium in menopausal atrophic vaginitis (short-term use)**

    - **FOR VAGINA**
      - Adult: Apply 1 applicatorful daily for 2–3 weeks, then reduced to 1 applicatorful twice weekly, discontinue every 2–3 months for 4 weeks to assess need for further treatment

  **Vaginal surgery for prolapse when there is epithelial atrophy in postmenopausal women (before surgery)**

    - **FOR VAGINA**
      - Adult: Apply 1 applicatorful daily for 2 weeks before surgery, resume 2 weeks after surgery

- **CONTRA-INDICATIONS** Active arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thrombophlebitis - Dubin-Johnson syndrome (or monitor closely) - history of breast cancer - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - oestrogen-dependent cancer - recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - Rotor syndrome (or monitor closely) - thrombophilic disorder - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

- **CAUTIONS** Acute porphyrias p. 930 - diabetes (increased risk of heart disease) - factors predisposing to thromboembolism - history of breast nodules—closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia - history of fibrocystic disease—closely monitor breast status (risk of breast cancer) - hypophyseal tumours - increased risk of gall-bladder disease - interrupt treatment periodically to assess need for continued treatment - migraine (or migraine-like headaches) - presence of antiphospholipid antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size

**CAUTIONS, FURTHER INFORMATION**

- **Risk of breast cancer** It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.
  - Radioiodination of breast cancer can be made more difficult as mammographic density can increase with HRT use.
  - **Risk of endometrial cancer** The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.
In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

- Risk of ovarian cancer: Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.
- Risk of venous thromboembolism: Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.

In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

- Risk of stroke: Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

- Risk of coronary heart disease: HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

Other conditions: The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- INTERACTIONS: Appendix 1 (oestrogens).
- SIDE-EFFECTS: Abdominal bloating, abdominal cramps, altered blood lipids (may lead to pancreatitis, rashes and chloasma), breast enlargement, breast tenderness, changes in libido, cholestatic jaundice, contact lenses may irritate, depression, dizziness, fluid retention, glucose intolerance, headache, leg cramps, local irritation, migraine, mood changes, nausea, premenstrual-like syndrome, sodium retention, vaginal candidiasis, vomiting, weight changes

SIDE-EFFECTS, FURTHER INFORMATION
- Leg Cramps: Venous thrombosis should be ruled out.
- Withdrawal Bleeding: Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

- CONCEPTION AND CONTRACEPTION: Effect on latex condoms and diaphragms not yet known.
- PREGNANCY: Not known to be harmful.
- BREAST FEEDING: Avoid; adverse effects on lactation.
Chapter 8

Immune system and malignant disease

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Immune system

1 Immune system disorders and transplantation

Immune response

Inflammatory bowel disease

Azathioprine p. 765, ciclosporin p. 766, mercaptopurine p. 816, and methotrexate p. 817 have a role in the treatment of inflammatory bowel disease.

Folic acid p. 898 should be given to reduce the possibility of methotrexate toxicity [unlicensed indication]. Folic acid is usually given weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

Immunosuppressant therapy

Immunosuppressants are used to suppress rejection in organ transplant recipients and to treat a variety of chronic inflammatory and autoimmune diseases. Solid organ transplant patients are maintained on drug regimens, which may include antiproliferative drugs (azathioprine or mycophenolate mofetil p. 773), calcineurin inhibitors (ciclosporin or tacrolimus p. 769), corticosteroids, or sirolimus p. 768. Choice is dependent on the type of organ, time after transplantation, and clinical condition of the patient. Specialist management is required and other immunomodulators may be used to initiate treatment or to treat rejection.

Impaired immune responsiveness

Modification of tissue reactions caused by corticosteroids and other immunosuppressants may result in the rapid spread of infection. Corticosteroids may suppress clinical signs of infection and allow diseases such as septicaemia or tuberculosis to reach an advanced stage before being recognised — important: normal immunoglobulin administration should be considered as soon as possible after measles exposure, and varicella–zoster immunoglobulin (VZIG) is recommended for individuals who have significant chickenpox (varicella) exposure. Specialist advice should be sought on the use of live vaccines for those being treated with immunosuppressive drugs.

Antiproliferative immunosuppressants

Azathioprine is widely used for transplant recipients and it is also used to treat a number of auto-immune conditions, usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced when allopurinol p. 980 is given concurrently.

Mycophenolate mofetil is metabolised to mycophenolic acid which has a more selective mode of action than azathioprine.

There is evidence that compared with similar regimens incorporating azathioprine, mycophenolate mofetil reduces the risk of acute rejection episodes; the risk of opportunistic infections (particularly due to tissue-invasive cytomegalovirus) and the occurrence of blood disorders such as leucopenia may be higher.

Cyclophosphamide p. 802 is less commonly prescribed as an immunosuppressant.

Corticosteroids and other immunosuppressants

Prednisolone p. 622 is widely used in oncology. It has a marked antitumour effect in acute lymphoblastic leukaemia, Hodgkin’s disease, and the non–Hodgkin lymphomas. It has a role in the palliation of symptomatic end-stage malignant disease when it may enhance appetite and produce a sense of well-being.

The corticosteroids are also powerful immunosuppressants. They are used to prevent organ transplant rejection, and in high dose to treat rejection episodes.

Ciclosporin a calcineurin inhibitor, is a potent immunosuppressant which is virtually non–myelotoxic but markedly nephrotoxic. It has an important role in organ and tissue transplantation, for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart, lung, and heart–lung transplantation, and for prophylaxis and treatment of graft–versus-host disease.

Tacrolimus is also a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects, but the incidence of neurotoxicity appears to be greater; cardiomyopathy has also been reported. Disturbance of glucose metabolism also appears to be significant.

Sirolimus is a non–calcineurin inhibiting immunosuppressant licensed for renal transplantation.

Basiliximab p. 772 is used for prophylaxis of acute rejection in allogeneic renal transplantation. It is given with ciclosporin and corticosteroid immunosuppression regimens; its use should be confined to specialist centres.

Belatacept p. 774 is a fusion protein and co-stimulation blocker that prevents T-cell activation; it is licensed for prophylaxis of graft rejection in adults undergoing renal transplantation who are seropositive for the Epstein–Barr virus. It is used with interleukin-2 receptor antagonist.
induction, in combination with corticosteroids and a mycophenolic acid.

Antithymocyte immunoglobulin (rabbit) below is licensed for the prophylaxis of organ rejection in renal and heart allograft recipients and for the treatment of corticosteroid-resistant allograft rejection in renal transplantation. Tolerability is increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

NICE technology appraisals (TAs)
For induction therapy in the prophylaxis of organ rejection, either basiliximab or daclizumab [discontinued] are options for combining with a calcineurin inhibitor. For each individual, ciclosporin or tacrolimus is chosen as the calcineurin inhibitor on the basis of side-effects.

Mycophenolate mofetil [mycophenolic acid also available but not licensed for use in children] is recommended as part of an immunosuppressive regimen only if:
- the calcineurin inhibitor is not tolerated, particularly if nephrotoxicity endangers the transplanted kidney; or
- there is very high risk of nephrotoxicity from the calcineurin inhibitor, requiring a reduction in the dose of the calcineurin inhibitor or its avoidance.

Sirolimus is recommended as a component of immunosuppressive regimen only if intolerance necessitates the withdrawal of a calcineurin inhibitor. These recommendations may not be consistent with the marketing authorisation of some of the products.

www.nice.org.uk/TA85

NICE has recommended that for induction therapy in the prophylaxis of organ rejection, either basiliximab or daclizumab [discontinued] are options for combining with a calcineurin inhibitor. For each individual, ciclosporin or tacrolimus is chosen as the calcineurin inhibitor on the basis of side-effects. Mycophenolate mofetil is recommended as part of an immunosuppressive regimen only if:
- the calcineurin inhibitor is not tolerated, particularly if nephrotoxicity endangers the transplanted kidney; or
- there is very high risk of nephrotoxicity from the calcineurin inhibitor, requiring a reduction in the dose of the calcineurin inhibitor or its avoidance.

Mycophenolic acid is not recommended as part of an immunosuppressive regimen for renal transplantation in children or adolescents.

Sirolimus [not licensed for use in children] is recommended as a component of immunosuppressive regimen only if intolerance necessitates the withdrawal of a calcineurin inhibitor.

These recommendations may not be consistent with the marketing authorisation of some of the products.

www.nice.org.uk/TA99

Other drugs used for Immune system disorders and transplantation Chloroquine, p. 569 · Everolimus, p. 865 · Hydroxychloroquine sulfate, p. 962 · Rituximab, p. 792

IMMUNE SERA AND IMMUNOGLOBULINS

Antithymocyte immunoglobulin (rabbit)

- **INDICATIONS AND DOSE**
  - Prophylaxis of organ rejection in heart allograft recipients
    - BY INTRAVENOUS INFUSION
      - Adult: 1–2.5 mg/kg daily for 3–5 days, to be given over at least 6 hours
  - Prophylaxis of organ rejection in renal allograft recipients
    - BY INTRAVENOUS INFUSION
      - Adult: 1–1.5 mg/kg daily for 3–9 days, to be given over at least 6 hours
  - Treatment of corticosteroid-resistant allograft rejection in renal transplantation
    - BY INTRAVENOUS INFUSION
      - Adult: 1.5 mg/kg daily for 7–14 days, to be given over at least 6 hours

- **DOSES AT EXTREMES OF BODY-WEIGHT**
  To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight.

- **CONTRA-INDICATIONS**
  - Infection

- **SIDE-EFFECTS**
  - Anaphylaxis · cytokine release syndrome · diarrhoea · dysphagia · fever · hypotension · increased susceptibility to infection · increased susceptibility to malignancy · infusion-related reactions · lymphopoenia · myalgia · nausea · neutropenia · pruritus · rash · serum sickness · shivering · thrombocytopenia · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  Tolerability is increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

- **PREGNANCY**
  - Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor blood count.

- **DIRECTIONS FOR ADMINISTRATION**
  - For continuous intravenous infusion (Thymoglobulin®) in Glucose 5% or Sodium chloride 0.9%; reconstitute each vial with 5 mL water for infusions to produce a solution of 5 mg/mL; gently rotate to dissolve. Dilute requisite dose with infusion fluid to a total volume of 50–500 mL (usually 50 mL/vial); begin infusion immediately after dilution; give through an in-line filter (pore size 0.22 micron); not to be given with unfractionated heparin and hydrocortisone in glucose infusion—precipitation reported.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for infusion**
  - **Antithymocyte immunoglobulin (rabbit) (Non-proprietary)**
    - Antithymocyte immunoglobulin (rabbit) 20 mg per 1 mL Grafalon 100mg/5mL concentrate for solution for infusion vials | 1 vial no price available

  **Powder and solvent for solution for infusion**
  - **Thymoglobulin** (Sanofi)
    - Antithymocyte immunoglobulin (rabbit) 25 mg Thymoglobulin 25mg powder and solvent for solution for infusion vials | 1 vial £158.77 (Hospital only)
Azathioprine

**DRUG ACTION** Azathioprine is metabolised to mercaptopurine.

### INDICATIONS AND DOSE

**Severe acute Crohn's disease | Maintenance of remission of Crohn's disease | Maintenance of remission of acute ulcerative colitis**

- **Adult:** 2–2.5 mg/kg daily, some patients may respond to lower doses

**Rheumatoid arthritis that has not responded to other disease-modifying drugs | Severe systemic lupus erythematosus and other connective tissue disorders**

- **Adult:** Initially up to 2.5 mg/kg daily in divided doses, adjusted according to response, rarely more than 3 mg/kg daily; maintenance 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months

**Autoimmune conditions**

- **Adult:** 1–3 mg/kg daily, adjusted according to response, consider withdrawal if no improvement within 3 months, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

**Suppression of transplant rejection**

- **Adult:** 1–2.5 mg/kg daily, adjusted according to response, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

**Severe refractory eczema, normal or high TPMT activity**

- **Adult:** 1–3 mg/kg daily

**Severe refractory eczema, intermediate TPMT activity**

- **Adult:** 0.5–1.5 mg/kg daily

**Generalised myasthenia gravis**

- **Adult:** Initially 0.5–1 mg/kg daily, then increased to 2–2.5 mg/kg daily, dose is increased over 3–4 weeks, azathioprine is usually started at the same time as the corticosteroid and allows a lower maintenance dose of the corticosteroid to be used, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

### UNLICENSED USE

Azathioprine doses given in BNF for suppression of transplant rejection and autoimmune conditions may differ from those in product literature. Use for severe refractory eczema is unlicensed.

### CONTRA-INDICATIONS

- When used for severe refractory eczema Absent thiopurine methyltransferase (TPMT) activity • very low thiopurine methyltransferase (TPMT) activity

### CAUTIONS

- Reduce dose in elderly - reduced thiopurine methyltransferase activity

### INTERACTIONS

- Appendix 1 (azathioprine).

### SIDE-EFFECTS

- Rare Hepatic veno-occlusive disease • lymphoma • pancreatitis • pneumonitis • red cell aplasia

- Frequency not known Arthralgia • cholestatic jaundice • colitis in patients also receiving corticosteroids • diarrhoea • dizziness • dose-related bone marrow suppression • fever • hair loss • herpes zoster infection • hypersensitivity reactions • hypotension • increased susceptibility to infections in patients also receiving corticosteroids • interstitial nephritis • liver impairment • malaise • myalgia • neutropenia • rash • rigors • thrombocytopenia • vomiting

### SIDE-EFFECTS, FURTHER INFORMATION

- Red cell aplasia Cases of pure red cell aplasia have been reported with azathioprine; dose reduction or discontinuation should be considered under specialist supervision.

- Neutropenia and thrombocytopenia Usually resolved by reducing the dose.

- Hypersensitivity reactions Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis) call for immediate withdrawal.

- Nausea, vomiting and diarrhoea Nausea, vomiting and diarrhoea may occur, usually starting early during the course of treatment, and in rheumatoid arthritis it may be appropriate to withdraw the drug.

### ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in hypersensitivity to mercaptopurine.

### PREGNANCY

Transplant patients immunosuppressed with azathioprine should not discontinue it on becoming pregnant. However, there have been reports of premature birth and low birth–weight following exposure to azathioprine, particularly in combination with corticosteroids. Spontaneous abortion has been reported following maternal or paternal exposure. Azathioprine is teratogenic in animal studies. The use of azathioprine during pregnancy needs to be supervised in specialist units. Treatment should not generally be initiated during pregnancy.

### BREAST FEEDING

Present in milk in low concentration. No evidence of harm in small studies—use if potential benefit outweighs risk.

### HEPATIC IMPAIRMENT

Reduce dose. Monitor liver function.

### RENAL IMPAIRMENT

Reduce dose.

### PRE-TREATMENT SCREENING

Thiopurine methyltransferase The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Consider measuring TPMT activity before starting azathioprine, mercaptopurine, or tioguanine therapy. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

### MONITORING REQUIREMENTS

- Monitor for toxicity throughout treatment.

- Monitor full blood count weekly (more frequently with higher doses or if severe hepatic or renal impairment) for first 4 weeks (manufacturer advises weekly monitoring for 8 weeks but evidence of practical value unsatisfactory), thereafter reduce frequency of monitoring to at least every 3 months.

- Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment.

### DIRECTIONS FOR ADMINISTRATION

For intravenous injection, give over at least 1 minute (followed by 50 mL sodium chloride intravenous infusion). For intravenous
Immune system and malignant disease

IMMUNOSUPPRESSANTS > CALCINEURIN INHIBITORS AND RELATED DRUGS

Ciclosporin

01-Sep-2016

Drug action
Ciclosporin inhibits production and release of lymphokines, thereby suppressing cell-mediated immune response.

Indications and dose
Severe acute ulcerative colitis refractory to corticosteroid treatment

- By continuous intravenous infusion
- Adult: 5 mg/kg, to be given over 24 hours, dose adjusted according to blood-ciclosporin concentration and response

Severe active rheumatoid arthritis when conventional second-line therapy inappropriate or ineffective (administered on expert advice)

- By mouth
- Adult: Initially 2.5 mg/kg daily in 2 divided doses, increased if necessary up to 4 mg/kg daily after 6 weeks, if dose increases are necessary they should be made gradually, discontinue if response insufficient after 3 months, dose adjusted according to response for maintenance and treatment reviewed after 6 months (continue only if benefits outweigh risks)

Short-term treatment of severe atopic dermatitis where conventional therapy ineffective or inappropriate (administered on expert advice)

- By mouth
- Adult: Initially 1.25 mg/kg twice daily (max. per dose 2.5 mg/kg twice daily) usual maximum duration of 8 weeks but may be used for longer under specialist supervision

Contra-indications
Abnormal baseline renal function (in non-transplant indications) - malignancy (in non-transplant indications) - uncontrolled hypertension (in non-transplant indications) - uncontrolled infections (in non-transplant indications)

Caution
Patients with active infections are not suitable for ciclosporin therapy

Short-term treatment of very severe atopic dermatitis where conventional therapy ineffective or inappropriate (administered on expert advice)

- By mouth
- Adult: 2.5 mg/kg twice daily usual maximum duration of 8 weeks but may be used for longer under specialist supervision

Severe psoriasis where conventional therapy ineffective or inappropriate (administered on expert advice)

- By mouth
- Adult: Initially 1.25 mg/kg twice daily (max. per dose 2.5 mg/kg twice daily), increased gradually to maximum if no improvement within 1 month, initial dose of 2.5 mg/kg twice daily justified if condition requires rapid improvement; discontinue if inadequate response after 3 months at the optimum dose; max. duration of treatment usually 1 year unless other treatments cannot be used

Bone marrow transplantation | Prevention and treatment of graft-versus-host disease

- Initially by intravenous infusion
- Adult: 3–5 mg/kg daily, to be administered over 2–6 hours from day before transplantation to 2 weeks postoperatively, alternatively (by mouth) initially 12.5–15 mg/kg daily, then (by mouth) 12.5 mg/kg daily for 3–6 months and then tailed off (may take up to a year after transplantation)

Nephrotic syndrome

- By mouth
- Adult: 5 mg/kg daily in 2 divided doses, for maintenance reduce to lowest effective dose according to proteinuria and serum creatinine measurements; discontinue after 3 months if no improvement in glomerulonephritis or glomerulosclerosis (after 6 months in membranous glomerulonephritis)

Unlicensed use
Not licensed for use in severe acute ulcerative colitis refractory to corticosteroid treatment

Important safety information
MHRA/CHM advice: Ciclosporin must be prescribed and dispensed by brand name (December 2009)

Patients should be stabilised on a particular brand of oral ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration.
psoriasis, treat patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option) - in uveitis, Behcet’s syndrome (monitor neurological status) - lymphoproliferative disorders (discontinue treatment) - malignancy

CAUTIONS, FURTHER INFORMATION

- **Malignancy**
  - In psoriasis, exclude malignancies (including those of skin and cervix) before starting (biopsy any lesions not typical of psoriasis) and treat patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option); discontinue if lymphoproliferative disorder develops.

- **INTERACTIONS**
  - Appendix 1 (ciclosporin).
  - For patients other than transplant recipients, preferably avoid other immunosuppressants (increased risk of infection and malignancies, including lymphoma and skin cancer).

- **SIDE-EFFECTS**
  - **Common or very common**
    - Abdominal pain
    - acne
    - anorexia
    - convulsion
    - diarrhoea
    - fatigue
    - flushing
    - gingival hyperplasia
    - headache
    - hepatic dysfunction
    - hirsutism
    - hyperglycaemia
    - hyperkalaemia
    - hyperlipidaemia
    - hypertension
    - hypertrichosis
    - hyperuricaemia
    - hypomagnesaemia
    - leucopenia
    - muscle cramps
    - myalgia
    - nausea
    - paraesthesia
    - peptic ulcer
    - pyrexia
    - renal dysfunction
    - tremor
    - vomiting
  - **Uncommon**
    - Anaemia
    - oedema
    - signs of encephalopathy
    - thrombocytopenia
    - weight gain
  - **Rare**
    - Gynaecomastia
    - haemolytic uraemic syndrome
    - menstrual disturbances
    - micro-angiopathic haemolytic anaemia
    - motor polyneuropathy
    - muscle weakness
    - myopathy
    - pancreatitis
  - **Very rare**
    - Visual disturbances secondary to benign intracranial hypertension
  - **Frequency not known**
    - With intravenous use
      - Anaphylaxis
    - With systemic use
      - Migraine
      - pain in lower extremities
  - **PREGNANCY**
    - Crosses placenta; manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.
  - **BREAST FEEDING**
    - Manufacturer advises avoid—present in milk.
  - **HEPATIC IMPAIRMENT**
    - Extensively metabolised by the liver—manufacturer advises consider dose adjustment based on bilirubin and liver enzyme levels.
  - **RENAL IMPAIRMENT**
    - In non-transplant indications, manufacturer advises establishing baseline renal function before initiation of treatment; if baseline function is impaired in non-transplant indications, except nephrotic syndrome—avoid.
    - In nephrotic syndrome, manufacturer advises initial dose should not exceed 2.5 mg/kg daily in patients with baseline renal impairment.
    - During treatment for non-transplant indications, manufacturer recommends if eGFR decreases by more than 25% below baseline on more than one measurement, reduce dose by 25–50%. If the eGFR decrease from baseline exceeds 35%, further dose reduction should be considered (even if within normal range); discontinue if reduction not successful within 1 month.
  - **MONITORING REQUIREMENTS**
    - Monitor whole blood ciclosporin concentration (trough level dependent on indication—consult local treatment protocol for details).
    - Dermatological and physical examination, including blood pressure and renal function measurements required at least twice before starting treatment for psoriasis or atopic dermatitis.
    - Monitor liver function.
    - Monitor serum potassium, especially in renal dysfunction (risk of hyperkalaemia).
    - Monitor serum magnesium.
    - Measure blood lipids before treatment and after the first month of treatment.
    - In psoriasis and atopic dermatitis monitor serum creatinine every 2 weeks for first 3 months then every month.
    - Investigate lymphadenopathy that persists despite improvement in atopic dermatitis.
    - Monitor kidney function—dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction in transplant patients (exclude rejection if kidney transplant) or discontinuation in non-transplant patients.
    - Monitor blood pressure—discontinue if hypertension develops that cannot be controlled by antihypertensives.
    - In long-term management of nephrotic syndrome, perform renal biopsies at yearly intervals.
    - In rheumatoid arthritis measure serum creatinine at least twice before treatment. During treatment, monitor serum creatinine every 2 weeks for first 3 months, then every month for a further 3 months, then every 4–8 weeks depending on the stability of the disease, concomitant medication, and concomitant diseases (or more frequently if dose increased or concomitant NSAIDs introduced or increased).
    - Monitor hepatic function if concomitant NSAIDs given.

- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use
    - Mix solution with orange or apple juice, or other soft drink (to improve taste) immediately before taking (and rinse with more to ensure total dose). Do not mix with grapefruit juice. Total daily dose should be taken in 2 divided doses.
  - With intravenous use
    - For intravenous infusion (Sandimmun®), give intermittently or continuously in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of 50 mg in 20–100 mL; give intermittent infusion over 2–6 hours; not to be used with PVC equipment. Observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Brand name prescribing
  - Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient to a different brand of ciclosporin, the patient should be monitored closely for changes in blood-ciclosporin concentration, serum creatinine, blood pressure, and transplant function (for transplant indications). Sandimmun® capsules and oral solution are available direct from Novartis for patients who cannot be transferred to a different oral preparation.

- **PATIENT AND CARER ADVICE**
  - Patients and carers should be counselled on the administration of different formulations of ciclosporin. Manufacturer advises avoid excessive exposure to UV light, including sunlight. In psoriasis and atopic dermatitis, avoid use of UBV or PUVA.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**EXCIPIENTS:**
- Ethanol, ethyl lactate, propylene glycol

- **Ciclosporin (Non-proprietary)**
  - **Ciclosporin 25 mg**
  - Ciclosporin 25mg capsules | 30 capsule

- **Ciclosporin 50 mg**
  - Ciclosporin 50mg capsules | 30 capsule

- **Ciclosporin 100 mg**
  - Ciclosporin 100mg capsules | 30 capsule

- **Capsimune (Mylan Ltd)**
  - **Ciclosporin 25 mg**
  - Capsimune 25mg capsules | 30 capsule

- **Ciclosporin 50 mg**
  - Capsimune 50mg capsules | 30 capsule

- **Ciclosporin 100 mg**
  - Capsimune 100mg capsules | 30 capsule

- **Ciclosporin 200 mg**
  - Capsimune 200mg capsules | 30 capsule

- **Ciclosporin 300 mg**
  - Capsimune 300mg capsules | 30 capsule

- **Ciclosporin 400 mg**
  - Capsimune 400mg capsules | 30 capsule

- **Ciclosporin 750 mg**
  - Capsimune 750mg capsules | 5 capsule

- **Ciclosporin 1500 mg**
  - Capsimune 1500mg capsules | 5 capsule
Ciclosporin 50 mg | Capimune 50mg capsules | 30 capsule | £25.50 DT price | £35.97
Ciclosporin 100 mg | Capimune 100mg capsules | 30 capsule | £48.50 DT price | £68.28
Capsorin (Morningside Healthcare Ltd) | Ciclosporin 25 mg | Capsorin 25mg capsules | 30 capsule | £13.05 DT price | £18.37
Ciclosporin 50 mg | Capsorin 50mg capsules | 30 capsule | £25.59 DT price | £35.97
Ciclosporin 100 mg | Capsorin 100mg capsules | 30 capsule | £48.89 DT price | £68.28
EXCIPIENTS: May contain Alcohol, polyoxyl castor oils
Solution for infusion | Deximune (Dexcel-Pharma Ltd) | Ciclosporin 25 mg | Deximune 25mg capsules | 30 capsule | £13.06 DT price | £18.37
Ciclosporin 50 mg | Deximune 50mg capsules | 30 capsule | £25.60 DT price | £35.97
Ciclosporin 100 mg | Deximune 100mg capsules | 30 capsule | £48.90 DT price | £68.28
Neoral (Novartis Pharmaceuticals UK Ltd) | Ciclosporin 10 mg | Neoral 10mg capsules | 60 capsule | £18.25 DT price | £28.25
Ciclosporin 25 mg | Neoral 25mg capsules | 30 capsule | £35.97 DT price | £51.67
Ciclosporin 50 mg | Neoral 50mg capsules | 30 capsule | £51.28 DT price | £72.82
Ciclosporin 100 mg | Neoral 100mg capsules | 30 capsule | £87.68 DT price | £125.48
Vanquoral (Teva UK Ltd) | Ciclosporin 10 mg | Vanquoral 10mg capsules | 30 capsule | £12.75 £60 capsule | £12.75 DT price | £18.25
Ciclosporin 25 mg | Vanquoral 25mg capsules | 30 capsule | £18.37 DT price | £27.06
Ciclosporin 50 mg | Vanquoral 50mg capsules | 30 capsule | £35.97 DT price | £51.28
Ciclosporin 100 mg | Vanquoral 100mg capsules | 30 capsule | £68.28 DT price | £97.68
Oral solution | Capsorin (Morningside Healthcare Ltd) | Ciclosporin 50 mg per 1 ml | Neoral 10mg/ml oral solution sugar-free | 50 ml | £10.30
Solution for infusion | Capsorin 100 mg per 1 ml | Neoral 100mg/ml oral solution sugar-free | 30 ml | £18.25
EXCIPIENTS: May contain Alcohol, propylene glycol
Neoral (Novartis Pharmaceuticals UK Ltd) | Ciclosporin 100 mg per 1 ml | Neoral 100mg/ml oral solution sugar-free | 60 ml | £28.25
Solution for infusion | Sandimmun (Novartis Pharmaceuticals UK Ltd) | Ciclosporin 50 mg per 1 ml | Sandimmun 250mg/5ml concentrate for solution for infusion ampoules | 10 ampoule | £11.05
Sandimmun 50mg/1ml concentrate for solution for infusion ampoules | 10 ampoule | £23.23

Sirolimus

**INDICATIONS AND DOSE**

**Prophylaxis of organ rejection in kidney allograft recipients**

- **BY MOUTH**
  - Adult: Initially 6 mg for 1 dose, to be given after surgery once wound has healed, then 2 mg once daily; to be given in combination with ciclosporin and corticosteroid for 2–3 months (sirolimus doses should be given 4 hours after ciclosporin), ciclosporin should then be withdrawn over 4–8 weeks (if not possible, sirolimus should be discontinued and an alternate immunosuppressive regimen used), dose to be adjusted according to whole blood-sirolimus trough concentration

**DOSE EQUIVALENCE AND CONVERSION**

- The 500 microgram tablet is not bioequivalent to the 1 mg and 2 mg tablets. Multiples of 500 microgram tablets should not be used as a substitute for other tablet strengths.

**CAUTIONS**

- Hyperlipidaemia - increased susceptibility to infection (especially urinary-tract infection) - increased susceptibility to lymphoma and other malignancies, particularly of the skin (limit exposure to UV light)

**INTERACTIONS** → Appendix 1 (sirolimus).

**SIDE-EFFECTS**


**Uncommon** Nephrotic syndrome - pancreatitis - pancytopenia - pericardial effusion - pulmonary embolism - pulmonary haemorrhage

- Rare Alveolar proteinosis - anaphylactic reactions - angioedema - exfoliative dermatitis - hepatic necrosis - hypersensitivity reactions - hypersensitivity vasculitis - interstitial lung disease - lymphoedema

**Frequency not known** Focal segmental glomerulosclerosis - reversible impairment of male fertility

**CONCEPTION AND CONTRACEPTION** Effective contraception must be used during treatment and for 12 weeks after stopping.

**PREGNANCY** Avoid unless essential—toxicity in animal studies.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** In severe impairment decrease dose by 50% and monitor whole blood-sirolimus trough concentration every 5–7 days until 3 consecutive measurements have shown stable blood-sirolimus concentration. Clearance reduced in mild to moderate impairment. Monitor whole blood-sirolimus level closely and consult local treatment protocol in hepatic impairment.

**MONITORING REQUIREMENTS**

- Monitor whole blood-sirolimus trough concentration (Afro-Caribbean patients may require higher doses).
- Manufacturer advises pre-dose ('trough') whole blood-sirolimus concentration (using chromatographic assay) when used with ciclosporin should be 4–12 micrograms/litre (local treatment protocols may differ); after withdrawal of ciclosporin pre-dose whole blood-sirolimus concentration should be 12–20 micrograms/litre (local treatment protocols may differ).
- Close monitoring of whole blood-sirolimus concentration required if concomitant treatment with potent inducers or inhibitors of metabolism and after discontinuing them, or if ciclosporin dose reduced significantly or stopped.
- When changing between oral solution and tablets, measurement of whole blood ’trough’ sirolimus concentration after 1–2 weeks is recommended.
- Therapeutic drug monitoring assays Sirolimus whole-blood concentration is measured using either high performance liquid chromatography (HPLC) or immunoassay. Switching between different immunoassays or between an immunoassay and HPLC can lead to clinically significant differences in results and therefore incorrect dose adjustments. Adjustment to the target therapeutic dose range should be made with knowledge of the assay used and corresponding reference range.
- Monitor kidney function when given with ciclosporin; monitor lipids; monitor urine proteins.

**DIRECTIONS FOR ADMINISTRATION** Food may affect absorption (take at the same time with respect to food). Sirolimus oral solution should be mixed with at least 60 mL water or orange juice in a glass or plastic container immediately before taking; refill container with at least
120 mL of water or orange juice and drink immediately (to ensure total dose). Do not mix with any other liquids.

**PATIENT AND CARER ADVICE** Patient or carers should be given advice on how to administer sirolimus. Patients should be advised to avoid excessive exposure to UV light.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Rapamune (Pfizer Ltd)**
  - Sirolimus 1 mg Rapamune 1mg tablets | 30 tablet [PO] £86.49 DT price = £86.49
  - Sirolimus 500 microgram Rapamune 0.5mg tablets | 30 tablet [PO] £69.00 DT price = £69.00
  - Sirolimus 2 mg Rapamune 2mg tablets | 30 tablet [PO] £172.98 DT price = £172.98

**Oral solution**
EXCIPIENTS: May contain Ethanol
- Sirolimus 1 mg per 1 ml Rapamune 1mg/ml oral solution sugar-free
  - 60 ml [PO] £162.41

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**Tacrolimus**

**INDICATIONS AND DOSE**

**ADOPORT®**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- **BY MOUTH**
  - Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- **BY MOUTH**
  - Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy
- **BY MOUTH**
  - Adult: Seek specialist advice

**ENVARSUS® MODIFIED-RELEASE TABLETS**

Prophylaxis of graft rejection following liver transplantation, starting within 24 hours of transplantation
- **BY MOUTH**
  - Adult: Initially 110–130 micrograms/kg once daily, to be taken in the morning

Prophylaxis of graft rejection following renal transplantation, starting within 24 hours of transplantation
- **BY MOUTH**
  - Adult: Initially 170 micrograms/kg once daily, to be taken in the morning

Rejection therapy
- **BY MOUTH**
  - Adult: Seek specialist advice

**MODIGRAF®**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- **BY MOUTH**
  - Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- **BY MOUTH**
  - Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

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Immune system disorders and transplantation

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Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Rejection therapy
- Adult: Seek specialist advice

**PROGRAF® CAPSULES**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation when oral route not appropriate**
- Adult: Initially 10–50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

**Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation when oral route not appropriate**
- Adult: Initially 50–100 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

**Allograft rejection resistant to conventional immunosuppressive therapy**
- Adult: Seek specialist advice (consult local protocol)

**TACNI®**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy
- Adult: Seek specialist advice

**VIVADEX®**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy
- Adult: Seek specialist advice

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: ORAL TACROLIMUS PRODUCTS: PRESCRIBE AND DISPENSE BY BRAND NAME ONLY, TO MINIMISE THE RISK OF INADVERTENT SWITCHING BETWEEN PRODUCTS, WHICH HAS BEEN ASSOCIATED WITH REPORTS OF TOXICITY AND GRAFT REJECTION (JUNE 2012)**

Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection.
rejection. To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only.

- **Adoport®, Prograf®, Capexion®, Tacn®, and Vivadex®** are immediate-release capsules that are taken twice daily, once in the morning and once in the evening;
- **Modigraf® granules** are used to prepare an immediate-release oral suspension which is taken twice daily, once in the morning and once in the evening;
- **Advagraf®** is a prolonged-release capsule that is taken once daily in the morning.

Switcthing between tacrolimus brands requires careful supervision and therapeutic monitoring by an appropriate specialist. Important: **Envarsus®** is not interchangeable with other oral tacrolimus containing products; the MHRA has advised (June 2012) that oral tacrolimus products should be prescribed and dispensed by brand only.

- **CAUTIONS** Increased risk of infections - lymphoproliferative disorders - malignancies - neurotoxicity - QT-interval prolongation - UV light (avoid excessive exposure to sunlight and sunlamps)
- **INTERACTIONS** → Appendix 1 (tacrolimus).

Contra-indication—avoid concurrent administration with ciclosporin (care if patient has previously received ciclosporin).

- **SIDE-EFFECTS**


  - **Rare** Blindness - dehydration - hirsutism - pericardial effusion - posterior reversible encephalopathy syndrome - respiratory distress syndrome - thrombotic thrombocytopenic purpura - toxic epidermal necrolysis

  - **Very rare** Haemorrhagic cystitis - myasthenia - Stevens-Johnson syndrome

  - **Frequency not known** Agranulocytosis - haemolytic anaemia - pure red cell aplasia

**SIDE-EFFECTS, FURTHER INFORMATION**

Cardiomyopathy Cardiomyopathy has been reported in children. Patients should be monitored by echocardiography for hypertrophic changes—consider dose reduction or discontinuation if these occur.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of hypersensitivity to macrolides.

**CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment.

**PREGNANCY** Avoid unless potential benefit outweighs risk—crosses the placenta and risk of premature delivery, intra-uterine growth restriction, and hyperkalaemia.

**BREAST FEEDING** Avoid—present in breast milk (following systemic administration).

**HEPATIC IMPAIRMENT** Dose reduction may be necessary in severe impairment.

**MONITORING REQUIREMENTS**

- After initial dosing, and for maintenance treatment, tacrolimus doses should be adjusted according to whole-blood concentration. Monitor whole blood-tacrolimus trough concentration (especially during episodes of diarrhoea)—consult local treatment protocol for details.

- Monitor blood pressure, ECG (for hypertrophic changes—risk of cardiomyopathy), fasting blood-glucose concentration, haematological and neurological (including visual) and coagulation parameters, electrolytes, hepatic and renal function.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Prograf®), give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute concentrate in infusion fluid to a final concentration of 4–100 micrograms/mL; give over 24 hours. Tacrolimus is incompatible with PVC.

**PATIENT AND CARER ADVICE** Avoid excessive exposure to UV light including sunlight.

Driving and skilled tasks May affect performance of skilled tasks (e.g. driving).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2010) that tacrolimus granules for oral suspension (Modigraf®) are accepted for restricted use within NHS Scotland in patients for whom tacrolimus is an appropriate choice of immunosuppressive therapy and where small changes (less than 500 micrograms) in dosing increments are required (such as, in paediatric patients) or in seriously ill patients who are unable to swallow tacrolimus capsules.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

- **Envarsus® (Chiesi Ltd)**
  - Tacrolimus (as Tacrolimus monohydrate) 1 mg Envarsus 1mg modified-release tablets | 30 tablet DT price = £59.10
  - Tacrolimus (as Tacrolimus monohydrate) 4 mg Envarsus 4mg modified-release tablets | 30 tablet DT price = £236.40

- **Tacrolimus (as Tacrolimus monohydrate)**
  - 750 microgram Envarsus 750microgram modified-release tablets | 30 tablet DT price = £44.33

**Capsule**

**CAUTIONARY AND ADVISORY LABELS** 23

- **Adoport® (Sandoz Ltd)**
  - Tacrolimus 500 microgram Adoport 0.5mg capsules | 50 capsule DT price = £61.88
  - Tacrolimus 750 microgram Adoport 0.75mg capsules | 50 capsule DT price = £51.75

- **Tacrolimus 1 mg** Adoport 1mg capsules | 50 capsule DT price = £55.69 | 100 capsule DT price = £111.36

- **Tacrolimus 2 mg** Adoport 2mg capsules | 50 capsule DT price = £111.00 | 100 capsule DT price = £205.74

- **Tacrolimus 5 mg** Adoport 5mg capsules | 50 capsule DT price = £296.55

- **Capexion® (Mylan Ltd)**
  - Tacrolimus 500 microgram Capexion 0.5mg capsules | 50 capsule DT price = £52.50 | 100 capsule DT price = £105.00

- **Prograf® (Astellas Pharma Ltd)**
  - Tacrolimus 500 microgram Prograf 0.5mg capsules | 50 capsule DT price = £61.88
  - Tacrolimus 1 mg Prograf 1mg capsules | 50 capsule DT price = £80.28 | 100 capsule DT price = £160.54

- **Tacrolimus 5 mg** Prograf 5mg capsules | 50 capsule DT price = £296.58
Modified-release capsule

**CAUTIONARY AND ADVISORY LABELS 23, 25**

- Advagraf (Astellas Pharma Ltd)
  - Tacrolimus (as Tacrolimus monohydrate) 500 microgram/5 ml modified-release capsules 50 capsule (£52.15)
  - Tacrolimus (as Tacrolimus monohydrate) 1 mg/1 ml modified-release capsules 50 capsule (£61.59)
  - Tacrolimus (as Tacrolimus monohydrate) 3 mg/3 ml modified-release capsules 50 capsule (£134.76)
  - Tacrolimus (as Tacrolimus monohydrate) 5 mg/5 ml modified-release capsules 50 capsule (£266.92)

**Granules**

**CAUTIONARY AND ADVISORY LABELS 13, 23**

- Modigraft (Astellas Pharma Ltd)
  - Tacrolimus (as Tacrolimus monohydrate) 200 microgram/2 ml granules sachets sugar-free 50 sachet (£131.30)
  - Tacrolimus (as Tacrolimus monohydrate) 1 mg/1 ml granules sachets sugar-free 50 sachet (£356.65)

**Solution for infusion**

**EXCIPIENTS** May contain Polyoxyly castor oils

- Prograf (Astellas Pharma Ltd)
  - Tacrolimus 5 mg per 1 ml Prograf 5mg/1ml solution for infusion ampoules 10 ampoule (£84.51)

**IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES**

### Canakinumab

**DRUG ACTION** Canakinumab is a recombinant human monoclonal antibody that selectively inhibits interleukin-1 beta receptor binding.

**INDICATIONS AND DOSE**

Acute gout in patients whose condition has not responded adequately to treatment with NSAIDs or colchicine, or who are intolerant of them

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 150 mg for 1 dose, dose may be repeated at least 12 weeks after initial response if symptoms recur, patients who do not respond to initial dose should not be retreated.

Treatment of cryopyrin-associated periodic syndromes, including severe forms of familial cold auto-inflammatory syndrome (or familial cold urticaria), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurological cutaneous and articular syndrome)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS** Active infection • leucopenia • neutropenia

**CAUTIONS** History of recurrent infection • latent and active tuberculosis • predisposition to infection

**CAUTIONS, FURTHER INFORMATION**

- Vaccinations: Patients should receive all recommended vaccinations (including pneumococcal and inactivated influenza vaccine) before starting treatment; avoid live vaccines unless potential benefit outweighs risk—consult product literature for further information.

**INTERACTIONS** → Appendix 1 (canakinumab).

- Contra-indicated with concomitant use with tumour necrosis factor inhibitors (possible increased risk of infections).

**SIDE-EFFECTS**

- Back pain • increased susceptibility to infection (including serious infection) • injection-site reactions • malaise • neutropenia • vertigo

- Common Gastro-oesophageal reflux

- Frequency not known Malignancy • vomiting

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment and for up to 3 months after last dose.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Consider if benefit outweighs risk—not known if present in human milk.

**HEPATIC IMPAIRMENT** No information available.

**RENAL IMPAIRMENT** Limited information available but manufacturer advises no dose adjustment required.

**PRE-TREATMENT SCREENING** Patients should be evaluated for latent and active tuberculosis before starting treatment.

**MONITORING REQUIREMENTS**

- Monitor full blood count including neutrophil count before starting treatment, 1–2 months after starting treatment, and periodically thereafter.

- Monitor for signs and symptoms of tuberculosis during and after treatment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- Ilaris (Novartis Pharmaceuticals UK Ltd) Canakinumab 150 mg Ilaris 150mg powder for solution for injection vials 1 vial (£50.00)

- Canakinumab 150 mg Ilaris 150mg powder for solution for injection vials 1 vial (£927.80)

**IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES > ANTI-LYMPHOCYTE**

### Basiliximab

**DRUG ACTION** Basiliximab is a monoclonal antibody that acts as an interleukin-2 receptor antagonist and prevents T-lymphocyte proliferation.

**INDICATIONS AND DOSE**

Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimens (specialist use only)

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 20 mg, administered within 2 hours before transplant surgery, followed by 20 mg after 4 days, dose to be administered after surgery, withhold second dose if severe hypersensitivity or graft loss occurs

**CAUTIONS** Off-label use in cardiac transplantation—increased risk of serious cardiac side-effects

**INTERACTIONS** → Appendix 1 (basiliximab).

**SIDE-EFFECTS** Atrial flutter • cardiac arrest • cytokine release syndrome • palpitations • severe hypersensitivity reactions

**CONCEPTION AND CONTRACEPTION** Adequate contraception must be used during treatment and for 16 weeks after last dose.

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Simulect®) give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute 10 mg with 2.5 mL water for injections then dilute to at least 25 mL with infusion fluid; reconstitute 20 mg with 5 mL water for injections then dilute to at least 50 mL with infusion fluid; give over 20–30 minutes.
BREAST FEEDING
Frequency not known

SIDE-EFFECTS

CAUTIONS
Do not initiate until active infections controlled; history or development of malignancy; predisposition to infection

INTERACTIONS ▶ Appendix 1 (belimumab).

SIDE-EFFECTS ▶ Common or very common Infusion-related reactions ▶ Frequency not known Depression; diarrhoea; hypersensitivity reactions; infections; insomnia; leucopenia; migraine; nausea; pain in extremities; pyrexia; vomiting
SIDE-EFFECTS, FURTHER INFORMATION Infusion-related side-effects are reported commonly, including severe or life-threatening hypersensitivity and infusion reactions. Premedication with an antihistamine, with or without an anti-pyretic may be considered.

CONCESSION AND CONTRACEPTION
Manufacturer advises adequate contraception during treatment and for at least 4 months after last dose.

PREGNANCY Avoid unless essential.

BREAST FEEDING Avoid—present in milk in animal studies.

RENAL IMPAIRMENT Caution in severe impairment—no information available.

MONITORING REQUIREMENTS Delay in the onset of acute hypersensitivity reactions has been observed; patients should remain under clinical supervision for several hours following at least the first 2 infusions.

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Benlysta®), give intermittently in Sodium chloride 0.9%; reconstitute with water for injections (120 mg in 1.5 mL, 400 mg in 4.8 mL) to produce a solution containing 80 mg/mL; gently swirl vial for 60 seconds, then allow to stand; swirl vial (without shaking) for 60 seconds every 5 minutes until dissolved; dilute requisite dose with infusion fluid to a final volume of 250 mL and give over 1 hour.

NATIONAL FUNDING/ACCESS DECISIONS NICE technology appraisals (TAs) ▶ Belimumab for treating active autoantibody-positive systemic lupus erythematosus (June 2016) NICE TA397 Belimumab is recommended as an add-on treatment option in adults with active autoantibody-positive systemic lupus erythematosus, only if all of the following criteria apply:
- there is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 despite standard therapy; treatment with belimumab is continued after 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more;
- the manufacturer provides belimumab with the discount agreed in the patient access scheme; and
- under the conditions specified in the NICE managed access agreement documentation. Patients whose treatment was started before this guidance was published should continue treatment until they and their clinician consider it appropriate to stop.

IMMUNOSUPPRESSANTS ▶ PURINE SYNTHESIS INHIBITORS

Mycophenolate mofetil

INDICATIONS AND DOSE Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and ciclosporin) (under expert supervision) ▶ BY MOUTH ▶ Adult: 1 g twice daily, to be started within 72 hours of transplantation ▶ BY INTRAVENOUS INFUSION ▶ Adult: 1 g twice daily for maximum 14 days, then transfer to oral therapy, to be started within 24 hours of transplantation Prophylaxis of acute rejection in cardiac transplantation (in combination with ciclosporin and corticosteroids) (under expert supervision) ▶ BY MOUTH ▶ Adult: 1.5 g twice daily, to be started within 5 days of transplantation Prophylaxis of acute rejection in hepatic transplantation (in combination with ciclosporin and corticosteroids) (under expert supervision) ▶ INITIALLY BY INTRAVENOUS INFUSION ▶ Adult: 1 g twice daily for 4 days, up to a maximum of 14 days, to be started within 24 hours of transplantation, then (by mouth) 1.5 g twice daily, the dose route should be changed as soon as is tolerated

MYFORTIC® Renal transplantation ▶ BY MOUTH ▶ Adult: 720 mg twice daily, to be started within 72 hours of transplantation

DOSE EQUIVALENCE AND CONVERSION ▶ For Myfortic®, Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences.

CAUTIONS Active serious gastro-intestinal disease (risk of haemorrhage, ulceration and perforation) · delayed graft function · elderly (increased risk of infection, gastrointestinal haemorrhage and pulmonary oedema) · increased susceptibility to skin cancer (avoid exposure to strong sunlight) · risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants
Immune system disorders and transplantation

CAUTIONS, FURTHER INFORMATION
- Hypogammaglobulinaemia or bronchiectasis: Measure serum immunoglobulin levels if recurrent infections develop, and consider bronchiectasis or pulmonary fibrosis if persistent respiratory symptoms such as cough and dyspnoea develop.
- INTERACTIONS: Appendix 1 (mycophenolate).
- Live vaccines: Specialist advice should be sought for those being treated with immunosuppressive drugs.

SIDE-EFFECTS
- Common or very common: Abdominal pain, acne, agitation, alopecia, anaemia, anorexia, anxiety, arthralgia, blood disorders, confusion, constipation, convulsions, cough, depression, disturbances of blood lipids, disturbances of electrolytes and blood lipids, dizziness, dysphonia, flatulence, gastro-intestinal bleeding, gastro-intestinal inflammation, gastro-intestinal ulceration, gingival hyperplasia, headache, hepatitis, hyperglycaemia, hypertension, hypotension, infections, influenza-like syndrome, insomnia, jaundice, leucopenia, malignancy (particularly of the skin), myasthenic syndrome, nausea, oedema, pancreatitis, pancytopenia, paraesthesia, rash, red cell aplasia, renal impairment, skin hypertrophy, stomatitis, tachycardia, taste disturbance, thrombocytopenia, tremor, vasodilatation, vomiting, weight loss.
- Frequency not known: Interstitial lung disease, intestinal villous atrophy, progressive multifocal leucoencephalopathy, pulmonary fibrosis.

SIDE-EFFECTS, FURTHER INFORMATION
Cases of pure red cell aplasia have been reported with mycophenolate mofetil; dose reduction or discontinuation should be considered under specialist supervision.

CONCEPTION AND CONTRACEPTION: In females of child-bearing potential, exclude pregnancy immediately before and during treatment.

Women should use 2 methods of effective contraception during treatment, and for 6 weeks after discontinuation. Men should use condoms during treatment and for at least 90 days after discontinuation of treatment; female partners of male patients should also use effective contraception during treatment and for 90 days after discontinuation.

MYFORTIC®: Manufacturer advises that men should use condoms during treatment and for 13 weeks after last dose.

PREGNANCY: Avoid unless no suitable alternative—congenital malformations and spontaneous abortions reported.

BREAST FEEDING: Manufacturer advises avoid—present in milk in animal studies.

RENAL IMPAIRMENT: No data available in cardiac or hepatic transplant patients with renal impairment.

MONITORING REQUIREMENTS: Monitor full blood count every week for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops).

DIRECTIONS FOR ADMINISTRATION: For intravenous infusion (CellCept®), give intermittently in Glucose 5%; reconstitute each 500–mg vial with 14 mL glucose 5% and dilute the contents of 2 vials in 140 mL infusion fluid; give over 2 hours.

PATIENT AND CARER ADVICE
Bone marrow suppression: Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.

MEDITICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension.

Tablet
- Mycophenolate mofetil (Non-proprietary): Mycophenolate mofetil 500 mg tablets 50 tablet (Roche Products Ltd) £42.50 DT price = £6.64
- CellCept (Roche Products Ltd): Mycophenolate mofetil 500 mg tablets 50 tablet (Roche Products Ltd) £82.26 DT price = £6.64
- Myfenax (Teva UK Ltd): Mycophenolate mofetil 500 mg tablets 50 tablet (Teva) £78.15 DT price = £6.64

Gastro-resistant tablet
CAUTIONARY AND ADVISORY LABELS: 25
- Myfortic (Novartis Pharmaceuticals UK Ltd): Mycophenolic acid (as Mycophenolate sodium) 180 mg Myfortic 180 mg gastro-resistant tablets 120 tablet (Roche) £96.72
- Mycophenolic acid (as Mycophenolate sodium) 360 mg Myfortic 360 mg gastro-resistant tablets 120 tablet (Roche) £193.43

Capsule
- Mycophenolate mofetil (Non-proprietary): Mycophenolate mofetil 250 mg capsules 100 capsule (Myfortic) £82.26 DT price = £82.26

- CellCept (Roche Products Ltd): Mycophenolate mofetil 250 mg capsules 100 capsule (Roche) £82.26 DT price = £82.26

- Myfenax (Teva UK Ltd): Mycophenolate mofetil 250 mg capsules 100 capsule (Teva) £78.15 DT price = £82.26

Oral suspension
EXCipients: May contain Aspartame
- CellCept (Roche Products Ltd): Mycophenolate mofetil 200 mg per 1 ml CellCept 1g/5ml oral suspension sugar-free 175 ml (Roche) £115.16 DT price = £115.16

Powder for solution for infusion
- Mycophenolate mofetil (Non-proprietary): Mycophenolate mofetil (as Mycophenolate mofetil hydrochloride) 500 mg Mycophenolate mofetil 500 mg powder for concentrate for solution for infusion vials 4 vial (Roche) £26.64

IMMUNOSUPPRESSANTS: T-CELL ACTIVATION INHIBITORS

Belatacept

- INDICATIONS AND DOSE: Prophylaxis of graft rejection in adults undergoing renal transplantation who are seropositive for the Epstein-Barr virus
  - By intravenous infusion

- Adult: (consult product literature)

- CAUTIONS: Increased risk of acute graft rejection—with tapering of corticosteroid, particularly in patients with high immunologic risk—increased risk of infection—latent and active tuberculosis—risk factors for post-transplant lymphoproliferative disorder

- SIDE-EFFECTS
  - Common or very common: Anaemia, constipation, cough, dehydration, diarrhoea, headache, hypotension, hypophosphataemia, infection, leucopenia, malignancy, nausea, peripheral oedema, pyrexia, vomiting
  - Uncommon: Infusion related reactions, progressive multifocal leucoencephalopathy

SIDE-EFFECTS, FURTHER INFORMATION
Side effects are reported when used in combination with basiliximab, mycophenolate mofetil and corticosteroids.
1.1 Multiple sclerosis

CHOLINERGIC RECEPTOR STIMULATING DRUGS

Fampridine

- **INDICATIONS AND DOSE**
  - Improvement of walking disability in multiple sclerosis (specialist use only)
    - **BY MOUTH**
    - Adult: 10 mg every 12 hours, discontinue treatment if no improvement within 2 weeks

- **CONTRA-INDICATIONS**
  - History of seizures (discontinue treatment if seizures occur)

- **CAUTIONS**
  - Atrophic cerebral conduction disorders - predisposition to seizures - sinoartrial conduction disorders - symptomatic cardiac rhythm disorders

- **INTERACTIONS**
  - Appendix 1 (fampridine).
  - Caution in concomitant use of drugs that lower seizure threshold.

- **SIDE-EFFECTS**
  - **Common or very common**
    - Anxiety
    - Back pain
    - Constipation
    - Dizziness
    - Dyspepsia
    - Dysphagia
    - Headache
    - Insomnia
    - Malaise
    - Nausea
    - Paraesthesia
    - Pharyngolaryngeal pain
    - Tremor
    - Urinary tract infection
    - Vomiting
  - **Uncommon**
    - Seizures

- **PREGNANCY**
  - Avoid - toxicity in animal studies.

- **BREAST FEEDING**
  - Avoid - no information available.

- **RENAI IMPAIRMENT**
  - Avoid if eGFR less than 80 ml/minute/1.73 m².

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Dispense in original container (pack contains a desiccant) and discard any tablets remaining 7 days after opening.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Modified-release tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 23, 25
    - **Fampyra** (Biogen Idec Ltd)
      - Fampyra 10 mg modified-release tablets | £181.00
      - 28 tablet pack
    - **Nulojix** (Bristol-Myers Squibb Pharmaceuticals Ltd)
      - Nulojix powder for solution for infusion vials | £709.04

- **INTERACTIONS**
  - Avoid excessive exposure to UV light including sunlight.
  - Avoid in concomitant use of drugs that lower seizure threshold.

- **CONCEPTION AND CONTRACEPTION**
  - Adequate contraception must be used during treatment and for up to 8 weeks after last dose.

- **PREGNANCY**
  - Use only if essential.

- **BREAST FEEDING**
  - Avoid - no information available.

- **PRE-TREATMENT SCREENING**
  - Patients should be evaluated for latent and active tuberculosis before starting treatment.

- **MONITORING REQUIREMENTS**
  - Patients should be monitored for signs and symptoms of tuberculosis during and after treatment.

- **PATIENT AND CARER ADVICE**
  - Patients should be advised to avoid excessive exposure to UV light including sunlight.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**
    - **Nulojix** (Bristol-Myers Squibb Pharmaceuticals Ltd)
      - Belatacept 250 mg Nulojix 250 mg powder for concentrate for solution for infusion vials | £354.52
      - 2 vial pack | £709.04

- **IMMUNOSTIMULANTS**
  - **INTERFERONS**
    - **Fampyra**
      - For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided
      - For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)
      - **BY INTRAVENOUS INJECTION**
      - Adult: (consult product literature)

    - **AVONEX® VIAL**
      - For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided
      - For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)
      - **BY INTRAMUSCULAR INJECTION**
      - Adult: (consult product literature)

    - **BETAFERON® INJECTION**
      - For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided
      - For secondary progressive multiple sclerosis with active disease
      - For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)
      - **BY SUBCUTANEOUS INJECTION**
      - Adult: (consult product literature)

    - **EXTAVIA®**
      - For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided
      - For secondary progressive multiple sclerosis with active disease
      - For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)
      - **BY INTRAMUSCULAR INJECTION**
      - Adult: (consult product literature)

    - **REBIF® CARTRIDGE**
      - For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided
      - For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)
      - **BY SUBCUTANEOUS INJECTION**
      - Adult: (consult product literature)
PRESCRIBING AND DISPENSING INFORMATION

Monitor for signs of hepatic injury

HEPATIC IMPAIRMENT

PREGNANCY

CONCEPTION AND CONTRACEPTION

SIDE-EFFECTS

CAUTIONS

CONTRA-INDICATIONS

CONTRA-INDICATIONS, FURTHER INFORMATION

Consult product literature for further information on contra-indications.

CAUTIONS

History of cardiac disorders · history of depressive disorders (avoid in severe depression or in those with suicidal ideation) · history of seizures · history of severe myelosuppression

CAUTIONS, FURTHER INFORMATION

Consult product literature for further information on cautions.

SIDE-EFFECTS

Alopecia · anaphylaxis · blood disorders · chills · confusion · convulsions · fever · hepatitis · hypersensitivity reactions · influenza-like symptoms (decreasing over time) · irritation at injection site (including inflammation, hypersensitivity, necrosis) · malaise · menstrual disorders · mood and personality changes · myalgia · nausea · nephrotic syndrome · suicide attempts · thrombotic microangiopathy · thyroid dysfunction · urticaria · vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Also consult product literature for all side effects.

CONCEPTION AND CONTRACEPTION

Effective contraception required during treatment—consult product literature.

PREGNANCY

Avoid unless potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING

Avoid—no information available.

HEPATIC IMPAIRMENT

Caution in severe hepatic impairment.

RENAL IMPAIRMENT

Caution in severe renal impairment.

MONITORING REQUIREMENTS

Monitor for signs of hepatic injury—hepatic failure has been reported rarely.

Patients should be monitored for clinical features of thrombotic microangiopathy (TMA), including thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion and paresis), and impaired renal function. Any signs of TMA should be investigated fully and, if diagnosed, interferon beta should be stopped immediately and treatment for TMA promptly initiated (consult product literature for details).

Patients should also be monitored for signs and symptoms of nephrotic syndrome, including oedema, proteinuria, and impaired renal function—monitor renal function periodically. If nephrotic syndrome develops, treat promptly and consider stopping interferon beta treatment.

PRESCRIBING AND DISPENSING INFORMATION

REBIF® PRE-FILLED PEN AND SYRINGE

For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided | For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

BY SUBCUTANEOUS INJECTION

Adult: (consult product literature)

CONTRA-INDICATIONS

Decompensated liver disease · severe depressive illness

REBIF® CARTRIDGE

Cartridges for use with RebiSmart® auto-injector device.

BETAFERON® INJECTION

An auto-injector device (Betaject® Light) is available from Bayer Schering.

EXTAVIA®

An auto-injector device (ExtaviPro® 30G) is supplied as part of the ExtaviPro® 30G kit.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Interferon beta and glatiramer for multiple sclerosis (January 2002) NICE TA32

Interferon beta and glatiramer acetate are not recommended for the treatment of multiple sclerosis in the NHS in England and Wales.

Patients who are currently receiving interferon beta or glatiramer acetate for multiple sclerosis, whether as routine therapy or as part of a clinical trial, should have the option to continue treatment until they and their consultant consider it appropriate to stop, having regard to the established criteria for withdrawal from treatment.

www.nice.org.uk/TA32

NHS restrictions

 Provision of disease-modifying therapies for multiple sclerosis

The Department of Health, the National Assembly for Wales, the Scottish Executive, the Northern Ireland Department of Health, Social Services & Public Safety, and the manufacturers have reached agreement on a risk-sharing scheme for the NHS supply of interferon beta and glatiramer acetate for multiple sclerosis. Health Service Circular (HSC 2002/004) explains how patients can participate in the scheme. It is available on the Department of Health website (www.dh.gov.uk).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol

Avonex (Biogen Idec Ltd)

Interferon beta-1a 12 mega u per 1 ml Avonex 30micrograms/0.5ml (6m units) solution for injection pre-filled syringes | 4 pre-filled disposable injection | £654.00 | 12 pre-filled disposable injection | £1,962.00

Aronex 30micrograms/0.5ml (6m units) solution for injection pre-filled pen | 4 pre-filled disposable injection | £654.00 | 12 pre-filled disposable injection | £1,962.00

Rebif (Merck Serono Ltd)

Interferon beta-1a 12 mega u per 1 ml Rebif 2micrograms/0.5ml (6m units) solution for injection 1.5ml cartridges | 4 cartridge | £613.52

Rebif 8.8micrograms/0.2ml (2.4ml units) solution for injection pre-filled syringes | 6 pre-filled disposable injection | no price available

Rebif 8.8micrograms/0.2ml (2.4ml units) solution for injection pre-filled pen | 6 pre-filled disposable injection | no price available

Rebif 2micrograms/0.5ml (6m units) solution for injection pre-filled pen | 6 pre-filled disposable injection | £613.52

Rebif 2micrograms/0.5ml (6m units) solution for injection pre-filled syringes | 6 pre-filled disposable injection | no price available

Rebif 2micrograms/0.5ml (6m units) solution for injection pre-filled syringes | 12 pre-filled disposable injection | £613.52

Rebif 4micrograms/0.5ml (12ml units) solution for injection pre-filled pen | 12 pre-filled disposable injection | £813.21

Rebif 4micrograms/0.5ml (12ml units) solution for injection pre-filled syringes | 12 pre-filled disposable injection | £813.21

Powder and solvent for solution for injection

Beterafor (Bayer Plc)

Interferon beta-1b 300 microgram Beterafor 300microgram powder and solvent for solution for injection vials | 15 vial | £596.63 (Hospital only)

Extavia (Novartis Pharmaceuticals UK Ltd)

Interferon beta-1b 300 microgram Extavia 300microgram powder and solvent for solution for injection vials | 15 vial | £596.63
Peginterferon beta-1a

- **DRUG ACTION** Peginterferon beta-1a is a polyethylene glycol-conjugated (‘pegylated’) derivative of interferon beta; pegylation increases the persistence of interferon in the blood.

- **INDICATIONS AND DOSE**
  - Treatment of relapsing, remitting multiple sclerosis
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: (consult product literature)

- **CONTRA-INDICATIONS** Severe depression - suicidal ideation

- **CAUTIONS** History of cardiac disorders - history of depressive disorders (avoid in severe depression or in those with suicidal ideation), history of seizures - history of severe myelosupression

- **MONITORING REQUIREMENTS**
  - Patients should also be monitored for:
    - Thrombotic microangiopathy: Patients should be monitored for signs of hepatic injury
    - Renal impairment: Caution in severe renal impairment.
  - **RENAL IMPAIRMENT**
    - Caution in severe renal impairment.
  - **SIDE-EFFECTS**
    - Consult product literature for information about side effects.

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment — consult product literature.

- **PREGNANCY**
  - Do not initiate during pregnancy. Avoid unless potential benefit outweighs risk.

- **BREAST FEEDING**
  - Avoid — no information available.

- **HEPATIC IMPAIRMENT**
  - Caution in severe hepatic impairment.

- **RENAI IMPAIRMENT**
  - Caution in severe renal impairment.

- **INDICATIONS AND DOSE**
  - Treatment of relapsing, remitting multiple sclerosis
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: 20 mg daily

**Glatiramer acetate**

- **DRUG ACTION** Glatiramer is an immunomodulating drug comprising synthetic polypeptides.

- **INDICATIONS AND DOSE**
  - Treatment of initial symptoms in patients at high risk of developing multiple sclerosis (initiated under specialist supervision)
  - Reducing frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis who have had at least 2 clinical relapses in the past 2 years (initiated under specialist supervision)
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: 20 mg daily

- **CONTRA-INDICATIONS** Severe depression

- **CAUTIONS**
  - Cardiac disorders
  - **SIDE-EFFECTS**
    - Common or very common: Anxiety - arthralgia - asthenia - back pain - chest pain - constipation - depression - dyspepsia - dyspnoea (may occur within minutes of injection) - flushing - headache - hypersensitivity reactions - hypertonia - influenza-like symptoms - injection-site reactions - lymphadenopathy - nausea - oedema - palpitation - rash - sweating - syncope - tachycardia - tremor
    - Rare: Seizures

- **PREGNANCY**
  - Manufacturer advises avoid — no information available.

- **BREAST FEEDING**
  - Manufacturer advises caution — no information available.

- **RENAL IMPAIRMENT**
  - No information available — manufacturer advises caution.

- **NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Interferon beta and glatiramer for multiple sclerosis (January 2002) NICE TA32**
  - Interferon beta and glatiramer acetate are not recommended for the treatment of multiple sclerosis in the NHS in England and Wales.
  - Patients who are currently receiving interferon beta or glatiramer acetate for multiple sclerosis, whether as routine therapy or as part of a clinical trial, should have the option to continue treatment until they and their consultant consider it appropriate to stop, having regard to the established criteria for withdrawal from treatment.
  - [www.nice.org.uk/TA32](http://www.nice.org.uk/TA32)

**NHS restrictions**

- **Provision of disease-modifying therapies for multiple sclerosis**
  - The Department of Health, the National Assembly for Wales, the Scottish Executive, the Northern Ireland Department of Health, Social Services & Public Safety, and the manufacturers have reached agreement on a risk-sharing scheme for the NHS supply of interferon beta and glatiramer acetate for multiple sclerosis. Health Service Circular (HSC 2002/004) explains how patients can participate in the scheme. It is available on the Department of Health website ([www.dh.gov.uk](http://www.dh.gov.uk)).

**MEDICINAL FORMS**

**Solution for injection**

- **Peginterferon beta-1a 126 microgram per 1 ml** Plegridy
  - 63 micrograms/0.5 ml solution for injection pre-filled pen £1,262.00
  - 94 micrograms/0.5 ml solution for injection pre-filled pen £1,262.00

- **Peginterferon beta-1a 188 microgram per 1 ml** Plegridy
  - 188 micrograms/0.5 ml solution for injection pre-filled pen £1,262.00

- **Peginterferon beta-1a 250 microgram per 1 ml** Plegridy
  - 250 micrograms/0.5 ml solution for injection pre-filled pen £1,262.00

**Glatiramer acetate**

- **Solution for injection**
  - **Copaxone** (Teva UK Ltd)
    - Glatiramer acetate 20 mg per 1 ml Copaxone 20 mg/1 ml solution for injection pre-filled syringes £513.95
    - Glatiramer acetate 40 mg per 1 ml Copaxone 40 mg/1 ml solution for injection pre-filled syringes £513.95
Dimethyl fumarate

**Indications and Dose**

Treatment of adults with relapsing-remitting multiple sclerosis (initiated by a specialist)

- **BY MOUTH**
  - Adult: 120 mg twice daily for 7 days, then increased to 240 mg twice daily, for dose adjustment due to side effects—consult product literature

- **Conception and Contraception**
  - Contraception required in women of child-bearing potential (consider non-hormonal methods).

- **Pregnancy**
  - Manufacturer advises avoid unless essential and potential benefit outweighs risk—toxicity in animal studies.

- **Breast Feeding**
  - Manufacturer advises avoid.

- **Renal Impairment**
  - Manufacturer advises caution in severe impairment.

- **Hepatic Impairment**
  - Manufacturer advises caution in severe impairment.

- **Drug Action**
  - Dimethyl fumarate has immunomodulatory and anti-inflammatory properties.

- **Monitoring Requirements**
  - Monitor full blood count (including lymphocytes) before treatment (within 6 months before initiation), then every 6 to 12 months thereafter, and as clinically indicated.
  - Monitor patient closely for features of progressive multifocal leukoencephalopathy (PML) (e.g. signs and symptoms of neurological dysfunction) and other opportunistic infections.
  - Monitor renal and hepatic function before treatment, after 3 and 6 months of treatment, then every 6 to 12 months thereafter, and as clinically indicated.

- **Patient and Carer Advice**
  - Patient information leaflet should be provided.
  - Counselling is advised on progressive multifocal leukoencephalopathy.

- **NICE Technology Appraisals (TAs)**
  - Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (August 2014) NICE TA320
  - Dimethyl fumarate is recommended for the treatment of active relapsing-remitting multiple sclerosis, only if:
    - the patient does not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and
    - the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme
  - Patients currently receiving dimethyl fumarate whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA320

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Gastro-resistant Capsule**
    - Tecfidera (Biogen Idec Ltd)
    - Dimethyl fumarate 120 mg Tecfidera 120mg gastro-resistant capsules | 14 capsule £343.00
    - Dimethyl fumarate 240 mg Tecfidera 240mg gastro-resistant capsules | 56 capsule £1,373.00

**Fingolimod**

**Indications and Dose**

Treatment of highly active relapsing-remitting multiple sclerosis in patients who have high disease activity despite treatment with at least one disease modifying therapy or in those with rapidly evolving severe relapsing-remitting multiple sclerosis (initiated under specialist supervision)

- **BY MOUTH**
  - Adult: 500 micrograms once daily

- **Monitoring Requirements**
  - Monitor heart rate and blood pressure measurement every hour

- **Drug Action**
  - Fingolimod is an immunomodulating drug.

**Important Safety Information**

- **MHRA/CHM Advice: Fingolimod—Not recommended for patients at known risk of cardiovascular events. Advice for extended monitoring for those with significant bradycardia or heart block after the first dose and following treatment interruption (January 2013)**
  - Fingolimod is known to cause transient bradycardias and heart block after the first dose. Fingolimod is not recommended in the following patient groups who are at high risk of cardiovascular events unless the anticipated benefits outweigh the potential risks, and advice from a cardiologist is sought before initiation:
    - Patients with the following medical conditions:
      - 2nd degree Mobitz Type II or higher degree atrioventricular block, sick sinus syndrome, or sino-atrial heart block
      - significant QT prolongation (QT-interval greater than 470 milliseconds in women, or greater than 450 milliseconds in men)
      - history of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.

  - Patients receiving the following antiarrhythmic or heart-rate lowering drugs:
    - class Ia or class III antiarrhythmics
    - beta blockers
    - heart rate-lowering calcium channel blockers
    - other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic drugs or pilocarpine).
  - All patients receiving fingolimod should be monitored at treatment initiation, (first dose monitoring), and after treatment interruption (see note below); monitoring should include:
    - Pre-treatment:
      - a 12-lead ECG and blood pressure measurement before starting
    - During the first 6 hours of treatment:
      - continuous ECG monitoring for 6 hours
      - blood pressure and heart rate measurement every hour
After 6 hours of treatment
- a further 12-lead ECG and blood pressure measurement
If heart rate at the end of the 6 hour period is at its lowest since fingolimod was first administered, monitoring should be extended by at least 2 hours and until heart rate increases.

Extended monitoring, (at least overnight), should be performed in patients with evidence of clinically important cardiac effects during first dose monitoring. Monitoring in patients requiring pharmacological intervention for bradycardia-related symptoms during first dose monitoring should be extended at least overnight, and first dose monitoring should be repeated after the second dose.

Note
First dose monitoring as above should be repeated in all patients whose treatment is interrupted for:
- 1 day or more during the first 2 weeks of treatment
- more than 7 days during weeks 3 and 4 of treatment
- more than 2 weeks after one month of treatment
If the treatment interruption is of shorter duration than the above, repeated monitoring is not required and treatment should be continued with the next dose as planned.

● CONTRA-INDICATIONS  Active malignancies · immunosuppression · severe active infection

● CAUTIONS  Check varicella zoster virus status—consult product literature for further information · chronic obstructive pulmonary disease · pulmonary fibrosis · risk of macular oedema · severe respiratory disease · susceptibility to QT-interval prolongation (including electrolyte disturbances)

CAUTIONS, FURTHER INFORMATION
- Washout period  A washout period is recommended when switching treatment from some disease modifying therapies—consult product literature for further information.

● INTERACTIONS  Appendix 1 (fingolimod).
Caution with concomitant use of drugs that prolong QT interval.

● SIDE-EFFECTS
- Common or very common  Alopecia · AV block · back pain · basal cell carcinoma · blurred vision · bradycardia · bronchitis · cough · depression · diarrhoea · dizziness · dyspnœa · eczema · gastroenteritis · headache · herpes · hypertension · influenza · leucopenia · lymphopenia · malaise · migraine · pruritus · sinusitis · tinea versicolor · tinea versicolor
- Uncommon  Macular oedema · neutropenia · pneumonia
- Rare  Lymphoma
- Frequency not known  Haemophagocytic syndrome · lymphoma · posterior reversible encephalopathy syndrome · progressive multifocal leukoencephalopathy

SIDE-EFFECTS, FURTHER INFORMATION
- Basal cell carcinoma  Patients should be advised to seek medical advice if they have any signs of basal cell carcinoma including skin nodules, patches or open sores that do not heal within weeks.
- Progressive multifocal leukoencephalopathy (PML) and other opportunistic infections  Patients should be advised to seek medical attention if they have any signs of PML or any other infections. Suspension of treatment should be considered if a patient develops a severe infection, taking into consideration the risk-benefit.

● CONCEPTION AND CONTRACEPTION  Exclude pregnancy before treatment. Ensure effective contraception during and for at least 2 months after treatment.

● PREGNANCY  Avoid (toxicity in animal studies).

● BREAST FEEDING  Avoid.

● HEPATIC IMPAIRMENT  Use with caution in mild to moderate impairment. Avoid in severe impairment.

● MONITORING REQUIREMENTS
- Manufacturer advises eye examination recommended 3–4 months after initiation of treatment (and before initiation of treatment in patients with diabetes or history of uveitis). Manufacturer also advises skin examination for signs of basal-cell carcinoma before starting treatment and then at least yearly thereafter.
- Monitor hepatic transaminases before treatment, then every 3 months for 1 year, then periodically thereafter.
- Monitor full blood count before treatment, at 3 months, then at least yearly thereafter and if signs of infection—interrupt treatment if lymphocyte count reduced—consult product literature.
- Monitor for signs and symptoms of haemophagocytic syndrome (including pyrexia, asthenia, hepatosplenomegaly and adenopathy)—may be associated with hepatic failure and respiratory distress; also progressive cytopenia, elevated serum-ferritin concentrations, hypertriglyceridaemia, hypofibrinogenaemia, coagulopathy, hepatic cytology, hyponatraemia)—initiate treatment immediately.
- Manufacturer advises to monitor routine MRI for lesions suggestive of progressive multifocal leukoencephalopathy (PML), particularly in patients considered at increased risk.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (April 2012) NICE TA254
Fingolimod is recommended as an option for the treatment of highly active relapsing-remitting multiple sclerosis in adults, only if:
- they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with interferon beta, and
- the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.
Patients currently receiving fingolimod whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.
www.nice.org.uk/TA254

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (August 2012) that fingolimod (Gilenya®) is accepted for restricted use within NHS Scotland as single disease modifying therapy in highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta, with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

MEdICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
- Gilenya (Novartis Pharmaceuticals UK Ltd) ▼
Fingolimod (as Fingolimod hydrochloride)
500 microgram  Gilenya 0.5mg capsules  7 capsule fas £367.50
| 28 capsule fas £1,470.00
Anti-lymphocyte monoclonal antibodies

- **DRUG ACTION** The anti-lymphocyte monoclonal antibodies cause lysis of B lymphocytes.

**IMPORTANT SAFETY INFORMATION**
All anti-lymphocyte monoclonal antibodies should be given under the supervision of an experienced specialist, in an environment where full resuscitation facilities are immediately available.

- **SIDE-EFFECTS**
  - **Common or very common** Allergic reactions - angioedema - bronchospasm - chills - cytokine release syndrome - dyspnoea - fever - flushing - nausea - pruritus - rash - tumour pain - vomiting
  - **Frequency not known** Cardiac events

**SIDE-EFFECTS, FURTHER INFORMATION**
Infusion-related side-effects In rare cases infusion reactions may be fatal. Infusion-related side-effects occur predominantly during the first infusion. Patients should receive premedication before administration of anti-lymphocyte monoclonal antibodies to reduce these effects—consult product literature for details of individual regimens.

The infusion may have to be stopped temporarily and the infusion-related effects treated—consult product literature for appropriate management.

Evidence of pulmonary infiltration and features of tumour lysis syndrome should be sought if infusion-related effects occur.

- **Cytokine release syndrome** Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred after infusions of anti-lymphocyte monoclonal antibodies. Patients with a high tumour burden as well as those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely (and a slower rate of infusion considered).

- **PRE-TREATMENT SCREENING** All patients should be screened for hepatitis B before treatment.

- **MONITORING REQUIREMENTS** Patients should also be monitored for cytopenias—consult product literature for specific recommendations.

Alemtuzumab

- **INDICATIONS AND DOSE**
  - Treatment of adults with relapsing-remitting multiple sclerosis with active disease defined by clinical or imaging features
    - **BY INTRAVENOUS INFUSION**
    - Adult: (consult product literature)

**UNLICENSED USE**
Although no longer licensed for oncological and transplant indications, alemtuzumab is also available through a patient access programme for these indications.

**IMPORTANT SAFETY INFORMATION**
Alemtuzumab should be given under the care of a specialist with facilities for the management of hypersensitivity and anaphylactic reactions.

- **CONTRA-INDICATIONS** Human immunodeficiency virus

**CAUTIONS**
Hepatitis B carriers - hepatitis C carriers - in patients with active infection, a delay in initiation of alemtuzumab treatment should be considered until the infection is fully controlled - not recommended for inactive disease - not recommended for stable disease - patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course - patients with previous autoimmune conditions other than multiple sclerosis - pretreatment before administration is required (consult product literature)

**CONCEPTION AND CONTRACEPTION**
Women of childbearing potential should use effective contraception during and for 4 months after treatment.

**PREGNANCY**
Manufacturer advises avoid unless potential benefit outweighs risk - toxicity in animal studies.

**BREAST FEEDING**
Manufacturer advises avoid during and for 4 months after each treatment course unless potential benefit outweighs risk.

**PRE-TREATMENT SCREENING**
Screening patients at high risk of hepatitis B or C is recommended before treatment. All patients should be evaluated for active or latent tuberculosis before starting treatment.

**MONITORING REQUIREMENTS**
HPV screening should be carried out annually in female patients.

**PRESCRIBING AND DISPENSING INFORMATION**
All patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course.

**PATIENT AND CARER ADVICE**
Patients should be provided with a patient alert card and patient guide.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**
  - Alemtuzumab for treating relapsing-remitting multiple sclerosis (May 2014) NICE TA312
    - Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing-remitting multiple sclerosis.

  [www.nice.org.uk/TA312](http://www.nice.org.uk/TA312)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Lemtrada** (Genzyme Therapeutics Ltd)
  - Alemtuzumab 10 mg per 1 ml
  - Lemtrada 12mg/1.2ml concentrate for solution for infusion 1 vial £7,045.00 (Hospital only)
Natalizumab

- **DRUG ACTION** Natalizumab is a monoclonal antibody that inhibits the migration of leucocytes into the central nervous system, hence reducing inflammation and demyelination.

- **INDICATIONS AND DOSE** Highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta or glatiramer acetate, or those patients with rapidly evolving severe relapsing-remitting multiple sclerosis (initiated under specialist supervision)
  - **BY INTRAVENOUS INFUSION**
    - Adult 18-65 years: 300 mg every 4 weeks, treatment should be discontinued if no response after 6 months.

- **CONTRA-INDICATIONS** Active infection, active malignancies (except cutaneous basal cell carcinoma), immunosuppression, progressive multifocal leucoencephalopathy.

- **CAUTIONS**
  - **CAUTIONS, FURTHER INFORMATION**
    - For information on cautions consult product literature.
  - Progressive Multifocal Leucoencephalopathy Natalizumab is associated with an increased risk of opportunistic infection and progressive multifocal leucoencephalopathy (PML) caused by JC virus. The risk of developing PML increases with the presence of anti-JCV antibodies, previous use of immunosuppressant therapy, and treatment duration (especially beyond 2 years of treatment); the risk beyond 4 years of treatment is not known. Patients with all three risk factors should only be treated with natalizumab if the benefits of treatment outweigh the risks. Treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued.

- **INTERACTIONS**
  - **Appendix 1 (natalizumab),** Concurrent use of interferon beta or glatiramer acetate contra-indicated.

- **SIDE-EFFECTS**
  - **Common or very common** Arthralgia, rash (during infusion), autoantibodies, dizziness (during infusion), fatigue (during infusion), headache (during infusion), nasopharyngitis, nausea (during infusion), pyrexia (during infusion), rigors (during infusion), urinary-tract infection, urticaria (during infusion), vomiting (during infusion).
  - **Uncommon** Hypersensitivity reactions (discontinue permanently), Progressive Multifocal Leucoencephalopathy (PML).
  - **Frequency not known** Flushing (during infusion), increased risk of opportunistic infection, liver toxicity.

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Progressive Multifocal Leucoencephalopathy If Progressive Multifocal Leucoencephalopathy (PML) is suspected, treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued.
  - Liver toxicity Discontinue treatment if significant liver injury occurs.

- **PREGNANCY** Avoid unless essential — toxicity in animal studies.

- **BREAST FEEDING** Present in milk in animal studies—avoid.

- **PRE-TREATMENT SCREENING**
  - Progressive Multifocal Leucoencephalopathy: A magnetic resonance image (MRI) scan is recommended before starting treatment with natalizumab.
  - Testing for serum anti-JCV antibodies before starting treatment or in those with unknown antibody status already receiving natalizumab is recommended and should be repeated every 6 months (consult product literature for full details).

- **MONITORING REQUIREMENTS**
  - Liver function.
  - Progressive Multifocal Leucoencephalopathy A magnetic resonance image (MRI) scan is recommended annually. Patients should be monitored for new or worsening neurological symptoms, and for cognitive and psychiatric signs of PML. All patients should continue to be monitored for signs and symptoms that may be suggestive of PML for approximately 6 months following discontinuation of treatment.
  - Hypersensitivity reactions Patients should be observed for hypersensitivity reactions, including anaphylaxis, during the infusion and for 1 hour after completion of the infusion.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Tysabri®), give intermittently in Sodium chloride 0.9%; dilute 300 mg in 100 mL infusion fluid; gently invert to mix, do not shake. Use within 8 hours of dilution and give over 1 hour.

- **PATIENT AND CARER ADVICE** A patient alert card should be provided.
  - Hypersensitivity reactions Patients should be told the importance of uninterrupted dosing, particularly in the early months of treatment (intermittent therapy may increase risk of sensitisation).
  - Progressive Multifocal Leucoencephalopathy Patients should be informed about the risks of PML before starting treatment with natalizumab and again after 2 years; they should be given an alert card which includes information about the symptoms of PML.
  - Liver toxicity Advise patients to seek immediate medical attention if symptoms such as jaundice or dark urine develop.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (August 2007)
      - NICE TA127

Natalizumab is an option for the treatment only of rapidly evolving severe relapsing-remitting multiple sclerosis (RES). RES is defined by 2 or more disabling relapses in 1 year, and 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. www.nice.org.uk/TA127

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (August 2007) that natalizumab is accepted for restricted use as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis only in patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for infusion**
    - ELECTROLYTES: May contain Sodium
      - **Tysabri** (Biogen Idec Ltd)

Natalizumab 20 mg per 1 ml Tysabri 300mg/15ml concentrate for solution for infusion vials | 1 vial (HEP) £1,130.00 (Hospital only)
Teriflunomide

**DRUG ACTION** Teriflunomide is a metabolite of leflunomide which has immunomodulating and anti-inflammatory properties.

**INDICATIONS AND DOSE** Treatment of relapsing-remitting multiple sclerosis (initiated under specialist supervision)

- **BY MOUTH**
  - Adult: 14 mg once daily

**CONTRA-INDICATIONS** Anaemia - leucopenia - neutropenia - serious infection - severe hypoproteinaemia - severe immunodeficiency - significantly impaired bone-marrow function - thrombocytopenia

**CAUTIONS** Adult over 65 years - anaemia - dyspnoea—assess for interstitial lung disease and consider suspending treatment - hypoproteinaemia (avoid if severe) - impaired bone-marrow function (avoid if severe) - latent tuberculosis - leucopenia - persistent cough—assess for interstitial lung disease and consider suspending treatment - severe infection—delay or suspend treatment until resolved - significant alcohol consumption - signs or symptoms of serious skin reactions (including ulcerative stomatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)—discontinue treatment - switching between other immunomodulating drugs - thrombocytopenia

**INTERACTIONS** → Appendix 1 (teriflunomide).

**SIDE-EFFECTS**

- **Common or very common** Acne - alopecia - anxiety - carpal tunnel syndrome - cystitis - diarrhoea - elevated liver enzymes - gastroenteritis - hyperaesthesia - hypertension - laryngitis - leucopenia - menorrhagia - musculoskeletal pain - myalgia - nausea - neuralgia - neutropenia - oral infection - paraesthesia - peripheral neuropathy - pollakiuria - rash - respiratory tract infection - sciatica - tinea pedis - urinary tract infection - vomiting - weight loss

- **Uncommon** Anaemia - thrombocytopenia

- **Very rare** Interstitial lung disease - pancreatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Accelerated elimination procedure **Important:** accelerated elimination procedure recommended following discontinuation due to serious adverse effects (consult product literature).
- Hepatic injury Discontinue treatment if signs or symptoms of hepatic injury, or if liver enzymes exceed 3 times the upper limit of reference range.

**CONCEPTION AND CONTRACEPTION** Effective contraception essential for women of child-bearing potential during treatment and for up to 2 years after treatment. In patients undergoing treatment with teriflunomide that are planning to conceive, the accelerated elimination procedure should be used prior to conception. Use of non-oral contraception is recommended during the accelerated elimination procedure—consult product literature.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.

**MONITORING REQUIREMENTS**

- Monitor full blood count (including differential white cell count and platelet count) before treatment and as clinically indicated during treatment.
- Monitor blood pressure before treatment and periodically thereafter.

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Hepatic monitoring** Monitor liver function before treatment and every 2 weeks for first 6 months then every 8 weeks thereafter or as clinically indicated (pre-existing liver disease may increase risk). Increase to weekly monitoring if alanine aminotransferase (ALT) is 2–3 times the upper limit of reference range; discontinue treatment if signs or symptoms of hepatic injury, or if liver enzymes exceed 3 times the upper limit of reference range.

**TREATMENT CESSATION** Accelerated elimination procedures To aid drug elimination in case of serious adverse effect or before conception, stop treatment and give either colestyramine p. 186 or charcoal, activated p. 1211. After the accelerated elimination procedure a plasma concentration of less than 20 micrograms/litre (measured on 2 occasions at least 14 days apart) and a waiting period of one and a half months are necessary before conception.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Teriflunomide for treating relapsing-remitting multiple sclerosis (January 2014) NICE TA303 Teriflunomide is recommended for the treatment of adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), in adults who:
  - do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and
  - the manufacturer provides teriflunomide with the discount agreed in the patient access scheme www.nice.org.uk/TA303

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (February 2014) that the use of teriflunomide (Aubagio® in NHS Scotland is restricted to use in patients with relapsing-remitting multiple sclerosis who do not have highly active disease, and only as an alternative to treatment with interferon beta or glatiramer acetate.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Aubagio** (Genzyme Therapeutics Ltd) ▼

  Teriflunomide 14 mg Aubagio 14mg tablets | 28 tablet | £1,037.84
Malignant disease

1 Antibody responsive malignancy

ANTINEOPLASTIC DRUGS › MONOCLONAL ANTIBODIES

Bevacizumab

- **DRUG ACTION** Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor.

- **INDICATIONS AND DOSE**
  
  Treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy | First-line treatment of metastatic breast cancer in combination with paclitaxel when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate | First-line treatment of metastatic breast cancer in combination with capetitabine when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate (patients who have received adjuvant taxane or anthracycline-containing regimens in the previous 12 months should not be treated with bevacizumab in combination with capetitabine) | Advanced or metastatic renal cell carcinoma in combination with interferon alfa-2a | First-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology (in combination with platinum-based chemotherapy) | First-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with carboplatin and paclitaxel) | First recurrence of platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who have not been treated previously with bevacizumab or other drugs that target vascular endothelial growth factor (in combination with carboplatin and gemcitabine)

  - **BY INTRAVENOUS INFUSION**
  - **Adult:** (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: BEVACIZUMAB AND SUNITINIB: RISK OF OSTEONECROSIS OF THE JAW (JANUARY 2011)

Treatment with bevacizumab or sunitinib may be a risk factor for the development of osteonecrosis of the jaw.

Patients treated with bevacizumab or sunitinib, who have previously received bisphosphonates, or are treated concurrently with bisphosphonates, may be particularly at risk.

Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib.

If possible, invasive dental procedures should be avoided in patients treated with bevacizumab or sunitinib who have previously received, or who are currently receiving, intravenous bisphosphonates.

- **CAUTIONS** Elective surgery (withhold treatment and avoid for at least 28 days after major surgery or until wound fully healed) | history of arterial thromboembolism | history of cardiovascular disease (increased risk of cardiovascular events, especially in the elderly) | history of hypertension (increased risk of proteinuria—discontinue if nephrotic syndrome) | increased risk of fistulas (discontinue permanently if tracheo-oesophageal or grade 4 fistula develops) | increased risk of haemorrhage | increased risk of tumour-associated haemorrhage | intra-abdominal inflammation (risk of gastro-intestinal perforation and gall bladder perforation) | uncontrolled hypertension | untreated CNS metastases

- **INTERACTIONS** 
  
  → Appendix 1 (bevacizumab).

- **SIDE-EFFECTS** Abdominal pain | alopaeia | anaemia | anorexia | arterial thromboembolism | asthenia | bone marrow suppression | chest pain | congestive heart failure | constipation | dehydration | diarrhoea | drowsiness | dry skin | dysarthria | dysphoea | exfoliative dermatitis | extravasation | eye disorders | fistulas | flushing | gall bladder perforation | gastro-intestinal perforation | haemorrhage | hand-foot syndrome | headache | hypersensitivity reactions | hypertension | hyperuricaemia | hypotension | hypoxia | impaired wound healing | infection | intestinal obstruction | lethargy | mucocutaneous bleeding | nausea | necrotising fasciitis (discontinue and initiate treatment promptly) | neutropenia | oral mucositis | osteonecrosis of the jaw | peripheral neuropathy | posterior reversible encephalopathy syndrome | proteinuria | pulmonary hypertension | pyrexia | rash | rhinitis | rinos | skin discoloration | supraventricular tachycardia | syncope | taste disturbances | thrombocytopenia | thromboembolism | tumour lysis syndrome | vomiting

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during and for at least 6 months after treatment in women.

- **PREGNANCY** Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING** Manufacturer advises avoid breast-feeding during and for at least 6 months after treatment.

- **MONITORING REQUIREMENTS**
  
  ▶ Monitor for necrotising fasciitis (usually secondary to wound healing complications, gastro-intestinal perforation or fistula formation)—discontinue and initiate treatment promptly.
  
  ▶ Monitor blood pressure.
  
  ▶ Monitor for congestive heart failure.
  
  ▶ Monitor for posterior reversible encephalopathy syndrome (presenting as seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without hypertension).
  
  ▶ Consider dental check-up before initiating treatment (risk of osteonecrosis of the jaw).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  
  NICE technology appraisals (Tas)
  
  ▶ Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (May 2013) NICE TA284
  
  Bevacizumab in combination with paclitaxel and carboplatin is not recommended for the first-line treatment of advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).
  
  www.nice.org.uk/TA284
  
  ▶ Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242
  
  Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy; see also NICE guidance Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007).
  
  www.nice.org.uk/TA242
Bevacizumab in combination with gemcitabine and carboplatin for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (May 2013) NICE TA285

Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) that has not been previously treated with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

www.nice.org.uk/TA285

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012) NICE TA263

Bevacizumab in combinations with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment in the previous 12 months.

www.nice.org.uk/TA263

Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011) NICE TA214

Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer.

www.nice.org.uk/TA214

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (December 2010) NICE TA212

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.

www.nice.org.uk/TA212

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007) NICE TA118

Bevacizumab in combination with fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer; see also NICE guidance Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy.

www.nice.org.uk/TA118

Bevacizumab (first-line), sorafenib (first and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178

Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma. Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma.

www.nice.org.uk/TA178

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (April 2012) that bevacizumab (Avastin®) is not recommended for use within NHS Scotland for the first line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.

The Scottish Medicines Consortium has advised (August 2015) that bevacizumab (Avastin®) is accepted for restricted use within NHS Scotland in combination with paclitaxel for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

The Scottish Medicines Consortium has advised (October 2015) that bevacizumab (Avastin®) is accepted for restricted use within NHS Scotland in combination with carboplatin and paclitaxel for the first-line treatment of advanced FIGO stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for infusion

Avastin (Roche Products Ltd)

Bevacizumab 25 mg per 1 ml Avastin 400mg/16ml solution for infusion vials | 1 vial £924.40 (Hospital only)

Avastin 100mg/4ml solution for infusion vials | 1 vial £242.66 (Hospital only)

Brentuximab vedotin

INDICATIONS AND DOSE

Treatment of relapsed or refractory CD-30 positive Hodgkin’s disease following autologous stem cell transplant or following at least two prior therapies, when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option | Relapsed or refractory systemic anaplastic large cell lymphoma

BY INTRAVENOUS INFUSION

Adult: (consult product literature)

CAUTIONS

Elevated BMI—risk of hyperglycaemia · high tumour burden—risk of tumour lysis syndrome · rapidly proliferating tumours—risk of tumour lysis syndrome

INTERACTIONS

Appendix 1 (brentuximab vedotin).

SIDE-EFFECTS

Common or very common

Anaphylaxis · arthralgia · back pain · constipation · cough · demyelinating polyneuropathy · diarrhoea · dizziness · dysphoenia · fatigue · hyperglycaemia · infusion-related reactions · myalgia · peripheral neuropathy · pruritus · rash

Uncommon

Stevens-Johnson syndrome

Frequency not known

Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · nausea · oral mucositis · progressive multifocal leuкоencephalopathy · thromboembolism · tumour lysis syndrome · vomiting

CONCEPTION AND CONTRACEPTION

Effective contraception required during treatment and for 6 months after treatment in men and women.

PREGNANCY

Avoid unless potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING

Avoid—no information available.

MONITORING REQUIREMENTS

Monitor for infusion-related (including anaphylactic) reactions.

Monitor for symptoms of progressive multifocal leuкоencephalopathy—consult product literature for treatment adjustment.

Routinely monitor hepatic function.

Monitor for pulmonary toxicity—treat symptoms promptly.

Monitor for thromboembolism.

Monitor for infusion-related (including anaphylactic) reactions.

Monitor for signs of peripheral neuropathy—consult product literature for treatment adjustment.
**Catumaxomab**

**INDICATIONS AND DOSE**
Treatment of malignant ascites in patients with epithelial cell adhesion molecule (EpCAM) positive carcinomas, where standard therapy is not available or no longer feasible

- BY INTRAPERITONEAL INFUSION
- Adults: consult product literature

**SIDE-EFFECTS, FURTHER INFORMATION**
Infusion-related side-effects
- Infusion-related side-effects have been reported with catumaxomab; premedication with analgesics, antipyretics, or NSAIDs is recommended by the manufacturer.

**CONCEPTION AND CONTRACEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY**
Avoid—limited information available.

**BREAST FEEDING**
Avoid—limited information available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- **Removab** (Neovii Biotech GmbH)
  - Catumaxomab 100 microgram per 1 ml
  - 50 micrograms/0.5 ml concentrate for solution for infusion pre-filled syringes | 1 pre-filled disposable injection POM £2,550.00 (Hospital only)
  - 10 micrograms/0.1 ml concentrate for solution for infusion pre-filled syringes | 1 pre-filled disposable injection POM £510.00 (Hospital only)

**INTERACTIONS**
Appendix 1 (catumaxomab).

**CAUTIONS**
- Haemodynamic insufficiency
- Hypoproteinaemia
- Oedema

**SIDE-EFFECTS**
- **Common or very common**
  - Abdominal pain
  - Anorexia
  - Anxiety
  - Arthralgia
  - Cholangitis
  - Constipation
  - Cough
  - Dehydration
  - Diarrhoea
  - Dizziness
  - Dyspepsia
  - Dyspnoea
  - Electrolyte disturbances
  - Flatulence
  - Flushing
  - Haematuria
  - Headache
  - Hyperglycaemia
  - Hypertension
  - Hypotension
  - Hypoxia
  - Ileus
  - Infection
  - Insomnia
  - Leucocyturia
  - Myalgia
  - Pleural effusion
  - Proteinuria
  - Rash
  - Skin reactions
  - Sweating
  - Tachycardia
  - Vertigo

- **Uncommon**
  - Acute renal failure
  - Gastro-intestinal haemorrhage
  - Intestinal obstruction
  - Seizures

- **Frequency not known**
  - Alopecia
  - Bone-marrow suppression
  - Extravasation
  - Hyperuricaemia
  - Infusion related side-effects
  - Nausea
  - Oral mucositis
  - Thromboembolism
  - Tumour lysis syndrome
  - Vomiting

**CONTRA-INDICATIONS**
Combination of cetuximab with oxaliplatin-containing chemotherapy is contra-indicated in patients with metastatic colorectal cancer who have mutant or unknown RAS status - RAS mutated colorectal tumours (or if RAS tumour status unknown)

**CAUTIONS**
Cardiopulmonary disease
- **History of keratitis**
- Pulmonary disease—discontinue if interstitial lung disease—risk factors for keratitis—severe dry eye—ulcerative keratitis (including contact lens use)

**INTERACTIONS**
Appendix 1 (cetuximab).

**SIDE-EFFECTS**
- **Common or very common**
  - Acne
  - Aseptic meningitis
  - Blepharitis
  - Bronchospasm
  - Chills
  - Conjunctivitis
  - Desquamation
  - Diarrhoea
  - Dizziness
  - Dry skin
  - Dyspnoea
  - Fever
  - Headache
  - Hypertension
  - Hypertrichosis
  - Hypocalcaemia
  - Hypomagnesaemia
  - Hypotension
  - Infusion-related reactions
  - Keratitis
  - Nail disorders
  - Nausea
  - Pruritus
  - Rash
  - Severe (sometimes fatal)
  - Hypersensitivity reactions (possibly delayed onset)
  - Shock
  - Skin reactions
  - Urticaria
  - Vomiting

- **Very rare**
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis

**CONCEPTION AND CONTRACEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY**
Use only if potential benefit outweighs risk—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Avoid breast-feeding during and for 2 months after treatment—no information available.

**PRE-TREATMENT SCREENING**
Evidence of non-mutated (wild-type) RAS status (at exons 2, 3 and 4 of KRAS and
Immune system and malignant disease

Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy. (August 2009) NICE TA176

Cetuximab in combination with bevacizumab is not recommended for the treatment of metastatic colorectal cancer under the following circumstances:

- the primary tumour has been resected or is potentially operable;
- the metastatic disease is confined to the liver and is unresectable; and
- the patient is fit to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.

In patients unable to tolerate oxaliplatin, or in whom oxaliplatin is contra-indicated, cetuximab in combination with fluorouracil, folinic acid, and irinotecan can be used as an alternative.

In addition, the manufacturer is required to rebate 16% of the amount of cetuximab used per patient when used in combination with fluorouracil, folinic acid, and oxaliplatin.

Patients who meet the above criteria should receive cetuximab for no more than 16 weeks. At 16 weeks, cetuximab should be stopped and the patient should be assessed for resection of liver metastases.

Iplimumab

DRUG ACTION

Iplimumab causes T-cell activation.

INDICATIONS AND DOSE

Treatment of unresectable or metastatic advanced melanoma

BY INTRAVENOUS INFUSION

Adult: (consult product literature)

CAUTIONS

CONCESSION AND CONTRACEPTION

Use effective contraception.

PREGNANCY

Avoid unless potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING

Discontinue breast-feeding—no information available.

HEPATIC IMPAIRMENT

Use with caution if plasma-bilirubin concentration greater than 3 times upper limit of normal range or if plasma-transaminase concentration 5 times or greater than the upper limit of normal range.

MONITORING REQUIREMENTS

For information on monitoring of side effects, consult product literature.

PRESCRIBING AND DISPENSING INFORMATION

Infusion-related side-effects have been reported; premedication with paracetamol and an antihistamine is recommended.

NATIONAL FUNDING/ACCESS DECISIONS

Iplimumab for previously untreated advanced (unresectable or metastatic) melanoma (July 2014) NICE TA319

Iplimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides iplimumab with the discount agreed in the patient access scheme.

www.nice.org.uk/TA319

Iplimumab for previously treated advanced (unresectable or metastatic) melanoma (December 2012) NICE TA268

Iplimumab is recommended as an option for the treatment of advanced (unresectable or metastatic) melanoma in patients who have received prior therapy, only if the manufacturer provides iplimumab with the discount agreed in the patient access scheme.

www.nice.org.uk/TA268

Nivolumab in combination with iplimumab for treating advanced melanoma (July 2016) NICE TA400

Nivolumab in combination with iplimumab is recommended, within its marketing authorisation, as a treatment option for advanced (unresectable or metastatic) melanoma.
metastatic) melanoma in adults, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme. 
www.nice.org.uk/TA400

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (March 2013) that ipilimumab (Yervoy<sup>®</sup>) is accepted for restricted use within NHS Scotland for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy, only whilst ipilimumab is available at the price agreed in the patient access scheme.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

- **Solution for Infusion**
  ELECTROLYTES: May contain Sodium
  - Yervoy (Bristol-Myers Squibb Pharmaceuticals Ltd) ▼
    - Ipilimumab 5 mg per 1 ml Yervoy 50mg/10ml concentrate for solution for infusion vials | 1 vial (£3,750.00 (Hospital only)
    - Yervoy 200mg/40ml concentrate for solution for infusion vials | 1 vial (£50 | £15,000.00 (Hospital only)

Nivolumab
19-Oct-2016

- **DRUG ACTION**
  Nivolumab is a human immunoglobulin G4 monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor thereby potentiating an immune response to tumour cells.

- **INDICATIONS AND DOSE**
  Treatment of unresectable or metastatic advanced melanoma in combination with ipilimumab
  - BY INTRAVENOUS INFUSION
  - Adult: (consult product literature)

  Treatment of unresectable or metastatic advanced melanoma (as monotherapy) | Treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy | Treatment of advanced renal cell carcinoma after prior therapy (as monotherapy)
  - BY INTRAVENOUS INFUSION
  - Adult: 3 mg/kg every 2 weeks, consult product literature for information on dose adjustments based on individual patient safety and tolerability

- **CAUTIONS**
  Patients may need pre-medications to minimise the development of infusion-related reactions

- **INTERACTIONS**
  → Appendix 1 (nivolumab).

- **SIDE-EFFECTS**
  - **Common or very common**
    - Abdominal pain • alopecia • arthralgia • blurred vision • colitis • constipation • cough • decreased appetite • diarrhoea • dizziness • dry eyes • dry mouth • dry skin • dyspnoea • erythema • headache • hyperglycaemia • hypertension • infusion-related reactions • malaise • musculoskeletal pain • nausea • oedema • peripheral neuropathy • pneumonitis • pruritus • pyrexia • rash • stomatitis • thyroid disorders • upper respiratory tract infection • vitiligo • vomiting
  - **Uncommon**
    - Adrenal insufficiency • anaphylactic reaction • arthritis • chest pain • dehydration • diabetic ketoacidosis • eosinophilia • erythema multiforme • hepatitis • hyperbilirubinaemia • hypophosphitism • hypopituitarism • metabolic acidosis • pancreatitis • pleural effusion • polymyalgia rheumatica • polynuropathy • psoriasis • renal failure • rosacea • tachycardia • tubulointerstitial nephritis • urticaria • uveitis • vasculitis
  - **Rare**
    - Arrhythmias • autoimmune neuropathy • cholestasis • demyelination • diabetes mellitus • duodenal ulcer • gastritis • Guillain–Barré syndrome • histocytic necrotising lymphadenitis (Kikuchi lymphadenitis) • lung infiltration • myasthenic syndrome • myopathy • toxic epidermal necrolysis
  - **Frequency not known**
    - Cardiac adverse events
    - SIDE-EFFECTS, FURTHER INFORMATION
      Side effects listed are reported when nivolumab is used as monotherapy; if combination therapy used, consult product literature for further information.

  - **Immune-related reactions**
    - Manufacturer advises that most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications—consult product literature for further information.

  - **Infusion-related reactions**
    - Manufacturer advises that patients with mild or moderate infusion reactions may continue treatment with close monitoring and use of pre-medication according to local guidelines; discontinue treatment if severe infusion reactions occur.

  - **CONCEPTION AND CONTRACEPTION**
    - Manufacturer advises effective contraception required during treatment and for at least 5 months after treatment in women of childbearing potential.

  - **PREGNANCY**
    - Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

  - **BREAST FEEDING**
    - Manufacturer advises avoid—no information available.

  - **HEPATIC IMPAIRMENT**
    - Manufacturer advises use with caution in moderate to severe impairment—limited information available.

  - **MONITORING REQUIREMENTS**
    - Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions, cardiac and pulmonary reactions, and electrolyte disturbances before and periodically during treatment. Patients should be monitored for adverse reactions for at least 5 months after the last dose.

  - **DIRECTIONS FOR ADMINISTRATION**
    - Manufacturer advises for intermittent intravenous infusion, give undiluted or dilute to a concentration of not less than 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 60 minutes through an in-line filter (pore size 0.2–1.2 micron).

  - **HANDLING AND STORAGE**
    - Manufacturer advises store in a refrigerator (2–8 °C)—consult product literature for storage conditions after preparation of the infusion.

  - **PATIENT AND CARER ADVICE**
    - Patients should be provided with a patient alert card with each prescription.

  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - NICE technology appraisals (TAs)
      - Nivolumab for treating advanced (unresectable or metastatic) melanoma (February 2016) NICE TA384
        - Nivolumab as monotherapy is recommended, within its marketing authorisation, as a treatment option for advanced (unresectable or metastatic) melanoma in adults.
        - www.nice.org.uk/TA384
      - Nivolumab in combination with ipilimumab for treating advanced melanoma (July 2016) NICE TA400
        - Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as a treatment option for advanced (unresectable or metastatic) melanoma in adults, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.
        - www.nice.org.uk/TA400

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2016) that nivolumab (Opdivo<sup>®</sup>) is accepted for use within NHS Scotland for the treatment of locally advanced or metastatic squamous non-small cell lung cancer after prior chemotherapy in adults; it has also advised (August 2016) that nivolumab (Opdivo<sup>®</sup>) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab, and (October 2016)
for restricted use for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer after prior chemotherapy in adults, subject to a 2-year clinical stopping rule.

This advice is contingent upon the continuing availability of the Patient Access Scheme (PAS) in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**CAUTIONARY AND ADVISORY LABELS**
- **3 ELECTROLYTES:** May contain Sodium
- **Opdivo** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Nivolumab 10 mg per 1 ml
  - Opdivo 40mg/4ml concentrate for solution for infusion vials | 1 vial (PSt) £439.00 (Hospital only)
  - Opdivo 100mg/10ml concentrate for solution for infusion vials | 1 vial (PSt) £1,097.00 (Hospital only)

**Obinutuzumab**

**INDICATIONS AND DOSE**

**Treatment of previously untreated chronic lymphocytic leukaemia in patients for whom full-dose fludarabine-based therapy is unsuitable due to co-morbidities**

- **BY INTRAVENOUS INFUSION**
- **Adult:** (consult product literature or local protocols)

**CONTRA-INDICATIONS**

**CONTRA-INDICATIONS, FURTHER INFORMATION**
For obinutuzumab contra-indications, consult product literature.

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**
For full details on the cautions of obinutuzumab, consult product literature.

**Hepatitis B infection and reactivation**
Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking **obinutuzumab**. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

**INTERACTIONS** → Appendix 1 (obinutuzumab).

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**
For full side effect details for obinutuzumab (including monitoring and management), consult product literature.

**CONCEPTION AND CONTRACEPTION**
Use effective contraception during and for 18 months after treatment.

**PREGNANCY**
Avoid unless potential benefit outweighs risk of B-lymphocyte depletion in fetus.

**BREAST FEEDING**
Avoid breast-feeding during and for 18 months after treatment—present in milk in animal studies.

**MONITORING REQUIREMENTS**
Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

**PRESCRIBING AND DISPENSING INFORMATION**
Infusion related side-effects have been reported; Patients should receive premedication with paracetamol, an antihistamine, and a corticosteroid before each dose—consult product literature for details.

**Ofatumumab**

**INDICATIONS AND DOSE**

**Treatment of chronic lymphocytic leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab**

**TREATMENT OF CLL IN patients who have not received prior therapy and who are not eligible for fludarabine based therapy (in combination with chlorambucil or bendamustine)**

- **BY INTRAVENOUS INFUSION**
- **Adult:** Premedication must be given 30 minutes to 2 hours before each dose—consult product literature for details

**CONTRA-INDICATIONS**

**CONTRA-INDICATIONS, FURTHER INFORMATION**
For full details on the contra-indications for ofatumumab, consult product literature.

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**
History of cardiac disease—monitor closely and discontinue treatment if cardiac arrhythmias occur

**INTERACTIONS**
For full details about the cautions for ofatumumab, consult product literature.

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**
Infusion-related side-effects (including cytokine release syndrome) have been reported with ofatumumab; premedication with paracetamol, an antihistamine, and a corticosteroid must be given—consult product literature.

For full details (including monitoring and management of side-effects) consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- **Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (June 2015)**
  - **NICE TA343**
  - Obinutuzumab, in combination with chlorambucil, is an option for untreated chronic lymphocytic leukaemia in patients who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if:
    - bendamustine-based therapy is not suitable and the manufacturer provides obinutuzumab with the discount agreed in the patient access scheme.
  - Patients currently receiving obinutuzumab that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.
  - [www.nice.org.uk/TA343](http://www.nice.org.uk/TA343)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Opdivo** (Roche Products Ltd)
  - Obinutuzumab 25 mg per 1 ml
  - Obinutuzumab 1000mg/40ml concentrate for solution for infusion vials | 1 vial (PSt) £3,312.00 (Hospital only)
  - Gazyvaro (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Nivolumab 10 mg per 1 ml
  - Nivolumab 40mg/4ml concentrate for solution for infusion vials | 1 vial £439.00 (Hospital only)
  - Nivolumab 100mg/10ml concentrate for solution for infusion vials | 1 vial £1,097.00 (Hospital only)
Panitumumab

- **DRUG ACTION** Panitumumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR).

- **INDICATIONS AND DOSE**
  - Treatment of non-mutated RAS metastatic colorectal cancer (combination therapy)
  - Treatment of non-mutated RAS metastatic colorectal cancer (monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens)
  - BY INTRAVENOUS INFUSION
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: SEVERE SKIN REACTIONS**

Severe skin reactions have been reported very commonly in patients treated with panitumumab. Patients receiving panitumumab who have severe skin reactions or develop worsening skin reactions should be monitored for the development of inflammatory or infectious sequelae (including cellulitis, sepsis, and necrotising fasciitis). Appropriate treatment should be promptly initiated and panitumumab withheld or discontinued.

**MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)**

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

- **CONTRA-INDICATIONS** Interstitial pulmonary disease - the combination of panitumumab with oxaliplatin-containing chemotherapy is contra-indicated in patients with mutant RAS metastatic colorectal cancer or for whom RAS status is unknown.

- **CAUTIONS** History of keratitis - history of severe dry eye - history of ulcerative keratitis - pulmonary disease—discontinue if interstitial lung disease develops - risk factors for keratitis - risk factors for severe dry eye - risk factors for ulcerative keratitis (including contact lens use)

- **INTERACTIONS** → Appendix 1 (panitumumab).

- **SIDE-EFFECTS**
  - Uncommon Bronchospasm - cyanosis - hirsutism - infusion-related reactions - nasal dryness
  - Rare Keratitis - skin necrosis - Stevens-Johnson syndrome - toxic epidermal necrolysis
  - Frequency not known Abdominal pain - acne - alopecia - bone-marrow suppression - conjunctivitis - constipation - dehydration - diarrhoea - dizziness - dry eyes - dry mouth - dry skin - erythema - extravasation - hand-foot syndrome - headache - hypertension - hypertrichosis - hyperuricaemia - hypocalcaemia - hypomagnesaemia - hypotension -
increased lacrimation - interstitial lung disease - mucosal inflammation - nail disorders - nausea - ocular disorders - ocular hyperaemia - oral mucositis - pruritus - rash - skin reactions - tachycardia - thromboembolism - tumour lysis syndrome - vomiting

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for 6 months after treatment.
- **PREGNANCY** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING** Manufacturer advises avoid breastfeeding during and for 2 months after treatment.
- **PRE-TREATMENT SCREENING** Evidence of non-mutated RAS status (at exons 2, 3 and 4 of KRAS and NRAS) is required before panitumumab treatment is initiated, and should be determined by an experienced laboratory using a validated test method.
- **MONITORING REQUIREMENTS**
  - Monitor for hypomagnesaemia.
  - Monitor for hypocalcaemia.
- **MEDICINAL FORMS**
- **PRE-TREATMENT SCREENING**
  - Evidence of non-mutated RAS status (at exons 2, 3 and 4 of KRAS and NRAS) is required before panitumumab treatment is initiated, and should be determined by an experienced laboratory using a validated test method.
- **MONITORING REQUIREMENTS**
  - Monitor for hypomagnesaemia.
  - Monitor for hypocalcaemia.
  - Monitor for dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (consult product literature).
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242
    - Panitumimab monotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy.
    - www.nice.org.uk/TA242

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for infusion**
    - **ELECTROLYTES**: May contain Sodium
      - **Vectibix** (Amgen Ltd)
        - Panitumumab 20 mg per 1 ml Vectibix 400mg/20ml concentrate for solution for infusion vials | 1 vial (Pharmaceutical only) Vectibix 100mg/5ml concentrate for solution for infusion vials | 1 vial (Pharm) £379.29 (Hospital only)

**Pembrolizumab**

**DRUG ACTION** Pembrolizumab is a monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor, thereby potentiating an immune response to tumour cells.

**INDICATIONS AND DOSE**
**Treatment of unresectable or metastatic advanced melanoma**
- **BY INTRAVENOUS INFUSION**
  - Adult: 2 mg/kg every 3 weeks

**CAUTIONS** Patients may need pretreatment to minimise the development of adverse reactions (consult product literature)

**INTERACTIONS**

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - alopecia - arthritis - blood dyscrasia - changes in hair colour - chills - colitis - constipation - cough - decreased appetite - depigmentation - diarrhoea - dizziness - dry eye - dry mouth - dry skin - eczema - erythema - headache - hepatitis - influenza-like symptoms - infusion-related reactions - insomnia - malaise - musculoskeletal pain - myositis - nausea - oedema - peripheral neuropathy - pneumonitis - pruritus - pyrexia - rash - shortness of breath - taste disturbances - thyroid dysfunction - vomiting
- **Rare** Guillain-Barré syndrome - myasthenic syndrome - small intestinal perforation

**SIDE-EFFECTS, FURTHER INFORMATION**
- Immune-related reactions Most immune-related adverse reactions are reversible and managed by temporarily stopping treatment and administration of a corticosteroid—consult product literature for further information.
- Infusion-related reactions Manufacturer advises to permanently discontinue treatment in patients with severe infusion reactions.
- **CONCEPTION AND CONTRACEPTION** Manufacturer recommends effective contraception during treatment and for at least 4 months after treatment in women of childbearing potential.
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—no information available
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **MONITORING REQUIREMENTS** Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions.
- **DIRECTIONS FOR ADMINISTRATION**
  - **For intravenous infusion (Keytruda®)**, give intermittently in Sodium chloride 0.9% or Glucose 5%. Reconstitute each 50 mg vial with 2.3 mL water for injection, to produce a 25 mg/mL solution. Gently swirl without shaking to dissolve, and allow up to 5 minutes for the bubbles to clear. Withdraw the required volume and transfer into an intravenous bag containing infusion fluid to prepare a final concentration ranging from 1–10 mg/mL; give over 30 minutes.
  - **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator at 2–8°C.
  - **PATIENT AND CARER ADVICE** Patients should be provided with an alert card and advised to keep it with them at all times.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- **Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (October 2015)** NICE TA357
  - Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma only if:
    - the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor and
    - the manufacturer provides pembrolizumab with the discount agreed in the patient access scheme.
    - www.nice.org.uk/guidance/TA357

- **Pembrolizumab for advanced melanoma not previously treated with ipilimumab (November 2015)** NICE TA366
  - Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, only if the manufacturer provides pembrolizumab with the discount agreed in the patient access scheme.
    - www.nice.org.uk/guidance/TA366
Pertuzumab

**DRUG ACTION** Pertuzumab is a recombinant humanised monoclonal antibody, and acts by inhibiting human epidermal growth factor receptor 2 protein (HER2) dimerisation.

**INDICATIONS AND DOSE**

Treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with trastuzumab and docetaxel, in patients who have not received previous anti-HER2 therapy or chemotherapy (initiated by a specialist)

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature

**SIDE-EFFECTS**

- **Common or very common**
  - Anaemia
  - Arthralgia
  - Chills
  - Constipation
  - Cough
  - Decreased appetite
  - Diarrhoea
  - Dizziness
  - Dry skin
  - Dyspepsia
  - Dysphonia
  - Febrile neutropenia
  - Headache
  - Increased lacrimation
  - Infusion-related reactions
  - Insomnia
  - Left ventricular dysfunction
  - Leucopenia
  - Malaise
  - Myalgia
  - Nail disorder
  - Nasopharyngitis
  - Neutropenia
  - Oedema
  - Pain
  - Paronychia
  - Peripheral neuropathy
  - Pleural effusion
  - Pruritus
  - Pyrexia
  - Rash
  - Severe hypersensitivity reactions
  - Taste disturbance
  - Upper respiratory-tract infection

- **Uncommon**
  - Intestinal ulcer disease

- **Frequency not known**
  - Alopecia
  - Bone-marrow suppression
  - Extravasation
  - Hyperuricaemia
  - Hypertension
  - Impaired left ventricular function
  - Impaired wound healing
  - Mucosal ulceration
  - Nausea
  - Oral mucositis
  - Pruritus
  - Rash
  - Severe hypersensitivity reactions
  - Tissue oedema
  - Upper respiratory tract infection
  - Upper respiratory tract infection
  - Vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Side effects mostly described for pertuzumab in combination with trastuzumab and docetaxel.

**CONCESSION AND CONTRACEPTION**

Ensure effective contraception during and for six months after treatment in women of childbearing potential.

**PREGNANCY**

Avoid (toxicity in animal studies). Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

**BREAST FEEDING**

Avoid—no information available.

**HEPATIC IMPAIRMENT**

Caution—no information available.

**RENAL IMPAIRMENT**

Caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Assess for signs and symptoms of congestive heart failure (including left ventricular ejection fraction) before and during treatment—consult product literature, and withhold treatment if necessary.
- Monitor for febrile neutropenia.

**CAUTIONS**

- Conditions that could impair left ventricular function.
- History of congestive heart failure.
- Impaired left ventricular function.
- Prior anthracycline exposure.
- Radiotherapy to the chest area.
- Recent myocardial infarction.
- Serious cardiac arrhythmia.
- Uncontrolled hypertension.

**INTERACTIONS**

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature

**DIRECTIONS FOR ADMINISTRATION**

Resuscitation facilities should be available.

**CAUTIONS**

Elective surgery—discontinue treatment for at least 4 weeks prior to surgery. Hypertension—must be controlled before initiation. Impaired wound healing—discontinue treatment until wound fully healed. Pretreatment is recommended to minimise the development of adverse reactions (consult product literature) risk of bleeding.

**INTERACTIONS**

- **Appendix 1 (pertuzumab).**

**SIDE-EFFECTS**

- **Common or very common**
  - Abdominal pain
  - Diarrhoea
  - Epistaxis
  - Gastro-intestinal haemorrhage
  - Headache
  - Hypertension
  - Hypoalbuninaemia
  - Hypokalaemia
  - Hyponatraemia
  - Leucopenia
  - Malaise
  - Mucosal

Ramucirumab

**DRUG ACTION**

Ramucirumab is a human monoclonal antibody that binds to the vascular endothelial growth factor receptor-2 (VEGFR-2), inhibiting VEGF-induced angiogenesis.

**INDICATIONS AND DOSE**

Treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, in combination with paclitaxel, in patients with disease progression after prior platinum and fluoropyrimidine chemotherapy

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature for dose adjustments due to side-effects and infusion-related reactions

**TREATMENT OF ADVANCED Gastric CANCER OR Gaстро-OESOPHAGEAL JUNCTION ADENOCARCINOMA, AS MONOTHERAPY, IN PATIENTS WITH DISEASE PROGRESSION AFTER PRIOR PLATINUM AND FLUOROPYRIMIDINE CHEMOTHERAPY**

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature for dose adjustments due to side-effects and infusion-related reactions

**TREATMENT OF ADVANCED Gastric CANCER OR Gastro-Oesophageal JUNCTION ADENOCARCINOMA, AS MONOTHERAPY, IN PATIENTS WITH DISEASE PROGRESSION AFTER PRIOR PLATINUM OR FLUOROPYRIMIDINE CHEMOTHERAPY, AND FOR WHOM TREATMENT IN COMBINATION WITH PACITAXEL IS NOT APPROPRIATE**

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature for dose adjustments due to side-effects and infusion-related reactions

**TREATMENT OF METASTATIC COLORECTAL CANCER, IN COMBINATION WITH FOLFIRI (IRINOTECAN, FLUOROURACIL AND FOLinic ACID), IN PATIENTS WITH DISEASE PROGRESSION ON, OR AFTER, PRIOR THERAPY WITH BEVACIZUMAB, OXAPlATIN AND A FLUOROPYRIMIDINE**

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature for dose adjustments due to side-effects and infusion-related reactions

**TREATMENT OF LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER, IN COMBINATION WITH DOCETAXEL, IN PATIENTS WITH DISEASE PROGRESSION AFTER PLATINUM-BASED CHEMOTHERAPY**

- **BY INTRAVENOUS INFUSION**
- Adult: consult product literature for dose adjustments due to side-effects and infusion-related reactions

**CAUTIONS**

- Conditions that could impair left ventricular function.
- History of congestive heart failure.
- Impaired left ventricular function.
- Prior anthracycline exposure.
- Radiotherapy to the chest area.
- Recent myocardial infarction.
- Serious cardiac arrhythmia.
- Uncontrolled hypertension.

**INTERACTIONS**

- **Appendix 1 (ramucirumab).**

**SIDE-EFFECTS**

- **Common or very common**
  - Abdominal pain
  - Diarrhoea
  - Epistaxis
  - Gastro-intestinal haemorrhage
  - Headache
  - Hypertension
  - Hypoalbuninaemia
  - Hypokalaemia
  - Hyponatraemia
  - Leucopenia
  - Malaise
  - Mucosal
  - Rash
  - Tissue oedema
  - Upper respiratory tract infection

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Perjeta (Roche Products Ltd)
- Pertuzumab 30 mg per 1 ml Perjeta 420mg/14ml concentrate for solution for infusion vials 1 vial (Product) £1,315.00 (hospital only)

**DIRECTIONS FOR ADMINISTRATION**

Resuscitation facilities should be available.
Immune system and malignant disease

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer in patients whose disease has progressed after platinum-based chemotherapy.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinicians consider it appropriate to stop.

www.nice.org.uk/TA403

SIDES-EFFECTS, FURTHER INFORMATION

Infusion-related reactions

Infusion-related hypersensitivity reactions have been reported with ramucirumab, particularly during or following the first or second infusion; if the patient experiences a grade 1 or 2 infusion-related reaction, the manufacturer advises to reduce rate of infusion by 50% and give premedication for all subsequent infusions—consult product literature. Manufacturer advises to permanently discontinue treatment in the event of a grade 3 or 4 infusion-related reaction.

CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception during treatment and for up to 3 months after treatment in women of childbearing potential.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

BREAST FEEDING

Manufacturer advises discontinue breast-feeding during treatment and for at least 3 months after treatment—no information available.

HEPATIC IMPAIRMENT

Manufacturer advises caution in severe cirrhosis, cirrhosis with hepatic encephalopathy, cirrhosis with clinically significant ascites, or hepatorenal syndrome—use only if potential benefit outweighs risk of progressive hepatic failure.

MONITORING REQUIREMENTS

Manufacturer advises monitor for signs of infusion-related hypersensitivity reactions; monitor blood pressure prior to each infusion; monitor for development or worsening of proteinuria during treatment—consult product literature; monitor blood counts and coagulation parameters in patients at risk of bleeding.

DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Cyramza®), give intermittently in Sodium chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and invert gently to mix. Do not exceed a rate of 25 mg/minute, and give over approximately 60 minutes via an infusion pump using a separate infusion line with a protein sparing 0.22 micron filter.

PRESCRIBING AND DISPENSING INFORMATION

For Cyramza®, each 10 mL vial contains sodium 17 mg (equivalent to Na+ 0.74 mmol).

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy (January 2016) NICE TA378

Ramucirumab alone or in combination with paclitaxel is not recommended for the treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy.

Patients whose treatment was started before this guidance was published, should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA378

Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (August 2016) NICE TA403

Ramucirumab, in combination with docetaxel, is not recommended for treating locally advanced or metastatic non-small-cell lung cancer in patients whose disease has progressed after platinum-based chemotherapy.

Rituximab

INDICATIONS AND DOSE

Treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them (in combination with methotrexate)

BY INTRAVENOUS INFUSION

Adult: 1 g, then 1 g after 2 weeks, patients should receive premedication before each infusion (consult product literature for details)

Treatment of previously untreated stage III–IV follicular lymphoma (in combination with other chemotherapy) Maintenance therapy in patients with follicular non-Hodgkin’s lymphoma that has responded to induction therapy (in combination with other chemotherapy)

Treatment of diffuse large B-cell non-Hodgkin’s lymphoma (in combination with other chemotherapy)

Treatment of chemotherapy-resistant or relapsed stage III–IV follicular non-Hodgkin’s lymphoma | Previously untreated or relapsed chronic lymphocytic leukaemia

Induction of remission in patients with severe, active granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis (in combination with glucocorticoids)

BY INTRAVENOUS INFUSION

Adult: Patients should receive premedication before each dose (consult product literature for details)

CONTRA-INDICATIONS

Severe heart failure (when used to treat granulomatosis with polyangiitis or microscopic polyangiitis) • severe infection • severe, uncontrolled heart disease (when used to treat granulomatosis with polyangiitis or microscopic polyangiitis)

CONTRA-INDICATIONS, FURTHER INFORMATION

For full details on contra-indications, consult product literature.

CAUTIONS

GENERAL CAUTIONS

History of cardiovascular disease; in adults exacerbation of angina, arrhythmia, and heart failure have been reported - patients receiving cardiotoxic chemotherapy; in adults exacerbation of angina, arrhythmia, and heart failure have been reported - transient hypotension occurs frequently during infusion (anti-hypertensives may need to be withheld for 12 hours before infusion)
SPECIFIC CAUTIONS

- When used for rheumatoid arthritis: Predisposition to infection.

CAUTIONS, FURTHER INFORMATION

- Hepatitis B infection and reactivation: Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking rituximab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

For full details on cautions, consult product literature or local treatment protocol.

- INTERACTIONS: Appendix 1 (rituximab).

- SIDE-EFFECTS: Abdominal pain, anaemia, antibody formation, aplastic anaemia, arthralgia, asthenia, blood disorders, depression, dyspepsia, headache, hypertension, hypotension, injection-site reactions, leucopenia, lupus erythematosus-like syndrome, migraine, muscle spasm, pancytopenia, paraesthesia, progressive multifocal leucoencephalopathy, pruritus, rhinitis, severe fatal skin reactions, severe skin reactions (permanently discontinue treatment if occurs), sore throat, Stevens-Johnson syndrome (permanently discontinue treatment if occurs), thrombocytopenia, toxic epidermal necrolysis (permanently discontinue treatment if occurs), urticaria, worsening heart failure.

SIDE-EFFECTS, FURTHER INFORMATION

- Associated with infections, sometimes severe, including tuberculosis, sepsicaemia, and hepatitis B reactivation.

- Progressive multifocal leucoencephalopathy: Progressive multifocal leucoencephalopathy (which is usually fatal or causes severe disability) has been reported in association with rituximab; patients should be monitored for cognitive, neurological, or psychiatric signs and symptoms. If progressive multifocal leucoencephalopathy is suspected, suspend treatment until it has been excluded.

For full details, including management of side-effects, consult product literature.

- CONCEPTION AND CONTRACEPTION: Effective contraception (in both sexes) required during and for 12 months after treatment.

- PREGNANCY: Avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus.

- BREAST FEEDING: Avoid breast-feeding during and for 12 months after treatment.

- MONITORING REQUIREMENTS: For full details on monitoring requirements consult product literature.

- DIRECTIONS FOR ADMINISTRATION: For intravenous infusion (MabThera®), give intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to 1-4 mg/mL and gently invert bag to avoid foaming.

- PATIENT AND CARER ADVICE: Alert card. Patients treated for granulomatosis with polyangiitis and microscopic polyangiitis or rheumatoid arthritis should be provided with a patient alert card with each infusion.

- NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis (March 2014) NICE TA308

This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener’s] and microscopic polyangiitis), only if:

- Further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose, or
- Cyclophosphamide is contra-indicated or not tolerated, or
- The patient has not completed their family, and treatment with cyclophosphamide may materially affect their fertility, or
- The disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months or
- The patient has had uroepithelial malignancy.

www.nice.org.uk/TA308

- Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195

Rituximab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least 1 tumour necrosis factor (TNF) inhibitor. Repeat courses of rituximab should be given no more frequently than every 6 months, and should only be continued if an adequate response is achieved and maintained.

www.nice.org.uk/TA195

- Rituximab for the first-line treatment of stage III-IV follicular lymphoma (January 2012) NICE TA243

This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with:

- Cyclophosphamide, vincristine and prednisolone (CVP);
- Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP);
- Mitoxantrone, chlorambucil and prednisolone (MCP);
- Cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alfa (CHVPi); or
- Chlorambucil is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.

www.nice.org.uk/TA243

- Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma (February 2008) NICE TA137

This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with chemotherapy, is an option for the induction of remission in patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma.

Rituximab monotherapy as maintenance therapy is an option for the treatment of patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma in remission induced with chemotherapy (with or without rituximab).

Rituximab monotherapy is an option for the treatment of patients with relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

www.nice.org.uk/TA137

- Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (July 2010) NICE TA193

This NICE guidance was issued for rituximab by intravenous infusion. Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition:

- Is refractory to fludarabine (that is, it has not responded to fludarabine, or has relapsed within 6 months of treatment), or
- Has previously been treated with rituximab, unless it was in the context of a clinical trial, at a dose lower than the
dose currently licensed for chronic lymphocytic leukemia or with chemotherapy other than fludarabine and cyclophosphamide. Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for patients with relapsed or refractory chronic lymphocytic leukemia that has previously been treated with rituximab, unless rituximab has been given as specified above. www.nice.org.uk/TA193

- **Rituximab for the first-line maintenance treatment of follicular non-Hodgkin’s lymphoma (June 2011) NICE TA226**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin’s lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. www.nice.org.uk/TA226

- **Rituximab for the first-line treatment of chronic lymphocytic leukaemia (July 2009) NICE TA174**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with fludarabine and cyclophosphamide, is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia. www.nice.org.uk/TA174

- **Idelalisib for treating chronic lymphocytic leukaemia (October 2015) NICE TA359**
  Rituximab, in combination with idelalisib, is recommended as an option for treatment in adults:
  - who have untreated chronic lymphocytic leukaemia or
  - who have chronic lymphocytic leukaemia when the disease has been treated but has relapsed within 24 months and
  - if the manufacturer provides idelalisib with the discount agreed in the simple discount agreement. Patients who are already receiving idelalisib should continue treatment until they or their clinician consider it appropriate to stop. www.nice.org.uk/guidance/TA359

  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone, is recommended for first-line treatment of CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV.
  The use of rituximab for localised (stage I) disease should be limited to clinical trials. www.nice.org.uk/TA65

**Scottish Medicines Consortium (SMC) Decisions**
*The Scottish Medicines Consortium* has advised (August 2013) that Rituximab (MabThera®) is accepted for restricted use within NHS Scotland, in combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis. It is restricted to use in patients who have relapsed following treatment with cyclophosphamide or who are intolerant to or unable to receive cyclophosphamide.

The *Scottish Medicines Consortium* has advised (June 2014) that subcutaneous rituximab (MabThera®) is accepted for restricted use within NHS Scotland, in accordance with UK licensing, except in the maintenance setting, where use is restricted to patients who have responded to induction therapy with rituximab plus chemotherapy.

**Siltuximab**

- **DRUG ACTION**  Siltuximab is a monoclonal antibody that inhibits interleukin-6 receptor binding.

- **INDICATIONS AND DOSE**
  **Treatment of multicentric Castleman’s disease (MCD) in patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative**
  - **BY INTRAVENOUS INFUSION**
    - Adult: 11 mg/kg every 3 weeks

- **CAUTIONS**
  Patients at increased risk of gastrointestinal perforation—promptly investigate those presenting with symptoms suggestive of gastrointestinal perforation—severe infection—withhold treatment until resolved • treat infection prior to treatment

**CAUTIONS, FURTHER INFORMATION**

- Hypersensitivity reactions • Infusion-related side-effects are reported commonly with siltuximab; resuscitation facilities should be available during treatment.
- Consult product literature for further information about siltuximab cautions.

- **INTERACTIONS**  → Appendix 1 (siltuximab).
  Live vaccines should not be given concurrently or within 4 weeks before starting siltuximab treatment.

- **SIDE-EFFECTS**
  - **Common or very common**  Infusion related side effects
  - **Frequency not known**  Abdominal pain • anaphylaxis • hepatitis B reactivation • hypersensitivity reactions • hypertension • hypertriglyceridaemia • hypoglobulinaemia • increased haemoglobin levels • infections • localised oedema • maculopapular rash • nasopharyngitis • neutropenia • pruritus • renal impairment • thrombocytopenia • upper respiratory tract infection • weight gain

**SIDE-EFFECTS, FURTHER INFORMATION**

- Infusion-related side effects  Siltuximab therapy should be discontinued permanently in the event of a severe infusion-related reaction, anaphylaxis, a severe allergic reaction, or the occurrence of cytokine-release syndrome. Mild to moderate infusion-related reactions may improve by temporarily reducing the rate or stopping the infusion. When restarting treatment, a reduced infusion rate and the administration of antihistamines, paracetamol, and corticosteroids should be considered. Consider discontinuation of siltuximab if more than 2 doses are delayed due to treatment-related toxicities during the first 48 weeks—for full details consult product literature.

- **CONCEPTION AND CONTRACEPTION**  Women of childbearing potential should use effective contraception during and for 3 months after treatment.

- **PREGNANCY**  Manufacturer advises avoid unless potential benefit outweighs risk.

- **BREAST FEEDING**  Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**  Use with caution in hepatic impairment.

- **MONITORING REQUIREMENTS**
  - Monitor neutrophil and platelet count, and haemoglobin levels prior to each dose of siltuximab treatment for the
first 12 months and thereafter prior to every third dosing cycle. Consider delaying treatment if required neutrophil, platelet, and haemoglobin levels not achieved—consult product literature for details.

- **Monitor for infection during treatment.**

### DIRECTIONS FOR ADMINISTRATION

**For intravenous infusion** (Sylvant®), give intermittently in Glucose 5%. Allow vials to reach room temperature over approximately 30 minutes, then reconstitute each 100 mg vial with 5.2 mL of water for injection, and each 400 mg vial with 20 mL of water for injection, to produce a 20 mg/mL solution. Gently swirl without shaking to dissolve. Further dilute to 250 mL with glucose 5% and gently mix. Use within 6 hours of dilution and give over 60 minutes using an administration set lined with polyvinyl chloride or polyurethane, through a low-protein binding in-line 0.2 micron filter.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  
  - Siltuximab 100 mg Sylvant 100mg powder for concentrate for solution for infusion vials | 1 vial £415.00 (Hospital only)
  
  - Siltuximab 400 mg Sylvant 400mg powder for concentrate for solution for infusion vials | 1 vial £1,661.00 (Hospital only)

### Trastuzumab

**INDICATIONS AND DOSE**

Treatment of early breast cancer which overexpresses human epidermal growth factor receptor-2 (HER2) (initiated by a specialist) | Treatment of metastatic breast cancer in patients with HER2-positive tumours who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (in combination with paclitaxel or docetaxel) (initiated by a specialist) | Treatment of metastatic breast cancer in postmenopausal patients with hormone-receptor positive HER2-positive tumours not previously treated with trastuzumab (in combination with an aromatase inhibitor) (initiated by a specialist) | **BY INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INJECTION**

- **Adults:** (consult product literature or local protocols)

  - **Monotherapy for metastatic breast cancer in patients with tumours that overexpress HER2 who have received at least 2 chemotherapy regimens including, where appropriate, an anthracycline and a taxane (initiated by a specialist)**

  - **BY INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INJECTION**

  - **Adults:** Women with oestrogen-receptor-positive breast cancer should also have received hormonal therapy (consult product literature or local protocols)

  - **Treatment of metastatic gastric cancer in patients with HER2-positive tumours who have not received treatment for metastatic gastric cancer (in combination with capecitabine or fluorouracil and cisplatin) (initiated by a specialist)**

  - **BY INTRAVENOUS INFUSION**

  - **Adults:** (consult product literature or local protocols)

- **CONTRA-INDICATIONS**
  
  Severe dyspnoea at rest

- **CAUTIONS**
  
  Coronary artery disease • history of hypertension • symptomatic heart failure • uncontrolled arrhythmias

- **INTERACTIONS**

  - Use with anthracyclines Cardiac function should be monitored closely on the concomitant use of trastuzumab with anthracyclines.

  - **SIDE-EFFECTS**

    - Acne • alopecia • anaphylaxis • angioedema • anxiety • arthralgia • arthritis • asthenia • bone pain • bone marrow suppression • cardiotoxicity • chest pain • chills • depression • diziness • drowsiness • dry eye • dry skin • ecchymosis • extravasation • fever • gastro-intestinal symptoms • headache • hepatitis • hypersensitivity reactions • hypertension • hypothyroidia • hyperuricaemia • hypotension • increased lacrimation • infection • infusion-related side-effects (possibly delayed onset) • insomnia • leg cramps • malaise • mastitis • myalgia • nail disorders • nausea • oedema • oral mucositis • paraesthesia • paresis • peripheral neuropathy • pruritus • pulmonary symptoms (possibly delayed onset) • rash • sweating • taste disturbance • thromboembolism • tremor • tumour lysis syndrome • urticaria • vomiting • weight loss

- **CONCEPTION AND CONTRACEPTION**

  Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **PREGNANCY**

  Manufacturer advises avoid—oligohydramnios reported. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**

  Avoid breast-feeding during treatment and for 7 months afterwards.

- **MONITORING REQUIREMENTS**

  - Cardiotoxicity Monitor cardiac function before and during treatment—for details of monitoring and managing cardiotoxicity, consult product literature.

- **DIRECTIONS FOR ADMINISTRATION**

  Resuscitation facilities should be available during administration of trastuzumab.

- **PRESCRIBING AND DISPENSING INFORMATION**

  When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab is not interchangeable with trastuzumab emtansine.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**

  - Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (June 2012) NICE TA257

    - Lapatinib or trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women of metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2).

    - Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor for this indication should have the option to continue treatment until they and their clinician consider it appropriate to stop.

    - [www.nice.org.uk/TA257](http://www.nice.org.uk/TA257)

  - Guidance on the use of trastuzumab for the treatment of advanced breast cancer (March 2002) NICE TA34

    - Trastuzumab in combination with paclitaxel is recommended as an option for patients with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer, and in whom anthracycline treatment is inappropriate.

    - Trastuzumab monotherapy is recommended as an option for patients with tumours expressing HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen–receptor-positive patients.

    - [www.nice.org.uk/TA34](http://www.nice.org.uk/TA34)
Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (August 2006) NICE TA107
Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as an option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
www.nice.org.uk/TA107

Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (November 2010) NICE TA208
Trastuzumab in combination with cisplatin and capecitabine or fluorouracil is recommended for human epidermal growth factor receptor-2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction in patients who:
- have not received treatment for metastatic disease and
- have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3.
www.nice.org.uk/TA208
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (December 2013) that subcutaneous trastuzumab injection (Herceptin®) is accepted for restricted use within NHS Scotland for the treatment of adults with HER2-positive metastatic breast cancer and early breast cancer, when used within licensed indications excluding use in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

The Scottish Medicines Consortium has advised (September 2015) that trastuzumab solution for infusion (Herceptin®) is accepted for restricted use within NHS Scotland in combination with capecitabine or fluorouracil and cisplatin for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, who have not received prior anti-cancer treatment for their metastatic disease. It is restricted to patients with metastatic gastric cancer whose tumours have HER2 over-expression, as determined by an accurate and validated assay.

Medicinal Forms
There can be variation in the licensing of different medicines containing the same drug.
Solution for injection
- Herceptin (Roche Products Ltd)
  Trastuzumab 120 mg per 1 ml Herceptin 600mg/5ml solution for injection vials | 1 vial £222.20 (Hospital only)
Powder for solution for infusion
- Herceptin (Roche Products Ltd)
  Trastuzumab 150 mg Herceptin 150mg powder for solution for infusion vials | 1 vial £407.40

Trastuzumab emtansine
15-Apr-2016
DRUG ACTION
Trastuzumab emtansine is an antibody-drug conjugate that contains trastuzumab covalently linked to DM1, a cytotoxic microtubule inhibitor.

INDICATIONS AND DOSE
Monotherapy for the treatment of HER2-positive, unresectable, locally advanced or metastatic breast cancer, in adult patients who have previously received trastuzumab and a taxane separately or in combination (initiated by a specialist) | Monotherapy for the treatment of HER2-positive, unresectable, locally advanced or metastatic breast cancer, in adult patients who have developed disease recurrence during or within 6 months of completing adjuvant therapy (initiated by a specialist)

BY INTRAVENOUS INFUSION
- Adult: (consult product literature or local protocols)

CAUTIONS
- Dyspnoea at rest—increased risk of pulmonary events · history of congestive heart failure · patients over 75 years · peripheral neuropathy (temporarily discontinue treatment—consult product literature) · recent history of myocardial infarction · recent history of unstable angina · risk of left ventricular dysfunction—consult product literature for specific risks with trastuzumab treatment · serious arrhythmias

INTERACTIONS
- Appendix 1 (trastuzumab). Caution with concomitant antiagulant medication—increased risk of thrombocytopenia with haemorrhagic events.

SIDE-EFFECTS
- Common or very common Abdominal pain · arthralgia · blurred vision · chills · conjunctivitis · constipation · cough · diarrhoea · dizziness · dry eye · dry mouth · dysgeusia · dyspepsia · dyspnoea · epistaxis · gingival bleeding · haemorrhage · hand-foot syndrome · headache · hypertension · hypokalaemia · increased lacrimation · infusion-related reactions · insomnia · left ventricular dysfunction · malaise · memory impairment · myalgia · nail disorder · peripheral neuropathy · peripheral oedema · pruritus · pyrexia · rash · thrombocytopenia · urinary tract infection · urticaria
- Uncommon Hepatic failure · hepatic toxicity · interstitial lung disease · nodular regenerative hyperplasia · pneumonitis · portal hypertension
- Frequency not known Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

CONCEPTION AND CONTRACEPTION
Effective contraception must be used during and for 6 months after stopping treatment in women and men.

PREGNANCY
Manufacturer advises avoid—oligohydranmios reported with trastuzumab. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

BREAST FEEDING
Manufacturer advises avoid breast-feeding during and for 6 months after treatment.

HEPATIC IMPAIRMENT
Consult product literature for dose modification in cases of abnormal liver function tests. Consult product literature for initiating treatment and discontinuation in cases of abnormal liver function tests.

RENAL IMPAIRMENT
No information available—manufacturer advises caution in severe impairment.

MONITORING REQUIREMENTS
- Monitor hepatic function before each dose.
- Monitor for signs and symptoms of neurotoxicity.
- Monitor closely for infusion-related and hypersensitivity reactions.
Monitor platelet count before each dose and as clinically indicated (consult product literature for treatment modification in thrombocytopenia).

Test cardiac function before treatment and regularly during treatment—delay or discontinue treatment in cases of left ventricular dysfunction.

Monitor for dyspnoea, cough, fatigue and pulmonary infiltrates—discontinue if interstitial lung disease or pneumonitis confirmed (fatal cases reported).

**DIRECTIONS FOR ADMINISTRATION** Resuscitation facilities should be available during administration of trastuzumab emtansine.

**PRESCRIBING AND DISPENSING INFORMATION** When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab emtansine and trastuzumab are not interchangeable.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane (December 2015) NICE TA371

Trastuzumab emtansine is not recommended for treating adults with human epidermal growth factor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

[www.nice.org.uk/TA371](http://www.nice.org.uk/TA371)

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (September 2014) trastuzumab emtansine (Kadcyla®) is not recommended for use within NHS Scotland as monotherapy for the treatment of adult patients with human epidermal growth factor type 2 (HER2)-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- Kadcyla® (Roche Products Ltd) Trastuzumab emtansine 100 mg Kadcyla 100mg powder for concentrate for solution for infusion vials | 1 vial POM £1,641.01
- Trastuzumab emtansine 160 mg Kadcyla 160mg powder for concentrate for solution for infusion vials | 1 vial POM £2,625.62

## 2 Cytotoxic responsive malignancy

### Cytotoxic drugs

#### Overview

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti-cancer activity and the potential to damage normal tissue; most cytotoxic drugs are teratogenic. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neo-adjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of subclinical metastatic disease is known to be high). All cytotoxic drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

Combinations of cytotoxic drugs, as continuous or pulsed cycles of treatment, are frequently more toxic than single drugs but have the advantage in certain tumours of enhanced response, reduced development of drug resistance and increased survival. However for some tumours, single-agent chemotherapy remains the treatment of choice.

Cytotoxic drugs fall into a number of classes, each with characteristic antitumour activity, sites of action, and toxicity. A knowledge of sites of metabolism and excretion is important because impaired drug handling as a result of disease is not uncommon and may result in enhanced toxicity.

### Guidelines for handling cytotoxic drugs

- Trained personnel should reconstitute cytotoxics
- Reconstitution should be carried out in designated pharmacy areas
- Protective clothing (including gloves, gowns, and masks) should be worn
- The eyes should be protected and means of first aid should be specified
- Pregnant staff should avoid exposure to cytotoxic drugs (all females of child-bearing age should be informed of the reproductive hazard)
- Use local procedures for dealing with spillages and safe disposal of waste material, including syringes, containers, and absorbent material
- Staff exposure to cytotoxic drugs should be monitored

#### Intrathecal chemotherapy

A Health Service Circular (HSC 2008/001) provides guidance on the introduction of safe practice in NHS Trusts where intrathecal chemotherapy is administered; written local guidance covering all aspects of national guidance should be available. Support for training programmes is also available. Copies, and further information may be obtained from:

**Department of Health**

PO Box 777
London
SE1 6XH
Fax: 01623 724524
It is also available from the Department of Health website ([www.dh.gov.uk](http://www.dh.gov.uk)).

### Safe systems for cytotoxic medicines

NHS cancer networks have been established across the UK to bring together all stakeholders in all sectors of care, to work collaboratively to plan and deliver high quality cancer services for a given population. NHS cancer networks have websites containing information on local chemotherapy services and treatment.

Safe system requirements:

- cytotoxic drugs for the treatment of cancer should be given as part of a wider pathway of care coordinated by a multidisciplinary team
- cytotoxic drugs should be prescribed, dispensed, and administered only in the context of a written protocol or treatment plan
- injectable cytotoxic drugs should only be dispensed if they are prepared for administration
- oral cytotoxic medicines should be dispensed with clear directions for use

**IMPORTANT SAFETY INFORMATION**

**RISK OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

The National Patient Safety Agency has advised (January 2008) that the prescribing and use of oral cytotoxic medicines should be carried out to the same standard as parenteral cytotoxic therapy.
Doses

Doses of cytotoxic drugs are determined using a variety of different methods including body-surface area or body-weight. Alternatively, doses may be fixed. Doses may be further adjusted following consideration of a patient’s neutrophil count, renal and hepatic function, and history of previous adverse effects to the cytotoxic drug. Doses may also differ depending on whether a drug is used alone or in combination.

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from some of the drug entries in this chapter. However, even where dose statements have been provided, detailed specialist literature, individual hospital chemotherapy protocols, or local cancer networks should be consulted before prescribing, dispensing, or administering cytotoxic drugs.

Prescriptions should not be repeated except on the instructions of a specialist.

Side-effects of cytotoxic drugs

Side-effects common to most cytotoxic drugs are discussed below whilst side-effects characteristic of a particular drug or class of drugs (e.g. neurotoxicity with vinca alkaloids) are mentioned in the appropriate sections. Manufacturers’ product literature, hospital-trust protocols, and cancer-network protocols should be consulted for full details of side-effects associated with individual drugs and specific chemotherapy regimes.

Many side-effects of cytotoxic drugs often do not occur at the time of administration, but days or weeks later. It is therefore important that patients and healthcare professionals can identify symptoms that cause concern and can contact an expert for advice. Toxicities should be accurately recorded using a recognised scoring system such as the Common Toxicity Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute.

Extravasation of intravenous drugs

A number of cytotoxic drugs will cause severe local tissue necrosis if leakage into the extravascular compartment occurs. To reduce the risk of extravasation injury it is recommended that cytotoxic drugs are administered by appropriately trained staff. See information on the prevention and management of extravasation injury.

Oral mucositis

A sore mouth is a common complication of cancer chemotherapy; it is most often associated with fluorouracil p. 815, methotrexate p. 817, and the anthracyclines. It is best to prevent the complication. Good oral hygiene (rinsing the mouth frequently and effective brushing of the teeth with a soft brush 2–3 times daily) is probably beneficial. For fluorouracil p. 815, sucking ice chips during short infusions of the drug is also helpful.

Once a sore mouth has developed, treatment is much less effective. Saline mouthwashes should be used but there is no good evidence to support the use of antiseptic or anti-inflammatory mouthwashes. In general, mucositis is self-limiting but with poor oral hygiene it can be a focus for blood-borne infection.

Tumour lysis syndrome

Tumour lysis syndrome occurs secondary to spontaneous or treatment-related rapid destruction of malignant cells. Patients at risk of tumour lysis syndrome include those with non-Hodgkin’s lymphoma (especially if high grade and bulky disease), Burkitt’s lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia (particularly if high white blood cell counts or bulky disease), and occasionally those with solid tumours. Pre-existing hyperuricaemia, dehydration, and renal impairment are also predisposing factors. Features include hyperkalaemia, hyperuricaemia (see below), and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow. Early identification of patients at risk, and initiation of prophylaxis or therapy for tumour lysis syndrome, is essential.

Hyperuricaemia

Hyperuricaemia, which may be present in high-grade lymphoma and leukaemia, can be markedly worsened by chemotherapy and is associated with acute renal failure. Allopurinol p. 980 should be started 24 hours before treating such tumours and patients should be adequately hydrated. The dose of mercaptopurine p. 816 or azathioprine p. 765 should be reduced if allopurinol needs to be given concomitantly. Febuxostat p. 981 may also be used and should be started 2 days before cytotoxic therapy is initiated.

Rasburicase p. 839, a recombinant urate oxidase, is licensed for hyperuricaemia in patients with haematological malignancy. It rapidly reduces plasma-urate concentration and may be of particular value in preventing complications following treatment of leukaemias or bulky lymphomas.

Bone-marrow suppression

All cytotoxic drugs except vincristine sulfate p. 830 and bleomycin p. 821 cause bone-marrow suppression. This commonly occurs 7 to 10 days after administration, but is delayed for certain drugs, such as carmustine p. 801, lomustine p. 804, and melphalan p. 805. Peripheral blood counts must be checked before each treatment, and doses should be reduced or therapy delayed if bone-marrow has not recovered.

Cytotoxic drugs may be contra-indicated in patients with acute infection; any infection should be treated before, or when starting, cytotoxic drugs.

Fever in a neutropenic patient (neutrophil count less than 1.06 × 10^7/litre) requires immediate broad-spectrum antibacterial therapy. Appropriate bacteriological investigations should be conducted as soon as possible. Patients taking cytotoxic drugs who have signs or symptoms of infection should be advised to seek prompt medical attention. All patients should initially be investigated and treated under the supervision of the appropriate oncology or haematology specialist.

In selected patients, the duration and the severity of neutropenia can be reduced by the use of recombinant human granulocyte-colony stimulating factors.

Symptomatic anaemia is usually treated with red blood cell transfusions. For guidance on the use of erythropoietins in patients with cancer, see MHRA/CHM advice and NICE guidance.

See advice on the use of live vaccines in individuals with impaired immune response, see Vaccines.

Alopecia

Reversible hair loss is a common complication, although it varies in degree between drugs and individual patients. No pharmacological methods of preventing this are available.
Thromboembolism
Venous thromboembolism can be a complication of cancer itself, but chemotherapy increases the risk.

Pregnancy and reproductive function
Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

Exclude pregnancy before treatment with cytotoxic drugs. Contraceptive advice should be given before cytotoxic therapy begins—women of childbearing age should use effective contraception during and after treatment.

Regimens that do not contain an alkylating drug or procarbazine may have less effect on fertility, but those with an alkylating drug or procarbazine carry the risk of causing permanent male sterility (there is no effect on potency). Pretreatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause. No increase in fetal abnormalities or abortion rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.

Nausea and vomiting
Nausea and vomiting cause considerable distress to many patients who receive chemotherapy and to a lesser extent abdominal radiotherapy, and may lead to refusal of further treatment; prophylaxis of nausea and vomiting is therefore extremely important. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Patients vary in their susceptibility to drug-induced nausea and vomiting; those affected more often include women, patients under 50 years of age, anxious patients, and those who experience motion sickness. Susceptibility also increases with repeated exposure to the cytotoxic drug. Drugs may be divided according to their emetogenic potential and some examples are given below, but the symptoms vary according to the dose, to other drugs administered and to the individual’s susceptibility to emetogenic stimuli.

Mildly emetogenic treatment—fluorouracil, etoposide p. 824, methotrexate p. 817 (less than 100 mg/m², low dose in children), the vinca alkaloids, and abdominal radiotherapy.

Moderately emetogenic treatment—the taxanes, doxorubicin hydrochloride p. 807, intermediate and low doses of cyclophosphamide p. 802, mitoxantrone p. 809, and high doses of methotrexate (0.1–1.2 g/m²).

Highly emetogenic treatment—cisplatin p. 823, dacarbazine p. 803, and high doses of cyclophosphamide.

Prevention of acute symptoms
For patients at low risk of emesis, pretreatment with dexamethasone p. 618 or lorazepam p. 317 may be used.

For patients at high risk of emesis, a SHT3-receptor antagonist, usually given by mouth in combination with dexamethasone and the neurokinin receptor antagonist aprepitant p. 404 is effective.

Prevention of delayed symptoms
For delayed symptoms associated with moderately emetogenic chemotherapy, a combination of dexamethasone and SHT3-receptor antagonist is effective; for highly emetogenic chemotherapy, a combination of dexamethasone and aprepitant is effective. Metoclopramide hydrochloride p. 403 is also licensed for delayed chemotherapy-induced nausea and vomiting.

Prevention of anticipatory symptoms
Good symptom control is the best way to prevent anticipatory symptoms. Lorazepam can be helpful for its amnesic, sedative, and anxiolytic effects.

Treatment for cytotoxic-induced side effects
Anthracycline side-effects
Anthracycline-induced cardiotoxicity
The anthracycline cytotoxic drugs are associated with dose-related, cumulative, and potentially life-threatening cardiotoxic side-effects.

Anthracycline extravasation
Local guidelines for the management of extravasation should be followed or specialist advice sought.

See further information on the prevention and management of extravasation injury.

Chemotherapy-induced mucositis and myelosuppression
Folinic acid p. 838 (given as calcium folinate) is used to counteract the folate-antagonist action of methotrexate p. 817 and thus speed recovery from methotrexate-induced mucositis or myelosuppression (‘folinic acid rescue’). Folinic acid is also used in the management of methotrexate overdose, together with other measures to maintain fluid and electrolyte balance, and to manage possible renal failure.

Folinic acid does not counteract the antibacterial activity of folate antagonists such as trimethoprim p. 529.

When folinic acid and fluorouracil p. 815 are used together in metastatic colorectal cancer the response-rate improves compared to that with fluorouracil alone.

The calcium salt of levofolinic acid p. 839, a single isomer of folinic acid, is also used for rescue therapy following methotrexate administration, for cases of methotrexate overdose, and for use with fluorouracil for colorectal cancer. The dose of calcium levofolinate is generally half that of calcium folinate.

The disodium salts of folinic acid and levofolinic acid are also used for rescue therapy following methotrexate therapy, and for use with fluorouracil for colorectal cancer.

Urothelial toxicity
Haemorrhagic cystitis is a common manifestation of urothelial toxicity which occurs with the oxazaphosphorines, cyclophosphamide p. 802 and ifosfamide p. 804; it is caused by the metabolite acrolein. Mesna p. 838 reacts specifically with this metabolite in the urinary tract, preventing toxicity. Mesna is used routinely (preferably by mouth) in patients receiving ifosfamide, and in patients receiving cyclophosphamide by the intravenous route at a high dose (e.g. more than 2 g) or in those who experienced urothelial toxicity when given cyclophosphamide previously.

Anthracyclines and other cytotoxic antibiotics
Drugs in this group are widely used. Many cytotoxic antibiotics act as radiomimetics and simultaneous use of radiotherapy should be avoided because it may markedly increase toxicity. Daunorubicin p. 807, doxorubicin hydrochloride p. 807, epirubicin hydrochloride p. 808 andidarubicin hydrochloride p. 809 are anthracycline antibiotics. Mitoxantrone p. 809 is an anthracycline derivative. Doxorubicin hydrochloride is available as both conventional and liposomal formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable. Conventional doxorubicin hydrochloride is used to treat the acute leukaemias, Hodgkin’s and non-Hodgkin’s lymphomas, paediatric malignancies, and some solid tumours including breast cancer.

Epirubicin hydrochloride is structurally related to doxorubicin hydrochloride and clinical trials suggest that it is as effective in the treatment of breast cancer.
Idarubicin hydrochloride has general properties similar to those of doxorubicin hydrochloride; it is mostly used in the treatment of haematological malignancies.

Daunorubicin also has general properties similar to those of doxorubicin hydrochloride.

Mitoxantrone is structurally related to doxorubicin hydrochloride.

Pixantrone p. 810 is licensed as monotherapy for the treatment of refractory or multiply relapsed aggressive non-Hodgkin B-cell lymphomas, although the benefits of using it as a fifth-line or greater chemotherapy in refractory patients has not been established.

Bleomycin p. 821 is given intravenously or intramuscularly to treat metastatic germ cell cancer and, in some regimens, non-Hodgkin’s lymphoma.

Dactinomycin is principally used to treat paediatric cancers. Its side-effects are similar to those of doxorubicin, except that cardiac toxicity is not a problem.

Mitomycin p. 822 is given intravenously to treat upper gastrointestinal and breast cancers and by bladder instillation for superficial bladder tumours. It causes delayed bone marrow toxicity and therefore it is usually administered at 6-weekly intervals.

**Antimetabolites**

Antimetabolites are incorporated into new nuclear material or combine irreversibly with cellular enzymes, preventing normal cellular division.

**Alkylating drugs**

Extensive experience is available with these drugs, which are among the most widely used in cancer chemotherapy. They act by damaging DNA, thus interfering with cell replication.

Cyclophosphamide is used mainly in combination with other agents for treating a wide range of malignancies, including some leukaemias, lymphomas, and solid tumours (e.g. breast and lung cancer).

Vinorelbine p. 831 is a semi-synthetic vinca alkaldoid. See also, role of vinorelbine in the treatment of breast cancer.

**Contraindications**

Jaundice - low leucocyte count - low platelet count - major surgery less than 30 days before start of treatment - severe bone marrow suppression

**Cautions** Avoid in acute porphyrias p. 930 - cardiac disorders—monitor serum potassium and ECG

**Interactions** Appendix 1 (bendamustine).

**Side-effects**

Acute circulatory failure - drowsiness - sweating - voice changes

**Very rare** Anticholinergic syndrome - ataxia - cardiac failure - encephalitis - haemorrhage - hypertension - hypokalaemia - hypotension - infection - insomnia - malaise - pain - palpitation - pyrexia - respiratory dysfunction

**Uncommon** Pericardial effusion

**Rare** Acute circulatory failure - drowsiness - sweating - voice changes

**Frequency not known** Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - male sterility - nausea - oral mucositis - premature menopause - secondary malignancy - Stevens-Johnson syndrome - thromboembolism - toxic epidermal necrolysis - tumour lysis syndrome - vomiting

**Side-effects, further information**

Secondary malignancy - Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

**Conception and contraception** Effective contraception is required during treatment in men or women, and for 6 months after treatment in men. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**Pregnancy** Avoid (teratogenic and mutagenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**Breast feeding** Discontinue breast-feeding.

**Hepatic impairment** Consider a 30% dose reduction in moderate impairment. Avoid in severe impairment.

**Renal impairment** No information available on use in patients with creatinine clearance less than 10 mL/minute.

**National funding/access decisions**

NICE technology appraisals (TAs)

**Bendamustine hydrochloride**

**Indications and dose**

Treatment of chronic lymphocytic leukaemia | Treatment of non-Hodgkin’s lymphoma | Treatment of multiple myeloma

**By intravenous infusion**

**Adult:** (consult local protocol)

**Contra-indications**

**Caution** Avoid in acute porphyrias p. 930 - cardiac disorders—monitor serum potassium and ECG

**Interactions** Appendix 1 (bendamustine).

**Side-effects**

Acute circulatory failure - drowsiness - sweating - voice changes

**Very rare** Anticholinergic syndrome - ataxia - cardiac failure - encephalitis - haemorrhage - hypertension - hypokalaemia - hypotension - infection - insomnia - malaise - pain - palpitation - pyrexia - respiratory dysfunction

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**Side-effects, further information**

Secondary malignancy - Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

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**Breast feeding** Discontinue breast-feeding.

**Hepatic impairment** Consider a 30% dose reduction in moderate impairment. Avoid in severe impairment.

**Renal impairment** No information available on use in patients with creatinine clearance less than 10 mL/minute.

**National funding/access decisions**

NICE technology appraisals (TAs)

**Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (February 2011)** NICE TA216

Bendamustine is recommended as an option for the treatment of chronic lymphocytic leukaemia in patients for whom fludarabine combination chemotherapy is not appropriate.

www.nice.org.uk/TA216
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (March 2011) that bendamustine (Levact™) is accepted for restricted use within NHS Scotland for the treatment of chronic lymphocytic leukaemia in patients for whom fludarabine combination chemotherapy is not appropriate.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**
    - **Bendamustine hydrochloride (Non-proprietary)**
    - **Bendamustine hydrochloride 25 mg** Bendamustine 25mg powder for concentrate for solution for infusion vials 1 vial (POM) £6.85–£65.98 | 5 vial (POM) £312.53–£347.26 (Hospital only) | 20 vial (POM) £1,241.14 (Hospital only)
    - **Bendamustine hydrochloride 100 mg** Bendamustine 100mg powder for concentrate for solution for infusion vials 1 vial (POM) £27.77–£262.02 | 5 vial (POM) £1,241.14–£1,379.04 (Hospital only)
    - **Levact** (Napp Pharmaceuticals Ltd.)
    - **Bendamustine hydrochloride 25 mg** Levact 25mg powder for concentrate for solution for infusion vials 1 vial (POM) £347.26 (Hospital only)
    - **Bendamustine hydrochloride 100 mg** Levact 100mg powder for concentrate for solution for infusion vials 1 vial (POM) £1,379.04 (Hospital only)

**Busulfan**
(Busulphan)

- **INDICATIONS AND DOSE**
  Chronic myeloid leukaemia, induction of remission
  > **BY MOUTH**
  > Adult: 60 micrograms/kg daily (max. per dose 4 mg); maintenance 0.5–2 mg daily

  Conditioning treatment before haematopoietic progenitor cell transplantation
  > **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  > Adult: (consult local protocol)

  Conditioning treatment before haematopoietic progenitor cell transplantation in patients who are candidates for a reduced-intensity conditioning (RIC) regimen
  > **BY INTRAVENOUS INFUSION**
  > Adult: (consult local protocol)

- **DOSES AT EXTREMES OF BODY-WEIGHT**
  Dose may need to be calculated based on body surface area or adjusted ideal body weight in obese patients—consult product literature.

- **IMPORTANT SAFETY INFORMATION**
  **RISKS OF INCOMPLETE DOSING OF ORAL ANTI-CANCER MEDICINES**
  See Cytotoxic drugs p. 797.

- **CAUTIONS**
  Avoid in acute porphyrias p. 930 · high dose (antiepileptic prophylaxis required) · history of seizures (antiepileptic prophylaxis required) · ineffective once in blast crisis phase · previous progenitor cell transplant (increased risk of hepatic veno-occlusive disease) · previous radiation therapy (increased risk of hepatic veno-occlusive disease) · risk of second malignancy · three or more cycles of chemotherapy (increased risk of hepatic veno-occlusive disease)

- **INTERACTIONS**
  > Appendix 1 (busulfan).

- **SIDE-EFFECTS**
  **COMMON SIDE-EFFECTS**
  Cardiac tamponade in thalassaemia · hepatic fibrosis · hepatic veno-occlusive disease · hepatotoxicity · hyperbilirubinaemia · jaundice · pneumonia · skin hyperpigmentation
  **RARE**
  Aplastic anaemia · seizures · visual disturbances
  **VERY RARE**
  Gynaecomastia · myasthenia gravis

- **FREQUENCY NOT KNOWN**
  Alopecia · bone-marrow suppression · hyperuricaemia · irreversible bone-marrow aplasia · lung toxicity · male sterility · nausea · oral mucositis · premature menopause · secondary malignancy · thromboembolism · tumour lysis syndrome · vomiting

**Carmustine**

- **INDICATIONS AND DOSE**
  Multiple myeloma · Non-Hodgkin’s lymphomas · Brain tumours
  > **BY INTRAVENOUS INFUSION**
  > Adult: (consult product literature)

  Recurrent glioblastoma multiforme as an adjunct to surgery · High-grade malignant glioma as adjunctive treatment to surgery and radiotherapy
  > **BY INTRALESIONAL INJECTION**
  > Adult: (consult product literature)

- **CAUTIONS**
  Avoid in acute porphyrias p. 930

- **INTERACTIONS**
  > Appendix 1 (carmustine).

- **SIDE-EFFECTS**
  **GENERAL SIDE-EFFECTS**
  Alopecia · bone-marrow suppression (delayed) · hyperuricaemia · irritant to tissues · male sterility · nausea · oral mucositis · premature menopause · secondary malignancy · thromboembolism · tumour lysis syndrome · vomiting

  **SPECIFIC SIDE-EFFECTS**
  > With intravenous use: Pulmonary fibrosis (delayed) · renal damage (cumulative)
Immune system and malignant disease

**SIDE-EFFECTS, FURTHER INFORMATION**

- Secondary malignancy: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **CONCEPTION AND CONTRACEPTION**: Manufacturer advises effective contraception during treatment in men or women. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

- **PREGNANCY**: Avoid (teratogenic and embryotoxic in animals). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

- **BREAST FEEDING**: Discontinue breast-feeding.

- **SIDE-EFFECTS**

- **CAUTIONS**: Avoid in acute porphyrias p. 930; history of epilepsy (increased seizure risk)

- **SIDE-EFFECTS**

- Uncommon: Skin rash

- Very rare: Male sterility (in prepubertal and pubertal males)

- Frequency not known: Alopecia; bone-marrow suppression; hyperuricaemia; nausea; oral mucositis; premature menopause; secondary malignancy; Stevens-Johnson syndrome; thromboembolism; toxic epidermal necrolysis; tumour lysis syndrome; vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**

- Secondary malignancy: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- Skin reactions: If a rash occurs further chlorambucil is contra-indicated and cyclophosphamide is substituted.

- **CONCEPTION AND CONTRACEPTION**: Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

- **PREGNANCY**: Avoid. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

- **BREAST FEEDING**: Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**: Manufacturer advises consider dose reduction in severe impairment—limited information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)**
  - Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (June 2007) NICE TA212
  - Carmustine implants are an option for the treatment of newly diagnosed high-grade (Grade 3 or 4) glioma only for patients in whom at least 90% of the tumour has been resected. Carmustine implants should only be used within specialist centres. www.nice.org.uk/TA212

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Implant**

  - Glialdel (Eisai Ltd)

    - Carmustine 7.7 mg: Glialdel 7.7mg implant | 8 device £5,203.00 (Hospital only)

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**Chlorambucil**

- **INDICATIONS AND DOSE**

  - Some lymphomas and chronic leukaemias (used either alone or in combination therapy)

  - **BY MOUTH**

  - Adult: (consult local protocol)

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**

    - Chlorambucil (Non-proprietary)

      - Chlorambucil 2 mg: Chlorambucil 2mg tablets | 25 tablet £42.87 DT price = £42.87

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**Cyclophosphamide**

- **INDICATIONS AND DOSE**

  - **Rheumatoid arthritis with severe systemic manifestations**

    - **BY MOUTH**

    - Adult: 1–1.5 mg/kg daily

  - **Severe systemic rheumatoid arthritis** / **Other connective tissue diseases (especially with active vasculitis)**

    - **BY INTRAVENOUS INJECTION**

    - Adult: 0.5–1 g every 2 weeks, then reduced to 0.5–1 g every month, frequency adjusted according to clinical response and haematological monitoring. To be given with prophylactic mesna

- **UNLICENSED USE**: Not licensed for rheumatoid arthritis with severe systemic manifestations.

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**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.
**CONTRA-INDICATIONS** Haemorrhagic cystitis

**CAUTIONS** Avoid in acute porphyrias p. 930 - diabetes mellitus - previous or concurrent mediastinal irradiation — risk of cardiotoxicity

**INTERACTIONS** → Appendix 1 (cyclophosphamide).

**SIDE-EFFECTS**

GENERAL SIDE-EFFECTS
* Common or very common  Anorexia - cardiotoxicity at high doses - disturbances of carbohydrate metabolism - inappropriate secretion of anti-diuretic hormone - interstitial pulmonary fibrosis - pancreatitis - pigmentation of nails - pigmentation of soles - urothelial toxicity

* Rare  Hepatotoxicity - renal dysfunction

* Frequency not known  Alopecia - bone-marrow suppression - haemorrhagic cystitis - hyperuricaemia - male sterility - nausea - oral mucositis - premature menopause - secondary malignancy - thromboembolism - tumour lysis syndrome - vomiting

**SPECIFIC SIDE-EFFECTS**

* With intravenous use  Extravasation

**SIDE-EFFECTS, FURTHER INFORMATION**

Haemorrhagic cystitis  A urinary metabolite of cyclophosphamide, acrolein, can cause haemorrhagic cystitis; this is a rare but serious complication; increased fluid intake for 24–48 hours after intravenous injection, can prevent this complication. When high-dose therapy (e.g. more than 2 g intravenously) is used or when the patient is considered to be at high risk of cystitis (e.g. because of pelvic irradiation), mesna (given initially intravenously then by mouth) can also help prevent cystitis.

Secondary malignancy  Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

**CONCEPTION AND CONTRACEPTION**  Manufacturer advises effective contraception during and for at least 3 months after treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY**  Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**  Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**  Reduce dose—consult local treatment protocol for details.

**RENAI IMPAIRMENT**  Reduce dose if serum creatinine concentration greater than 120 micromol/litre.

**DIRECTIONS FOR ADMINISTRATION**  For intravenous infusion (cyclophosphamide injection; Baxter) give via drip tubing in Glucose 5% or Sodium chloride 0.9%; reconstitute 500 mg with 25 mL sodium chloride 0.9%; reconstitute 1 g with 50 mL sodium chloride 0.9%.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Cyclophosphamide (Non-proprietary)**
  - Cyclophosphamide (as Cyclophosphamide monohydrate) 50 mg  $\text{DT price } = \text{£}139.00$
  - Cyclophosphamide (as Cyclophosphamide monohydrate) 100 mg  $\text{DT price } = \text{£}180.00$
  - Cyclophosphamide (as Cyclophosphamide monohydrate) 200 mg  $\text{DT price } = \text{£}220.00$

- **Cyclophosphamide (as Cyclophosphamide monohydrate) 500 mg**  $\text{DT price } = \text{£}375.00$

- **Cyclophosphamide (as Cyclophosphamide monohydrate) 1 gram**  $\text{DT price } = \text{£}700.00$

**Dacarbazine**

**INDICATIONS AND DOSE**

Metastatic melanoma | Soft-tissue sarcomas (combination therapy) | Hodgkin's disease (combination therapy)

- BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION
- Adult: (consult local protocol)

**CAUTIONS**  Caution in handling—irritant to tissues

**INTERACTIONS** → Appendix 1 (dacarbazine).

**SIDE-EFFECTS**

* Rare  Irritant to skin - irritant to tissues - liver necrosis due to hepatic vein thrombosis

* Frequency not known  Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - myelosuppression - oral mucositis - severe nausea - severe vomiting - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION**  Ensure effective contraception during and for at least 6 months after treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY**  Avoid (carcinogenic and teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**  Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**  Dose reduction may be required in combined renal and hepatic impairment. Avoid in severe impairment.

**RENAI IMPAIRMENT**  Dose reduction may be required in combined renal and hepatic impairment. Avoid in severe impairment.

**PRESCRIBING AND DISPENSING INFORMATION**  Dacarbazine is a component of a commonly used combination for Hodgkin's disease (ABVD—doxorubicin [previously Adriamycin®], bleomycin, vinblastine, and dacarbazine).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Dacarbazine (Non-proprietary)**
  - Dacarbazine (as Dacarbazine citrate) 100 mg  $\text{DT price } = \text{£}160.00$
  - Dacarbazine (as Dacarbazine citrate) 200 mg  $\text{DT price } = \text{£}180.00$
  - Dacarbazine (as Dacarbazine citrate) 500 mg  $\text{DT price } = \text{£}375.00$
  - Dacarbazine (as Dacarbazine citrate) 1 gram  $\text{DT price } = \text{£}700.00$
Estramustine phosphate

- **INDICATIONS AND DOSE**
  - Prostate cancer
  - **BY MOUTH**
  - Adult: Initially 560–840 mg daily in divided doses; maintenance 140–1400 mg daily in divided doses

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 797.

- **CONTRA-INDICATIONS**
  - Peptic ulceration
  - Severe cardiovascular disease
  - Thromboembolic disorders

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930
  - Cardiac failure
  - Gynaecomastia

- **INTERACTIONS** → Appendix 1 (estramustine).
- **SIDE-EFFECTS**
  - Rare Angioedema
  - Frequency not known Alopecia

**SIDE-EFFECTS, FURTHER INFORMATION**

- Secondary malignancy
  - Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- CONCEPTION AND CONTRACEPTION
  - Men should use contraceptive methods during treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution. Avoid in severe impairment. In hepatic impairment, manufacturer advises regular liver function tests.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution.

- **DIRECTIONS FOR ADMINISTRATION**
  - Each dose should be taken not less than 1 hour before or 2 hours after meals and should not be taken with products containing calcium, magnesium or aluminium, including dairy products and antacid medication.

- **PATIENT AND CARER ADVICE**
  - Patients should be given advice on how to administer estramustine capsules.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - CAUTIONARY AND ADVISORY LABELS 5, 23
  - **Estracyt** (Pfizer Ltd)
    - Estramustine phosphate (as Estramustine sodium phosphate)
    - 140 mg
  - Estracyt 140mg capsules | 100 capsule [Pack] £171.28

Ifosfamide

- **INDICATIONS AND DOSE**
  - Malignant disease
  - **BY INTRAVENOUS INFUSION**
  - Adult: (consult local protocol)

**CONTRA-INDICATIONS**

- Acute infection
- Urinary-tract infection
- Urinary-tract obstruction
- Urothelial damage

**CAUTIONS**

- Avoid in acute porphyrias p. 930

**SIDE-EFFECTS**

- Acute porphyrias
- Pregnancy and reproductive function
  - Men should use oral contraceptive methods during treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Secondary malignancy
  - Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

**CONCEPTION AND CONTRACEPTION**

- Men should use contraceptive methods during treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**MEDICINAL FORMS**

<table>
<thead>
<tr>
<th>Powder for solution for injection</th>
</tr>
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<tbody>
<tr>
<td>Ifosfamide (Non-proprietary)</td>
</tr>
<tr>
<td>Ifosfamide 1 gram</td>
</tr>
<tr>
<td>1 gram powder for concentrate for solution</td>
</tr>
<tr>
<td>Ifosfamide 2 gram</td>
</tr>
<tr>
<td>2 gram powder for concentrate for solution</td>
</tr>
</tbody>
</table>

Lomustine

- **DRUG ACTION**
  - Lomustine is a lipid-soluble nitrosourea.

- **INDICATIONS AND DOSE**
  - Hodgkin's disease resistant to conventional therapy
  - Hodgkin's disease resistant to conventional therapy
  - **BY MOUTH**
  - Adult: 120–130 mg/m² every 6–8 weeks, dose is for when lomustine is used alone

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 797.

- **CONTRA-INDICATIONS**
  - Coeliac disease

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **INTERACTIONS** → Appendix 1 (lomustine).

- **SIDE-EFFECTS**
  - Alopecia
  - Bone-marrow suppression
  - Cardiac failure
  - Gynaecomastia
mucositis - permanent bone marrow damage (with prolonged use) - premature menopause - secondary malignancy - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Secondary malignancy**: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.
- **CONCEPTION AND CONTRACEPTION**: Manufacturer advises adequate contraception during treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **PREGNANCY**: Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING**: Discontinue breast-feeding.
- **RENAL IMPAIRMENT**: Reduce dose initially (consult product literature).
- **MONITORING REQUIREMENTS**: Monitor full blood count before and throughout treatment.
- **MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug.

**Melphalan**

- **INDICATIONS AND DOSE**
  - **Multiple myeloma**
    - Adult: 150 micrograms/kg daily for 4 days, dose to be repeated every 6 weeks, dose may vary according to regimen
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - Adult: (consult product literature)
  - **Polycythaemia vera**
    - **BY MOUTH**
      - Adult: Initially 6–10 mg daily for 5–7 days, then reduced to 2–4 mg daily until satisfactory response, then reduced to 2–6 mg once weekly
  - **Localised malignant melanoma of the extremities**
    - **BY REGIONAL ARTERIAL PERFUSION**
      - Adult: (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

- **CAUTIONS**: Avoid in acute porphyrias p. 930
- **INTERACTIONS**: Appendix 1 (melphalan).
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Rare**: Intestinal pneumonitis - life threatening pulmonary fibrosis
    - **Frequency not known**: Alopecia - bone-marrow suppression (delayed) - hyperuricaemia - male sterility - nausea - oral mucositis - premature menopause - secondary malignancy - thromboembolism - tumour lysis syndrome - vomiting
  - **SPECIFIC SIDE-EFFECTS**
    - With intravenous use: Extravasation

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Secondary malignancy**: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.
- **CONCEPTION AND CONTRACEPTION**: Manufacturer advises adequate contraception during treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **PREGNANCY**: Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING**: Discontinue breast-feeding.
- **RENAL IMPAIRMENT**: Reduce dose initially (consult product literature).
- **MONITORING REQUIREMENTS**: Monitor full blood count before and throughout treatment.
- **MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug.

**Temozolomide**

- **INDICATIONS AND DOSE**
  - **Newly diagnosed glioblastoma multiforme in adults** (in combination with radiotherapy) and subsequently as monotherapy / Second-line treatment of malignant glioma in adults
    - **BY MOUTH**
      - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

- **CAUTIONS**: Pneumocystis jirovecii pneumonia—consult product literature for monitoring and prophylaxis requirements
- **INTERACTIONS**: Appendix 1 (temozolomide).
- **SIDE-EFFECTS**
  - Alopecia - bone-marrow suppression - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting
  - **SIDE-EFFECTS, FURTHER INFORMATION**: For further information on side-effects consult product literature.
- **CONCEPTION AND CONTRACEPTION**: Manufacturer advises adequate contraception during treatment. Men should avoid fathering a child during and for at least 6 months after treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **PREGNANCY**: Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING**: Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT**: Use with caution in severe impairment—no information available.
- **RENAL IMPAIRMENT**: Manufacturer advises caution—no information available.
METHOTREXATE

- **INDICATIONS AND DOSE**
  - Conditioning treatment before haematopoietic stem cell transplantation in the treatment of haematological disease or solid tumours, in combination with other chemotherapy
  - **BY INTRAVENOUS INJECTION**
  - Adult: (consult local protocol)

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **INTERACTIONS**
  - Appendix 1 (thiotepa).

- **SIDE-EFFECTS**
  - Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · male sterility · nausea · oral mucositis · premature menopause · secondary malignancy · thromboembolism · tumour lysis syndrome · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Secondary malignancy · Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **PREGNANCY**
  - Avoid (teratogenic and embryotoxic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - British National Formulary 73 (BNF 73)
  - Scottish Medicines Consortium (SMC) Decisions

  - The Scottish Medicines Consortium has advised (June 2012) that thiotepa (Tepadina®) is not recommended for use within NHS Scotland in combination with other chemotherapy as conditioning treatment in adults or children with haematological diseases, or solid tumours prior to haematopoietic stem cell transplantation.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 23, 25
  - **Temozolomide (Non-proprietary)**
    - Temozolomide 5 mg Temozolomide 5mg capsules | 5 capsule (POM) £16.44
    - Temozolomide 20 mg Temozolomide 20mg capsules | 5 capsule (POM) £65.74
    - Temozolomide 100 mg Temozolomide 100mg capsules | 5 capsule (POM) £328.70
    - Temozolomide 140 mg Temozolomide 140mg capsules | 5 capsule (POM) £455.00
    - Temozolomide 180 mg Temozolomide 180mg capsules | 5 capsule (POM) £586.00
    - Temozolomide 250 mg Temozolomide 250mg capsules | 5 capsule (POM) £814.00
  - **Temodal** (Merck Sharp & Dohme Ltd)
    - Temozolomide 5 mg Temozolomide 5mg capsules | 5 capsule (POM) £10.59 (Hospital only)
    - Temozolomide 20 mg Temozolomide 20mg capsules | 5 capsule (POM) £42.35 (Hospital only)
    - Temozolomide 100 mg Temozolomide 100mg capsules | 5 capsule (POM) £211.77 (Hospital only)
    - Temozolomide 140 mg Temozolomide 140mg capsules | 5 capsule (POM) £296.48 (Hospital only)
    - Temozolomide 180 mg Temozolomide 180mg capsules | 5 capsule (POM) £381.19 (Hospital only)
    - Temozolomide 250 mg Temozolomide 250mg capsules | 5 capsule (POM) £529.43 (Hospital only)
  - **Temomedac** (median UK)
    - Temozolomide 5 mg Temomedac 5mg capsules | 5 capsule (POM) £16.12
    - Temozolomide 20 mg Temomedac 20mg capsules | 5 capsule (POM) £64.49
    - Temozolomide 100 mg Temomedac 100mg capsules | 5 capsule (POM) £322.43
    - Temozolomide 140 mg Temomedac 140mg capsules | 5 capsule (POM) £451.40
    - Temozolomide 180 mg Temomedac 180mg capsules | 5 capsule (POM) £580.37
    - Temozolomide 250 mg Temomedac 250mg capsules | 5 capsule (POM) £806.08

- **Thiotepa**

- **INDICATIONS AND DOSE**
  - Conditioning treatment before haematopoietic stem cell transplantation in the treatment of haematological disease or solid tumours, in combination with other chemotherapy
  - **BY INTRAVENOUS INJECTION**
  - Adult: (consult local protocol)

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **INTERACTIONS**
  - Appendix 1 (thiotepa).

- **SIDE-EFFECTS**
  - Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · male sterility · nausea · oral mucositis · premature menopause · secondary malignancy · thromboembolism · tumour lysis syndrome · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Secondary malignancy · Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **PREGNANCY**
  - Avoid (teratogenic and embryotoxic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions

  - The Scottish Medicines Consortium has advised (June 2012) that thiotepa (Tepadina®) is not recommended for use within NHS Scotland in combination with other chemotherapy as conditioning treatment in adults or children with haematological diseases, or solid tumours prior to haematopoietic stem cell transplantation.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **Tepadina** (Adienne Pharma & Biotech)
    - Thiotepa 15 mg Thiotepa 15mg powder for concentrate for solution for infusion vials | 1 vial (POM) no price available
    - Thiotepa 100 mg Thiotepa 100mg powder for concentrate for solution for infusion vials | 1 vial (POM) no price available

- **Tresosulfan**

- **INDICATIONS AND DOSE**
  - Ovarian cancer
  - **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAPERITONEAL INSTILLATION**
  - Adult: (consult product literature)

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **SIDE-EFFECTS**
  - Common or very common Skin pigmentation
  - Rare Allergic alveolitis · haemorrhagic cystitis · pulmonary fibrosis
  - Frequency not known Alopecia · bone-marrow suppression · extravasation of intravenous drugs · hyperuricaemia · nausea · oral mucositis · premature menopause · secondary malignancy · thromboembolism · tumour lysis syndrome · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Secondary malignancy · Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **PREGNANCY**
  - Avoid (teratogenic and embryotoxic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

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    - Thiotepa 100 mg Thiotepa 100mg powder for concentrate for solution for infusion vials | 1 vial (POM) no price available

- **Tresosulfan**

- **INDICATIONS AND DOSE**
  - Ovarian cancer
  - **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAPERITONEAL INSTILLATION**
  - Adult: (consult product literature)

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **SIDE-EFFECTS**
  - Common or very common Skin pigmentation
  - Rare Allergic alveolitis · haemorrhagic cystitis · pulmonary fibrosis
  - Frequency not known Alopecia · bone-marrow suppression · extravasation of intravenous drugs · hyperuricaemia · nausea · oral mucositis · premature menopause · secondary malignancy · thromboembolism · tumour lysis syndrome · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Secondary malignancy · Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.
malignancy • thromboembolism • tumour lysis syndrome • vomiting

SIDE-EFFECTS, FURTHER INFORMATION
- Secondary malignancy Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.
- CONCEPTION AND CONTRACEPTION Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- PREGNANCY Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- BREAST FEEDING Discontinue breast-feeding.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Capsule
- CAUTIONARY AND ADVISORY LABELS 25
  - Tresulfan (Non-proprietary)
    - Tresulfan 250 mg Tresulfan 250mg capsules | 100 capsule [POM] £622.10–£653.20
- Powder for solution for injection
  - Tresulfan (Non-proprietary)
    - Tresulfan 1 gram Tresulfan 1g powder for solution for injection vials | 5 vial [POM] £269.17
    - Tresulfan 5 gram Tresulfan 5g powder for solution for injection vials | 5 vial [POM] £1,040.17

ANTINEOPLASTIC DRUGS > ANTHRACYCLINES AND RELATED DRUGS

Doxorubicin hydrochloride 10-Jun-2016

Indications and Dose
- Acute leukaemias | Hodgkin’s lymphoma | Non-Hodgkin’s lymphoma | Some solid tumours including breast cancer
  - By intravenous injection
    - Adult: (consult product literature)
- Some papillary bladder tumours (bladder instillation) | Recurrent superficial bladder tumours (bladder instillation) | Transitional cell carcinoma (bladder instillation) | Carcinoma in situ (bladder instillation)
  - By intravesical instillation
    - Adult: (consult product literature)
- CAELYX®
  - For AIDS-related Kaposi’s sarcoma in patients with low CD4 count and extensive mucocutaneous or visceral disease | Advanced ovarian cancer when platinum-based chemotherapy has failed | Progressive multiple myeloma (in combination with bortezomib) in patients who have undergone or are unsuitable for bone-marrow transplantation | Monotherapy for metastatic breast cancer in patients with increased cardiac risk
  - By intravenous injection
    - Adult: (consult product literature)
- MYOCET®
  - For use with cyclophosphamide for metastatic breast cancer
    - Adult: (consult product literature)

Contra-indications
- Myocardial insufficiency • previous treatment with maximum cumulative doses of daunorubicin or other anthracycline • recent myocardial infarction • severe arrhythmia
- CAUTIONS Caution in handling—irritant to tissues
- Interactions > Appendix 1 (daunorubicin).
  - Caution is necessary with concomitant use of cardiotoxic drugs, or drugs that reduce cardiac contractility. Cardiac function should be monitored closely on the concomitant use of anthracyclines with trastuzumab.
- Side-effects Alopecia • bone-marrow suppression • extravasation • hyperuricaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting
- Side-effects, Further information
  - Cardiotoxicity All anthracycline antibiotics have been associated with varying degrees of cardiac toxicity—this may be idiosyncratic and reversible, but is commonly related to total cumulative dose and is irreversible
- Conception and Contraception Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- Pregnancy Avoid (teratogenic and carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- Breast feeding Discontinue breast-feeding.
  - HEPATIC IMPAIRMENT Reduce dose according to serum bilirubin concentration—consult local protocol for details. Avoid in severe impairment.
  - RENAL IMPAIRMENT Reduce dose by 25% if serum creatinine 105–265 micromol/litre. Reduce dose by 50% if serum creatinine greater than 265 micromol/litre. Avoid in severe impairment.
- Monitoring requirements Cardiac monitoring essential.

Medicinal forms
- There can be variation in the licensing of different medicines containing the same drug.
- Powder for solution for infusion
  - Daunorubicin (Non-proprietary)
    - Daunorubicin (as Daunorubicin hydrochloride) 20 mg Daunorubicin 20mg powder for solution for infusion vials | 10 vial [POM] £550.00 (Hospital only)
  - Emulsion for infusion
    - DaunoXome (Galen Ltd) Daunorubicin (as Daunorubicin hydrochloride citrate) 50 mg DaunoXome 50mg emulsion for infusion vials | 1 vial [POM] £250.00

Pregnancy and reproductive function
- Prolonged use of alkylating drugs, or drugs that reduce cardiac contractility. Cardiac function should be monitored closely on the concomitant use of anthracyclines with trastuzumab.
Cytotoxic responsive malignancy

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BNF 73

Immune system and malignant disease

product literature • extravasation • heart failure (potentially fatal) • hyperuricaemia • nausea • oral mucositis • renal damage • thromboembolism • tumour lysis syndrome • vomiting

SIDE-EFFECTS, FURTHER INFORMATION

• Extravasation Extravasation can cause severe tissue necrosis.

• Cardiomyopathy Higher cumulative doses are associated with cardiomyopathy and it is usual to limit total cumulative doses to 450 mg/m² because symptomatic and potentially fatal heart failure is common above this dose.

• Cardiotoxic Some evidence suggests that weekly low-dose administration may be less cardiotoxic.

• Liposomal formulations Liposomal formulations of doxorubicin may reduce the incidence of cardiotoxicity and lower the potential for local necrosis, but infusion reactions, sometimes severe, may occur. Hand-foot syndrome (painful, macular reddening skin eruptions) occurs commonly with liposomal doxorubicin and may be dose limiting. It can occur after 2–3 treatment cycles and may be prevented by cooling hands and feet and avoiding socks, gloves, or tight-fitting footwear for 4–7 days after treatment.

• Elevated bilirubin concentration Doxorubicin is largely excreted in the bile and an elevated bilirubin concentration can be an indication for reducing the dose.

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

PREGNANCY Avoid (teratogenic and toxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

BREAST FEEDING Discontinue breast-feeding.

HEPATIC IMPAIRMENT Reduce dose according to bilirubin concentration—consult product literature or local treatment protocol for details. Avoid in severe impairment.

RENAL IMPAIRMENT Consult product literature in severe impairment.

MONITORING REQUIREMENTS Patients should be assessed before treatment, by echocardiography. Cardiac monitoring during treatment may assist in determining safe dosage.

DIRECTIONS FOR ADMINISTRATION Conventional doxorubicin is given by injection into a fast-running infusion, commonly at 21-day intervals.

PRESCRIBING AND DISPENSING INFORMATION Doxorubicin is available as both conventional and liposomal formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable.

NATIONAL FUNDING/ACCESS DECISIONS NICE technology appraisals (TAs)

• Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA389

Pegylated liposomal doxorubicin hydrochloride (PLDH) monotherapy or in combination with platinum, is recommended as an option for treating recurrent ovarian cancer.

PLDH, in combination with trabectedin, is not recommended for treating the first recurrence of platinum-sensitive ovarian cancer.

Patients currently receiving PLDH in combination with trabectedin should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA389

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

Solution for injection

• Doxorubicin hydrochloride (Non-proprietary)

Doxorubicin hydrochloride 2 mg per 1 ml Doxorubicin 10mg/5ml solution for injection vials 1 vial £18.54 (Hospital only)

Doxorubicin 50mg/25ml solution for injection CytoSaves vials 1 vial £103.00

Doxorubicin 50mg/25ml solution for infusion vials 1 vial £103.00 (Hospital only)

Doxorubicin 10mg/5ml solution for injection CytoSaves vials 1 vial £20.60

Doxorubicin 10mg/5ml solution for infusion vials 1 vial no price available

Doxorubicin 10mg/5ml solution for infusion vials 1 vial £20.60 (Hospital only)

Doxorubicin 50mg/25ml solution for injection CytoSaves vials 1 vial £92.70 (Hospital only)

Doxorubicin 50mg/25ml concentrate for solution for infusion vials 1 vial no price available

Powder for solution for injection

• Doxorubicin (medac UK)

Doxorubicin hydrochloride 10 mg Doxorubicin 10mg powder for solution for injection vials 10 vial £182.80

Doxorubicin hydrochloride 50 mg Doxorubicin 50mg powder for solution for injection vials 10 vial £914.00

Solution for infusion

• Doxorubicin hydrochloride (Non-proprietary)

Doxorubicin hydrochloride 2 mg per 1 ml Doxorubicin 200mg/100ml solution for injection CytoSaves vials 1 vial £412.00

Doxorubicin 200mg/100ml solution for injection CytoSaves vials 1 vial £370.80–£412.00 (Hospital only)

Doxorubicin 200mg/100ml concentrate for solution for infusion vials 1 vial no price available

Caelyx (Janssen-Cilag Ltd)

Doxorubicin hydrochloride (as Doxorubicin hydrochloride liposomal pegylated) 2 mg per 1 ml

Doxorubicin 50mg/25mg concentrate for solution for infusion vials 1 vial £112.49

Caelyx 20mg/100ml concentrate for solution for infusion vials 1 vial £360.23

Powder and solvent for suspension for infusion ELECTROLYTES: May contain Sodium

• Myocet (Teva UK Ltd)

Doxorubicin hydrochloride 50 mg Myocet 50mg powder and solvent for suspension for infusion vials 2 vial £912.26 (Hospital only)

Epirubicin hydrochloride

INDICATIONS AND DOSE

Treatment of breast cancer • Treatment and prophylaxis of certain forms of superficial bladder cancer

BY INTRAVENOUS INFUSION, OR BY INTRAVESICAL INSTILLATION

Adult: (consult product literature or local protocols)

CONTRA-INDICATIONS Bladder inflammation or contraction (when used as a bladder instillation) • catheterisation difficulties (when used as a bladder instillation) • haematuria (when used as a bladder instillation) • invasive tumours penetrating the bladder (when used as a bladder instillation) • myocardopathy • previous treatment with maximum cumulative doses of epirubicin or other anthracycline • recent myocardial infarction • severe arhythmia • severe myocardial insufficiency • unstable angina • urinary tract infections (when used as a bladder instillation)

CAUTIONS Caution in handling—irritant to tissues

INTERACTIONS Appendix 1 (epirubicin). Caution is necessary with concomitant use of cardiotoxic drugs, or drugs that reduce cardiac contractility. Cardiac function should be monitored closely on the concomitant use of anthracyclines with trastuzumab.
IDARUBICIN HYDROCHLORIDE

INDICATIONS AND DOSE

Acute non-lymphocytic leukaemias monotherapy
- **BY MOUTH**
  - Adult: 30 mg/m² daily for 3 days; maximum 400 mg/m² per course

Acute non-lymphocytic leukaemia in combination therapy
- **BY MOUTH**
  - Adult: 15–30 mg/m² daily for 3 days; maximum 400 mg/m² per course

Advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines)—monotherapy
- **BY MOUTH**
  - Adult: 45 mg/m² for 1 dose, repeat treatment every 3–4 weeks, alternatively 15 mg/m² daily for 3 consecutive days, repeat treatment every 3–4 weeks; maximum 400 mg/m² per course

MITOXANTRONE

(Mitozantrone)

INDICATIONS AND DOSE

Metastatic breast cancer | Non-Hodgkin’s lymphoma
- **BY INTRAVENOUS INFUSION**
  - Adult: (consult local protocol)

CAUTIONS

Intrathecal administration not recommended

Acute leukaemias | Advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines)
- **BY INTRAVENOUS INJECTION**
  - Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 797.

CONTRA-INDICATIONS

Previous treatment with maximum cumulative dose of idarubicin or other anthracycline • recent myocardial infarction • severe arrhythmias • severe myocardial insufficiency

CAUTIONS

Caution in handling—irritant to tissues

INTERACTIONS
  - Appendix I (idarubicin).
  - Cardiac function should be monitored closely on the concomitant use of anthracyclines with trastuzumab.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Common or very common Abdominal pain • cardiac disorders • diarrhoea • haemorrhage • rash • red pigmentation of the urine
- Uncommon Nail hyperpigmentation • skin hyperpigmentation
- Frequency not known Alopecia • bone-marrow suppression • hyperuricaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting

SPECIFIC SIDE-EFFECTS
- With intravenous use Extravasation

CONCEPTION AND CONTRACEPTION

Contraceptive advice required, see *Pregnancy and reproductive function in Cytotoxic drugs* p. 797.

PREGNANCY

Avoid (teratogenic and toxic in animal studies). See also *Pregnancy and reproductive function in Cytotoxic drugs* p. 797.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Reduce dose according to bilirubin concentration—consult local treatment protocol for details. Avoid in severe impairment.

RENAL IMPAIRMENT

Dose reduction may be necessary in severe impairment.
Pixuvri

**INDICATIONS AND DOSE**
Treatment of refractory or multiply relapsed aggressive non-Hodgkin B-cell lymphomas (monotherapy)

- **BY INTRAVENOUS INFUSION**
- **Adult:** (consult product literature)

**CONTRA-INDICATIONS** Active severe infection - risk factors for severe infection

**CAUTIONS** Active cardiovascular disease - cardiac risk factors - caution in handling - irritant to tissues - concurrent radiotherapy to the mediastinal area - history of cardiovascular disease - previous radiotherapy to the mediastinal area - previous therapy with anthracyclines - previous therapy with anthracyclines

**INTERACTIONS** → Appendix 1 (pixantrone).
Caution with concurrent use of cardiotoxic drugs - increased risk of cardiotoxicity. Contra-indicated with concurrent immunisation with live virus vaccines.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - abnormal liver function tests - biochemical disturbances - bone pain - cardiac disorders - cardiac toxicity (during or following treatment) - chromaturia - conjunctivitis - constipation - cough - diarrhoea - drowsiness - dry mouth - dyspepsia - dyspnoea - electrolyte disturbances - haematuria - headache - hypotension - infection - loss of appetite - malaise - nail disorder - oedema - pallor - paraesthesia - proteinuria - pruritus - pyrexia - severe myelosuppression - skin discolouration - tachycardia - taste disturbances - vein discolouration - weight loss
- **Uncommon** Anxiety - arrhythmia - arthralgia - arthritis - dizziness - dry eye - keratitis - musculoskeletal pain - musculoskeletal weakness - night sweats - oesophagitis - oliguria - petechiae - pleural effusion - pneumonia - rash - rectal haemorrhage - rhinorrhea - skin ulcer - sleep disorder - spontaneous erection - tumour progression - vein disorder - vertigo
- **Frequency not known** Alpoeia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - photosensitivity - thromboembolism - transient blue-green discolouration of urine - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Cardiotoxicity Cardiac examinations are recommended after a cumulative dose of 160 mg/m².

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

**PREGNANCY** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Use with caution—consult local treatment protocol.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- **Mitoxantrone (Non-proprietary)**
  Mitoxantrone (as Mitoxantrone hydrochloride) 2 mg per 1 ml Mitoxantrone 20mg/10ml concentrate for solution for infusion vials | 1 vial £121.85
- **Onkotrone (Baxter Healthcare Ltd)**
  Mitoxantrone (as Mitoxantrone hydrochloride) 2 mg per 1 ml Onkotrone 20mg/10ml concentrate for infusion vials | 1 vial no price available
  Onkotrone 25mg/12.5ml solution for infusion vials | 1 vial no price available

**Monograph**
**Pixuvri** (CTI Life Sciences Ltd)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
**ELECTROLYTES:** May contain Sodium
- **Pixuvri**

Pixuvri (as Pixuvri dimaleate) 29 mg Pixuvri 29mg powder for concentrate for solution for infusion vials | 1 vial no price available
Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (July 2016) NICE TA399

Azacitidine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia with greater than 30% bone marrow blasts in patients aged 65 years or above who are not eligible for haematopoietic stem cell transplant.

Patients whose treatment was started before this guidance was published should continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA399
Capecitabine for the treatment of advanced gastric cancer

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic colorectal cancer (August 2012) NICE TA263

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (December 2010) NICE TA212

Capecitabine for the treatment of advanced gastric cancer (July 2010) NICE TA191

Cladribine

INDICATIONS AND DOSE

LEUSTAT®

B-cell chronic lymphocytic leukaemia in patients who have failed to respond to standard regimens containing an alkylating agent | Hairy cell leukaemia

BY INTRAVENOUS INFUSION

Adult: (consult product literature or local protocols)

LITAK®

Hairy cell leukaemia

BY SUBCUTANEOUS INJECTION

Adult: (consult product literature or local protocols)

CAUTIONS

Use irradiated blood only

CAUTIONS, FURTHER INFORMATION

Immunosuppressive effect of cladribine | Cladribine has a potent and prolonged immunosuppressive effect. Patients treated with cladribine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in those at risk. To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs.

INTERACTIONS

Appendix 1 (cladribine).

SIDE-EFFECTS

Abdominal pain | acute renal failure (with high doses) | alopecia | anxiety | arthralgia | arthrosis | bone-marrow suppression | chills | constipation | cough | diarrohoea | dizziness | dyspnoea | extravasation | flatulence | haemolytic anaemia | headache | hyperuricaemia | insomnia | malaise | myalgia | nausea | oedema | oral mucositis | pruritus | purpura | rash | severe myelosupression (with neutropenia, anaemia and thrombocytopenia) | severe neurotoxicity (with high doses) | sweating | tachycardia | thromboembolism | tumour lysis syndrome | vomiting
**Cytarabine**

**DRUG ACTION** Cytarabine acts by interfering with pyrimidine synthesis.

**INDICATIONS AND DOSE**

- Induction of remission of acute myeloblastic leukaemia
  - By intravenous infusion, or by intravenous injection, or by subcutaneous injection
  - Adult: (consult local protocol)

- Lymphomatous meningitis
  - By intrathecal injection
  - Adult: (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

Not all cytarabine preparations can be given by intrathecal injection—consult product literature.

**INTERACTIONS** → Appendix 1 (cytarabine).

**SIDE-EFFECTS**

- Alopecia
- Bone-marrow suppression
- Cough
- Dizziness
- Extravasation
- Hyperuricaemia
- Hyperthermia
- Lassitude
- Leucopenia
- Pruritus
- Rash
- Restlessness
- Thromboembolism
- Tumour lysis syndrome
- Vomiting

**CONCEPTION AND CONTRACEPTION**

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Reduce dose—consult product literature.

**MONITORING REQUIREMENTS**

- Haematological monitoring Cytarabine is a potent myelosuppressant and requires careful haematological monitoring.

**NATIONAL FUNDING/ACCESS DECISIONS**

**DEPOCYTE®**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (July 2007) that liposomal cytarabine suspension (DepoCyte®) is not recommended for use within NHS Scotland for the intrathecal treatment of lymphomatous meningitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - Cytarabine (Non-proprietary)
    - Cytarabine 20 mg per 1 ml Cytarabine 500 mg/25 ml solution for injection vials | 1 vial £9.50
    - Cytarabine 1000 mg/50 ml solution for injection vials | 5 vial £20.99–£30.00
    - Cytarabine 2500 mg/100 ml solution for injection vials | 10 vial £40.00

**Suspension for injection**

- DepoCyte (Napp Pharmaceuticals Ltd)
  - Cytarabine 10 mg per 1 ml DepoCyte 50 mg/5 ml suspension for injection vials | 1 vial £1,223.75 (Hospital only)

**Clofarabine**

**INDICATIONS AND DOSE**

Relapsed or refractory acute lymphoblastic leukaemia in patients who have received at least two previous regimens

- By intravenous infusion
- Adult 18–20 years: (consult local protocol)

**CAUTIONS** Cardiac disease

**SIDE-EFFECTS**

- Abdominal pain
- Agitation
- Alopecia
- Anxiety
- Arthralgia
- Bone-marrow suppression
- Cough
- Diarrhoea
- Dizziness
- Drowsiness
- Dyspnoea
- Extravasation
- flushing
- Haematoma
- Haematuria
- Headache
- Hyperuricaemia
- Hypotension
- Jaundice
- Myalgia
- Nausea
- Oedema
- Oral mucositis
- Pancreatitis
- Paraesthesia
- Pericardial effusion
- Peripheral neuropathy
- Pruritus
- Rash
- Restlessness
- Sweating
- Tachycardia
- Thromboembolism
- Tumour lysis syndrome
- Vomiting

**CONCEPTION AND CONTRACEPTION**

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY** Manufacturer advises avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Solution for infusion**
  - Clofarabine 1 mg per 1 ml  Evoltra 20 mg/20 ml concentrate for solution for infusion vials | 4 vial £5,304.72 (Hospital only)

**BNF 73**

Cytotoxic responsive malignancy 813

**Immune system and malignant disease**
Decitabine

- **DRUG ACTION** Decitabine is a pyrimidine analogue.

- **INDICATIONS AND DOSE**
  - Treatment of newly diagnosed acute myeloid leukaemia in patients over 65 years of age who are not candidates for standard induction chemotherapy
    - **BY INTRAVENOUS INFUSION**

- **CAUTIONS**
  - History of severe congestive heart failure
  - History of unstable cardiac disease

- **INTERACTIONS**
  - **Common or very common**
    - Diarrhoea
    - Epistaxis
    - Headache
  - **Uncommon**
    - Acute febrile neutrophilic dermatosis
  - **Frequency not known**
    - Alopecia
    - Bone-marrow suppression
    - Extravasation
    - Hyperuricaemia
    - Nausea
    - Oral mucositis
    - Thromboembolism
    - Tumour lysis syndrome
    - Vomiting

- **SIDE-EFFECTS**
  - **Rare**
    - Arrhythmia
    - Blurred vision
    - Blindness
  - **Very rare**
    - Alopecia
    - Bone-marrow suppression
    - Extravasation
    - Haemorrhagic cystitis
    - Hyperuricaemia
    - Nausea
    - Oral mucositis
    - Thromboembolism
    - Tumour lysis syndrome
    - Vomiting

- **RENEWAL IMPAIRMENT**
  - Manufacturer advises caution if creatinine clearance less than 30 mL/minute — no information available.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for infusion**
    - **ELECTROLYTES:** May contain Potassium, sodium
    - **Dacogen** (Janssen-Cilag Ltd)
      - **Decitabine 50 mg** Dacogen 50mg powder for concentrate for solution for infusion vials — 1 vial £970.86

Fludarabine phosphate

- **INDICATIONS AND DOSE**
  - Initial treatment of advanced B-cell chronic lymphocytic leukaemia (CLL) or after first line treatment in patients with sufficient bone-marrow reserves
    - **BY MOUTH**
    - Adult: 40 mg/m² for 5 days every 28 days, usually given for 6 cycles
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - Adult: (consult product literature)

  - **RENEWAL IMPAIRMENT**
    - Manufacturer advises caution if creatinine clearance less than 30 mL/minute — no information available.

- **SIDE-EFFECTS**
  - **Common or very common**
    - Diarrhoea
    - Epistaxis
    - Headache
  - **Uncommon**
    - Acute myeloid leukaemia
    - Anorexia
    - Chills
    - Cough
    - Diarrhoea
    - Fever
    - Immunosuppression
    - Malaise
    - Myelodysplastic syndrome
    - Myelosuppression (may be cumulative)
    - Oedema
    - Peripheral neuropathy
    - Pneumonitis
    - Pulmonary toxicity
    - Thrombocytopenia
  - **Frequency not known**
    - Alopecia
    - Bone-marrow suppression
    - Extravasation
    - Haemorrhagic cystitis
    - Hyperuricaemia
    - Nausea
    - Oral mucositis
    - Thromboembolism
    - Tumour lysis syndrome
    - Vomiting
  - **SIDE-EFFECTS**
    - **Very rare**
    - Alopecia
    - Bone-marrow suppression
    - Extravasation
    - Haemorrhagic cystitis
    - Hyperuricaemia
    - Nausea
    - Oral mucositis
    - Thromboembolism
    - Tumour lysis syndrome
    - Vomiting

- **RENEWAL IMPAIRMENT**
  - Reduce dose by up to 50% if creatinine clearance 30–70 mL/minute. Avoid if creatinine clearance less than 30 mL/minute.

- **MONITORING REQUIREMENTS**
  - Monitor for signs of haemolysis.
  - Monitor for neurological toxicity.
  - Assess creatinine clearance in patients over 65 years before treatment initiation.

- **DIRECTIONS FOR ADMINISTRATION**
  - Concentrate for intravenous injection or infusion must be diluted before administration (consult product literature).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (February 2007) NICE TA119
    - Fludarabine monotherapy is not recommended for the first-line treatment of chronic lymphocytic leukaemia.
      - [www.nice.org.uk/TA119](http://www.nice.org.uk/TA119)

    - Fludarabine for the treatment of B-cell chronic lymphocytic leukaemia (September 2001) NICE TA29
      - Oral fludarabine is recommended for the second-line treatment of B-cell chronic lymphocytic leukaemia in patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combination chemotherapy of either:
        - Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
        - Cyclophosphamide, doxorubicin and prednisolone (CAP)
      - Intravenous fludarabine should only be used when oral fludarabine is contra-indicated.
      - [www.nice.org.uk/TA29](http://www.nice.org.uk/TA29)

- **Scottish Medicines Consortium (SMC) Decisions**
  - The Scottish Medicines Consortium has advised (October 2006) that fludarabine is accepted for restricted use for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First-line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease-related symptoms or evidence of progressive disease.
## MEDICINAL FORMS

### Tablet

- **Fludara** (Sanofi)
  - Fludarabine phosphate 10 mg Fludara 10mg tablets | 15 tablet (Pom) £302.48 (Hospital only) | 20 tablet (Pom) £403.31 (Hospital only)

### Solution for injection

- **Fludarabine phosphate (Non-proprietary)**
  - Fludarabine phosphate 25 mg per 1 ml Fludarabine phosphate 50mg/2ml concentrate for solution for injection vials | 1 vial (Pom) £156.00 (Hospital only) | 1 vial (Pom) £155.00 (Hospital only)

- **Fludara** (Sanofi)
  - Fludara 50mg powder for solution for injection vials | 5 vial (Pom) £735.34 (Hospital only)

### Powder for solution for injection

- **Fludarabine phosphate (Non-proprietary)**
  - Fludarabine phosphate 50 mg Fludarabine phosphate 50mg powder for solution for injection vials | 1 vial (Pom) £155.00 (Hospital only)

## Fluorouracil

### INDICATIONS AND DOSE

Treatment of some solid tumours including gastro-intestinal tract cancers and breast cancer | In combination with folinic acid in advanced colorectal cancer

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRA-ARTERIAL INFUSION**
- **Adult:** (consult product literature)

### INTERACTIONS

- **Appendix 1** (fluorouracil).

### SIDE-EFFECTS

- **Rare** Cerebellar syndrome
- **Frequency not known** Alopecia, bone-marrow suppression, desquamative hand-foot syndrome (on prolonged infusion), extravasation, hyperuricaemia, mucositis, myelosuppression, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting

### CONCEPTION AND CONTRACEPTION

- Contra-advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

### PREGNANCY

- Avoid (teratogenic). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

### BREAST FEEDING

- Discontinue breast-feeding.

### HEPATIC IMPAIRMENT

- Manufacturer advises caution.

### HANDLING AND STORAGE

- Caution in handling—irritant to tissues.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

### Solution for injection

- **Fluorouracil (as Fluorouracil sodium)** 25 mg per 1 ml Fluorouracil 500mg/20ml solution for injection vials | 10 vial (Pom) £64.00

### Solution for infusion

- **Fluorouracil (as Fluorouracil sodium)** 25 mg per 1 ml Fluorouracil 2.5g/100ml solution for infusion vials | 1 vial (Pom) £32.00

## Gemcitabine

### INDICATIONS AND DOSE

First-line treatment for locally advanced or metastatic non-small cell lung cancer (as monotherapy in elderly patients and in palliative treatment; otherwise in combination with cisplatin) | Treatment of locally advanced or metastatic pancreatic cancer | Treatment of advanced or metastatic bladder cancer (in combination with cisplatin) | Treatment of locally advanced or metastatic epithelial ovarian cancer which has relapsed after a recurrence-free interval of at least 6 months following previous platinum-based therapy (in combination with carboplatin) | Treatment of metastatic breast cancer which has relapsed after previous chemotherapy including an anthracycline (in combination with paclitaxel) | **BY INTRAVENOUS INFUSION**

### INTERACTIONS

- **Appendix 1** (gemcitabine).

### SIDE-EFFECTS

- **Rare** Haemolytic uraemic syndrome

### CONTRA-INDICATIONS

- **Frequency not known** Alopecia, bone-marrow suppression, mild gastro-intestinal side-effects, musculoskeletal pain, nausea, oral mucositis, microangiopathic haemolytic anaemia, myelosuppression, oral mucositis, renal impairment, thromboembolism, tumour lysis syndrome, vomiting

### CONCEPTION AND CONTRACEPTION

- Contra-advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

### PREGNANCY

- Avoid (teratogenic in animal studies). See Pregnancy and reproductive function in Cytotoxic drugs p. 797.

### BREAST FEEDING

- Discontinue breast-feeding.

### HEPATIC IMPAIRMENT

- Manufacturer advises caution.

### RENAL IMPAIRMENT

- Manufacturer advises caution.

### NATIONAL FUNDING/ACCESS DECISIONS

- **NICE technology appraisals (TAs)**
  - Gemcitabine is an option for first-line chemotherapy for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnovsky score of at least 50 [Karnovsky score is a measure of the ability to perform ordinary tasks].
  - Gemcitabine is not recommended for patients who can have potentially curative surgery. There is insufficient evidence about its use for second-line treatment of pancreatic adenocarcinoma.
  - www.nice.org.uk/TA25

  - Gemcitabine, in combination with paclitaxel, is an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capcetabine are also considered appropriate.
  - www.nice.org.uk/TA116

- Bevacizumab in combination with gemcitabine and carboplatin for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (May 2013) NICE TA285
  - Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for the treatment of the first
recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) that has not been previously treated with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents.

www.nice.org.uk/TA285

- Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer (October 2015) NICE TA360

Gemcitabine in combination with albumin-bound paclitaxel (nab-paclitaxel, Abraxane®) is not recommended for the treatment of previously untreated metastatic adenocarcinoma of the pancreas.

Patients whose treatment was started before this guidance was published should continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA360

- Topotecan, pegylated liposomal doxorubicin hydrochloride, anthracycline (unless contra-indicated).

relapsed following previous chemotherapy including an the treatment of metastatic breast cancer, which has recommended for treating the

Gemcitabine (Non-proprietary)

Gemcitabine (as Gemcitabine hydrochloride) 10 mg per

0.25 mg powder for solution for infusion vials | 1 vial £797.55

0.50 mg powder for solution for infusion vials | 1 vial £1595.10

1.00 mg powder for solution for infusion vials | 1 vial £2390.20

粉末 for solution for infusion

- Gemcitabine (Non-proprietary)

Gemcitabine (as Gemcitabine hydrochloride) 1 gram Gemcitabine 2g powder for solution for infusion vials | 1 vial £250.00

Gemcitabine (as Gemcitabine hydrochloride) 2 gram Gemcitabine 2g powder for solution for infusion vials | 1 vial £324.00

Gemcitabine (as Gemcitabine hydrochloride) 200 mg Gemcitabine 200mg powder for solution for infusion vials | 1 vial £110.00

Gemcitabine (as Gemcitabine hydrochloride) 1 gram Gemzar 1g powder for solution for infusion vials | 1 vial £162.76

Gemcitabine (as Gemcitabine hydrochloride) 200 mg Gemzar 200mg powder for solution for infusion vials | 1 vial £32.55

Mercaptopurine

(6-Mercaptopurine)

- INDICATIONS AND DOSE

Severe acute Crohn's disease | Maintenance of remission of Crohn's disease | Ulcerative colitis

by mouth

Adult: 1–1.5 mg/kg daily, some patients may respond to lower doses

Acute leukaemias | Chronic myeloid leukaemia

by mouth using tablets

Adult: Initially 2.5 mg/kg daily, adjusted according to response, alternatively initially 50–75 mg/m² daily, adjusted according to response

by mouth using oral suspension

Adult: Initially 25–75 mg/m² daily, adjusted according to response

DOSE EQUIVALENCE AND CONVERSION

Mercaptopurine tablets and Xalquip® oral suspension are not bioequivalent, haematological monitoring is advised when switching formulations.

- UNLICENSED USE

Not licensed for use in severe ulcerative colitis and Crohn's disease.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOsing OF ORAL ANTI-CANCeR MEDICINES

See Cytotoxic drugs p. 797.

- CONTRA-INDICATIONS

Absent thiopurine methyltransferase activity

- CAUTIONS

Reduced thiopurine methyltransferase activity

CAUTIONS, FURTHER INFORMATION

- Thiopurine methyltransferase The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

- INTERACTIONS

a Appendix 1 ( mercaptopurine).

- SIDE-EFFECTS

Rare Pancreatitis - transient oligospermia

Very rare Intestinal ulceration - lymphoma

Frequency not known Alopecia - anorexia - bone-marrow suppression - hepatotoxicity - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Gastro-intestinal side-effects Tioguanine has a lower incidence of gastrointestinal side-effects than mercaptopurine.

CONCEPTION AND CONCEPTION

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.
Methotrexate

**DRUG ACTION** Methotrexate inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines.

**INDICATIONS AND DOSE**

**Severe Crohn’s disease**

- **By intramuscular injection**
  - Adult: Initially 25 mg once weekly until remission induced; maintenance 15 mg once weekly

**Maintenance of remission of severe Crohn’s disease**

- **By mouth**
  - Adult: 10–25 mg once weekly

**Moderate to severe active rheumatoid arthritis**

- **By mouth**
  - Adult: 7.5 mg once weekly, adjusted according to response; maximum 20 mg per week

**Severe active rheumatoid arthritis**

- **By intravenous injection, or by intramuscular injection, or by subcutaneous injection**
  - Adult: Initially 7.5 mg once weekly; then increased in steps of 2.5 mg once weekly, adjusted according to response; maximum 25 mg per week

**Neoplastic diseases**

- **By intravenous injection, or by intrathecal injection, or by intra-arterial infusion, or by intramuscular injection, or by intravenous infusion, or by mouth**
  - Adult: (consult product literature)

**Severe psoriasis unresponsive to conventional therapy (specialist use only)**

- **By mouth, or by intramuscular injection, or by intravenous injection, or by subcutaneous injection**
  - Adult: Initially 2.5–10 mg once weekly, then increased in steps of 2.5–5 mg, adjusted according to response, dose to be adjusted at intervals of at least 1 week; usual dose 7.5–15 mg once weekly, stop treatment if inadequate response after 3 months at the optimum dose; maximum 30 mg per week

**PRESCRIBING AND DISPENSING INFORMATION**

**Flavours of oral liquid formulations may include raspberry.**

**PRE-TREATMENT SCREENING**

**Hepatic impairment**

- Monitor liver function.
- Consider measuring thiopurine methyltransferase (TPMT) activity before starting mercaptopurine therapy.
- May need dose reduction.
- May need dose adjustment in Cytotoxic drugs p. 930.
- Bone marrow suppression can occur abruptly; treatment may be started or should be discontinued if any abnormality of liver function tests or liver biopsy is present or develops.
- Factors likely to increase toxicity include advanced age, impaired renal function, and concomitant use with other antifolate drug (e.g. trimethoprim). A clinically significant drop in white cell count or platelet count calls for immediate withdrawal of methotrexate and introduction of supportive therapy.

**CONTRA-INDICATIONS**

- Active infection (in non-malignant conditions) - ascites - immunodeficiency syndromes (in non-malignant conditions) - significant pleural effusion
- Acute porphyrias p. 930 - photosensitivity — psoriasis lesions aggravated by UV radiation (skin ulceration reported) - diarrhoea - extreme caution in blood disorders (avoid if severe) - peptic ulceration - risk of accumulation in pleural effusion or ascites — drain before treatment - ulcerative colitis - ulcerative stomatitis

**SIDE-EFFECTS**


**IMPORTANT SAFETY INFORMATION**

- Note that the dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:
  - the patient is carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
  - only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
  - the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
  - the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

**CONTRA-INDICATIONS**

**Active infection (in non-malignant conditions) - ascites - immunodeficiency syndromes (in non-malignant conditions) - significant pleural effusion**

**CAUTIONS**

- Blood count - Bone marrow suppression can occur abruptly; factors likely to increase toxicity include advanced age, renal impairment, and concomitant use with another antifolate drug (e.g. trimethoprim). A clinically significant drop in white cell count or platelet count calls for immediate withdrawal of methotrexate and introduction of supportive therapy.
- **Gastro-intestinal toxicity** - Withdrawal treatment if stomatitis develops — may be first sign of gastro-intestinal toxicity.
- **Liver toxicity** - Liver cirrhosis reported. Treatment should not be started or should be discontinued if any abnormality of liver function tests or liver biopsy is present or develops during therapy. Abnormalities can return to normal within 2 weeks after which treatment may be recommenced if judged appropriate.
- **Pulmonary toxicity** - Pulmonary toxicity may be a special problem in rheumatoid arthritis (patient to seek medical attention if dyspnoea, cough or fever); monitor for symptoms at each visit — discontinue if pneumonitis suspected.

**INTERACTIONS**

- Appendix 1 (methotrexate).

If aspirin or other NSAIDs are given concurrently the dose of methotrexate should be carefully monitored.

**SIDE-EFFECTS**

- Rare - Pneumonitis

**UNLICENSED USE** Not licensed for use in severe Crohn’s disease.

**METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)**

- Resistance to methicillin developed as a result of mutation. The prevalence of MRSA in the community may exceed 5% and is rising. Methicillin is active against S. aureus and S. epidermidis, though resistance is increasing.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension

**Tablet**

  - Mercaptopurine (Non-proprietary)
  - Mercaptopurine 50 mg Mercaptopurine 50mg tablets | 25 tablet | £49.15 DT price = £49.15

**Oral suspension**

EXCIPIENTS: May contain Aspartame

- Xaluprine (Nova Laboratories Ltd)
  - Mercaptopurine 20 mg per 1 ml Xaluprine 20mg/ml oral suspension | 100 ml | £170.00

**SIDE-EFFECTS**

Cytotoxic responsive malignancy

Immune system and malignant disease

In view of reports of blood dyscrasias (including fatalities) in patients taking methotrexate for non-malignant conditions who experience side-effects, folic acid given on a different day from the methotrexate, may help to reduce the frequency of such side-effects.

 Withdraw treatment if stomatitis develops—may be first sign of gastro-intestinal toxicity.

 Treatment with folinic acid (as calcium folinate) may be required in acute toxicity.

**Monitoring Requirements**

- **Conception and Contraception** Effective contraception required during and for at least 3 months after treatment in men or women.
- **Pregnancy** Avoid (teratogenic; fertility may be reduced during therapy but this may be reversible).
- **Breastfeeding** Discontinue breast-feeding—present in milk.
- **Hepatic Impairment** When used for malignancy, avoid in severe hepatic impairment—consult local treatment protocol for details. Avoid with hepatic impairment in non-malignant conditions—dose-related toxicity.
- **Pre-treatment Screening** Exclude pregnancy before treatment.

 Patients should have full blood count and renal and liver function tests before starting treatment.

 **Prescribing and Dispensing Information**

- In view of reports of blood dyscrasias (including fatalities) and liver cirrhosis with low-dose methotrexate patients should:
  - have full blood count and renal and liver function tests repeated every 1–2 weeks until therapy stabilised, thereafter patients should be monitored every 2–3 months.
  - be advised to report all symptoms and signs suggestive of infection, especially sore throat.
- Local protocols for frequency of monitoring may vary.
- Treatment with folinic acid (as calcium folinate) may be required in acute toxicity.

 **Tablet**

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 **Solution for Injection**

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 **Oral Solution**

- **Methotrexate (as Methotrexate sodium) 0.2 mg per ml**
  - 20 ml | £1.52 |

 **Injectable Solution**

- **Methotrexate (as Methotrexate sodium) 0.45 mg per ml**
  - 10 ml | £1.42 |

 **Prescribing and Dispensing Information**

- Methotrexate treatment booklets Methotrexate treatment booklets should be issued where appropriate.

- **Patient and Carer Advice**

 Methotrexate treatment booklets

 Methotrexate treatment booklets should be issued where appropriate.

 In England, Wales, and Northern Ireland, they are available for purchase from: Gorse Street, Chadderton Oldham OL9 9QH Tel: 0845 610 1112 GP practices can obtain supplies through their Local Area Team stores.

 NHS Hospitals can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mnm.com.

 In Scotland, treatment booklets can be obtained by emailing stockorders.dpas@theapsgroup.com or by fax on 0131 629 9967.

 These booklets include advice for adults taking oral methotrexate for inflammatory conditions, and a section for recording results of blood tests and dosage information.

 Patients and their carers should be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).

 Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen.

 Patients should be counselled on the dose, treatment booklet, and the use of NSAIDs.

 **Medicinal Forms**

 There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection.
**Pemetrexed**

**DRUG ACTION** Pemetrexed inhibits thymidylate transferase and other folate-dependent enzymes.

**INDICATIONS AND DOSE**

Treatment of unresectable malignant pleural mesothelioma which has not previously been treated with chemotherapy (in combination with cisplatin).

First-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (in combination with cisplatin).

Second-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (monotherapy).

Maintenance treatment in locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology that has not progressed immediately following platinum-based chemotherapy (monotherapy).

**CAUTIONS**

Diabetes - history of cardiovascular disease - prophylactic folic acid supplementation required (consult product literature) - prophylactic vitamin B12 supplementation required (consult product literature).

**INTERACTIONS**

Appendix 1 (pemetrexed). Caution with concomitant nephrotoxic drugs including non-steroidal anti-inflammatory drugs (consult product literature).

**SIDE-EFFECTS**

- Common or very common
  - Neurotoxicity (discontinue)
  - Concomitant nephrotoxic drugs including non-steroidal anti-inflammatory drugs (consult product literature).

- Uncommon
  - Arrhythmias
  - Arthralgia
  - Gastro-intestinal disturbances
  - Nephrotoxicity
  - Peripheral neurological disorders
  - Pleural effusion
  - Pyrexia
  - Seizures
  - Taste disturbance
  - Thromboembolism
  - Tremor
  - Tumour lysis syndrome
  - Vomiting
  - Wheezing

**CONCEPTION AND CONTRACEPTION**

Manufacturer advises effective contraception during and for at least 3 months after treatment in men and women.

**PREGNANCY**

Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**

Discontinue breast-feeding.

**MONITORING REQUIREMENTS**

- Neurotoxicity: Close monitoring for neurological events is strongly recommended—discontinue if neurotoxicity occurs.

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks
  - Drowsiness may affect performance of skilled tasks (e.g. cycling or driving).

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (March 2008) that the use of nelarabine (Atriance®) within NHS Scotland is restricted to bridging treatment before stem cell transplantation.

**MEDICINAL FORMS**

There can be a variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Atriance** (Novartis Pharmaceuticals UK Ltd) 
  - Nelarabine 5 mg per 1 ml Atriance 250mg/50ml solution for infusion vials | 6 vial £1,332.00

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**Zlatal**

- 22.5mg/0.9ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £16.61
- 15mg/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £14.92

**Solution for infusion**

- **Methotrexate (Non-proprietary)**
  - Methotrexate (as Methotrexate sodium) 25 mg per 1 ml Methotrexate 5g/200ml solution for infusion vials | 1 vial | £200.57
  - Methotrexate (as Methotrexate sodium) 100 mg per 1 ml Methotrexate 5g/50ml solution for infusion vials | 1 vial | £400.00
non-small cell lung cancer only if the histology of the tumour has been confirmed as adenocarcinoma or large cell carcinoma.

www.nice.org.uk/TA181

▶ Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (August 2016) NICE TA402

Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer when a patient’s disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy; their Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment; the company provides the drug according to the terms of the commercial access agreement as agreed with NHS England.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinicians consider it appropriate to stop.

www.nice.org.uk/TA402

▶ Pemetrexed for the treatment of malignant pleural mesothelioma (January 2008) NICE TA135

Pemetrexed is an option for the treatment of malignant pleural mesothelioma only in patients who have a WHO performance status of 0 or 1 [WHO performance status is a measure of the ability to perform ordinary tasks], who are considered to have advanced disease and for whom surgical resection is considered inappropriate.

www.nice.org.uk/TA135

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (August 2008) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland as monotherapy for the second-line treatment of locally advanced or metastatic non-small cell lung cancer without predominantly squamous cell histology; it is restricted for use in patients with good performance status who would otherwise be eligible for docetaxel treatment.

The Scottish Medicines Consortium has advised (January 2010) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland in combination with cisplatin for the first-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology; it is restricted to patients in whom the histology of the tumour has been confirmed as adenocarcinoma or large cell carcinoma.

The Scottish Medicines Consortium has advised (July 2005) that pemetrexed (Alimta®) in combination with cisplatin is accepted for restricted use within NHS Scotland for previously untreated patients with stage III/IV unresectable malignant pleural mesothelioma.

▶ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

▶ Pemetrexed (Non-proprietary)

Pemetrexed (as Pemetrexed ditomotamol) 25 mg per 1 ml Pemetrexed 100mg/4ml concentrate for solution for infusion vials | 1 vial £140.00

Pemetrexed 500mg/20ml concentrate for solution for infusion vials | 1 vial £700.00

Pemetrexed 1000mg/40ml concentrate for solution for infusion vials | 1 vial £1,400.00

Powder for solution for infusion

ELECTROLYTES: May contain Sodium

▶ Pemetrexed (Non-proprietary)

Pemetrexed (as Pemetrexed disodium) 100 mg Pemetrexed 100mg powder for concentrate for solution for infusion vials | 1 vial £144.00 (Hospital only)

Pemetrexed (as Pemetrexed disodium) 500 mg Pemetrexed 500mg powder for concentrate for solution for infusion vials | 1 vial £720.00 (Hospital only)

Alimta (Eli Lilly and Company Ltd)

Pemetrexed (as Pemetrexed disodium) 100 mg Alimta 100mg powder for concentrate for solution for infusion vials | 1 vial £160.00 (Hospital only)

Pemetrexed (as Pemetrexed disodium) 500 mg Alimta 500mg powder for concentrate for solution for infusion vials | 1 vial £800.00 (Hospital only)

Tegafur with gimeracil and oteracil

▶ DRUG ACTION

Tegafur is a prodrug of fluorouracil. Gimeracil inhibits the degradation of fluorouracil and oteracil decreases the activity of fluorouracil in normal gastrointestinal mucosa.

▶ INDICATIONS AND DOSE

Treatment of advanced gastric cancer when used in combination with cisplatin

▶ BY MOUTH

Adult: (consult local protocol)

IMPORTANT SAFETY INFORMATION

Risks of incorrect dosing of oral anti-cancer medicines

See Cytotoxic drugs p. 797.

▶ CONTRA-INDICATIONS

Dihydropyrimidine dehydrogenase deficiency

▶ INTERACTIONS

→ Appendix 1 (tegafur).

▶ SIDE-EFFECTS

Alopecia • bone-marrow suppression • hyperuricaemia • nausea • neuropathy • ocular toxicity • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting

▶ CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception during and for up to 6 months after treatment.

▶ PREGNANCY

Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

▶ BREAST FEEDING

Discontinue breast-feeding.

▶ RENAL IMPAIRMENT

Reduce dose if creatinine clearance 30–50 mL/minute—consult product literature. Manufacturer advises avoid if creatinine clearance less than 30 mL/minute.

▶ NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (August 2012) that tegafur with gimeracil and oteracil (Teysuno®) is accepted for restricted use within NHS Scotland for the treatment of advanced gastric cancer, when given in combination with cisplatin, in patients who are unsuitable for an anthracycline, fluorouracil and platinum triplet first-line regimen.

▶ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 23

Tegafur 15 mg Teysuno 15mg | 126 capsules £279.72

Gimeracil 5.8 mg, Oteracil (as Oteracil potassium) 15.8 mg, Teysuno 20 mg Teysuno 20mg/5.8mg/15.8mg capsules | 84 capsules £248.40

Gimeracil 4.35 mg, Oteracil (as Oteracil potassium) 11.8 mg, Teysuno 15 mg Teysuno 15mg/4.35mg/11.8mg capsules | 126 capsules £279.72

Gimeracil 5.8 mg, Oteracil (as Oteracil potassium) 15.8 mg, Teysuno 20 mg Teysuno 20mg/5.8mg/15.8mg capsules | 84 capsules £248.40
Tioguanine
(Thioguanine)

**INDICATIONS AND DOSE**

**Acute leukaemia** | **Chronic myeloid leukaemia**

- **BY MOUTH**
- **Adult:** 100–200 mg/m² daily, can be given at various stages of treatment in short-term cycles

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**CONTRA-INDICATIONS**

- Absent thiopurine methyltransferase activity

**CAUTIONS**

- Thiopurine methyltransferase status

**CAUTIONS, FURTHER INFORMATION**

- Thiopurine methyltransferase  The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

- Long-term therapy  Long-term therapy is no longer recommended because of the high risk of liver toxicity.

**INTERACTIONS**

- **Appendix 1** (tioguanine).

**SIDE-EFFECTS**

- **Rare**  Intestinal necrosis  - intestinal perforation

- **Frequency not known**  Alopecia  - bone-marrow suppression  - hepatotoxicity (discontinue)  - hyperuricaemia  - nausea  - oral mucositis  - stomatitis  - thromboembolism  - tumour lysis syndrome  - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Gastro-intestinal side-effects  Tioguanine has a lower incidence of gastrointestinal side-effects than mercaptopurine.

**CONCEPTION AND CONTRACEPTION**

- Ensure effective contraception during treatment in men or women.

**PREGNANCY**

- Avoid (teratogenicity reported when men receiving tioguanine therapy.

**PREGNANCY AND REPRODUCTIVE FUNCTION**

- See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**

- Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

- Reduce dose.

**RENAL IMPAIRMENT**

- Reduce dose.

**PRE-TREATMENT SCREENING**

- Consider measuring thiopurine methyltransferase (TPMT) activity before starting tioguanine therapy.

**MONITORING REQUIREMENTS**

- Monitor liver function weekly—discontinue if liver toxicity develops.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

**Tablet**

- **Tioguanine (Non-proprietary)**
- Tioguanine 40 mg  Tioguanine 40mg tablets  | 25 tablet  £109.57

**ANTINEOPLASTIC DRUGS > CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES**

**Bleomycin**

**INDICATIONS AND DOSE**

- **Squamous cell carcinoma**  |  **Metastatic germ cell cancer**  |  **Non-Hodgkin's lymphoma**

- **BY INTRAVENOUS INJECTION, OR BY LOCAL INFILTRATION, OR BY INTRA-ARTERIAL INFUSION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION**

- **Adult:** (consult product literature or local protocols)

**CAUTIONS**

- Caution in handling—irritant to tissues

**INTERACTIONS**

- **Appendix 1** (bleomycin).

**SIDE-EFFECTS**

- **Common or very common**  Dermatological toxicity  - mucositis

- **Frequency not known**  Alopecia  - chills (after drug administration)  - extrava satisive-fever (after drug administration)  - hypersensitivity reactions  - hyperuricaemia  - increased pigmentation particularly affecting the flexures and subcutaneous sclerotic plaques  - less bone marrow suppression  - nausea  - oral mucositis  - progressive pulmonary fibrosis (dose-related)  - pulmonary toxicity  - Raynaud’s phenomenon  - thromboembolism  - tumour lysis syndrome  - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Hypersensitivity reactions  Hypersensitivity reactions manifest by chills and fevers commonly occur a few hours after drug administration and may be prevented by simultaneous administration of a corticosteroid, for example hydrocortisone intravenously.

- Progressive pulmonary fibrosis  This is dose-related, occurring more commonly at cumulative doses greater than 300 000 units and in the elderly. Basal lung crepitations or suspicious chest X-ray changes are an indication to stop therapy with this drug.

- Respiratory failure  Patients who have received extensive therapy with bleomycin (e.g. cumulative dose more than 100 000 units) may be at risk of developing respiratory failure if a general anaesthetic is given with high inspired oxygen concentrations. Anaesthetists should be warned of this.

**CONCEPTION AND CONTRACEPTION**

- Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY**

- Avoid (teratogenic and carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797

**BREAST FEEDING**

- Discontinue breast feeding.

**RENAL IMPAIRMENT**

- Reduce dose by half if serum creatinine 177–354 micromol/litre; reduce dose further if serum-creatinine greater than 354 micromol/litre.

**PRESCRIBING AND DISPENSING INFORMATION**

- To conform to the European Pharmacopoeia vials previously labelled as containing ‘15 units’ of bleomycin are now labelled as containing 15 000 units. The amount of bleomycin in the vial has not changed.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Bleo-Kyowa** (Kyowa Kirin Ltd)
- Bleomycin (as Bleomycin sulfate) 15000 unit  Bleo-Kyowa 15,000unit powder for solution for injection vials  | 10 vial  £190.60
Mitomycin

**INDICATIONS AND DOSE**

Recurrent superficial bladder tumours (bladder instillation)

- **BY INTRAVESICAL INSTILLATION**
  - Adult: (consult product literature or local protocols)

Upper gastro-intestinal cancers | Breast cancers

- **BY INTRAVENOUS INJECTION**
  - Adult: (consult product literature or local protocols)

**SIDE-EFFECTS**

GENERAL SIDE-EFFECTS
Alopecia, bone marrow damage, bone-marrow suppression, hyperuricaemia, lung fibrosis, nausea, oral mucositis, renal damage, thromboembolism, tumour lysis syndrome, vomiting

- With intravenous use Extravasation

SIDE-EFFECTS, FURTHER INFORMATION
Bone-marrow toxicity. Prolonged use may result in a permanent effect.

**CONCEPTION AND CONTRACEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY**
Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Mitomycin-C** (Kyowa Kirin Ltd)
  - Mitomycin 2 mg
  - Mitomycin 10 mg
  - Mitomycin 20 mg
  - Mitomycin 40 mg

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**INDICATIONS AND DOSE**

Hairy cell leukaemia (initiated in specialist centres)

- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INFUSION**
  - Adult: To be given on alternate weeks (consult product literature)

**SIDE-EFFECTS**
Alopecia, bone-marrow suppression, extravasation, hyperuricaemia, immunosuppression, myelosuppression, nausea, neurotoxicity (withhold or discontinue), oral mucositis, severe rash (withhold treatment), thromboembolism, tumour lysis syndrome, vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Pentostatin can cause myelosuppression, immunosuppression, and a number of other side-effects that may be severe. Treatment should be withheld in patients who develop a severe rash, and withheld or discontinued in patients showing signs of neurotoxicity.

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises that men should not father children during and for 6 months after treatment.

**PREGNANCY**
Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution—limited information available.

**RENAAL IMPAIRMENT**
Avoid if creatinine clearance less than 60 mL/minute.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Pentostatin 10 mg** Nipent 10mg powder for solution for injection vials | 1 vial | £734.21 (Hospital only)

**ANTINEOPLASTIC DRUGS > PLANT ALKALOIDS**

Trabectedin

**INDICATIONS AND DOSE**

Treatment of advanced soft-tissue sarcoma when treatment with anthracyclines and ifosfamide has failed or is contra-indicated. Treatment of relapsed platinum-sensitive ovarian cancer (in combination with pegylated liposomal doxorubicin)

- **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature or local protocols)

**CONTRA-INDICATIONS**
Elevated creatine phosphokinase (consult product literature)

**SIDE-EFFECTS**
Caution in concomitant use with hepatotoxic drugs (avoid alcohol).

**INTERACTIONS**

- **Frequency not known**
  - Abdominal pain, alopecia, anorexia, arthralgia, asthenia, back pain, bone-marrow suppression, constipation, cough, dehydration, diarrhoea, dizziness, dyspepsia, dysphonia, extravasation, fatigue, flushing, headache, hepatobiliary disorders, hyperuricaemia, hypokalaemia, hypotension, increased blood creatine kinase, insomnia, myalgia, nausea, oedema, oral mucositis, paraesthesia, peripheral neuropathy, pyrexia, taste disturbance, thromboembolism, tumour lysis syndrome, vomiting

SIDE-EFFECTS, FURTHER INFORMATION
A corticosteroid, such as dexamethasone by intravenous infusion, must be given 30 minutes before therapy for its anti-emetic and hepatoprotective effects (consult product literature).

**CONCEPTION AND CONTRACEPTION**
Effective contraception recommended during and for at least 3 months after treatment in women and during and for at least 5 months after treatment in men.

**PREGNANCY**
See Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Manufacturer advises avoid breast-feeding during and for 3 months after treatment.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in impairment—consider dose reduction. Avoid in patients with raised bilirubin. Monitor hepatic function closely in patients with hepatic impairment.

**RENAAL IMPAIRMENT**
Avoid monotherapy if creatinine clearance less than 30 mL/minute. Avoid combination regimens if creatinine clearance less than 60 mL/minute.
Cytotoxic responsive malignancy

- **MONITORING REQUIREMENTS**
  - Specific haematological, renal and hepatic parameters must be monitored and within certain ranges prior to starting treatment and repeated weekly during the first 2 cycles and at least once between treatments in subsequent cycles—consult product literature for full details.
  - Monitor for signs and symptoms of rhabdomyolysis (including myelotoxicity, severe liver function disorder, renal failure, muscle weakness or pain)—monitor creatine phosphokinase closely and discontinue treatment (consult product literature).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Trabectedin for the treatment of advanced soft tissue sarcoma (February 2010) NICE TA185
      - Trabectedin is an option for advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed, is inappropriate or is not tolerated. The cost of trabectedin for treatment after the fifth cycle is met by the manufacturer. www.nice.org.uk/TA185
    - Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA389
      - Trabectedin in combination with pegyalted liposomal doxorubicin hydrochloride (PLDH) is not recommended for treating the first recurrence of platinum-sensitive ovarian cancer.
      - Patients currently receiving trabectedin in combination with PLDH should have the option to continue their treatment until they or their clinician consider it appropriate to stop. www.nice.org.uk/TA389

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **Yondelis (Pharma Mar, S.A.)**
    - **Trabectedin 250 microgram** Yondelis 0.25mg powder for concentration for solution for infusion vials | 1 vial **[POM]** no price available (Hospital only)
    - **Trabectedin 1 mg** Yondelis 1mg powder for concentration for solution for infusion vials | 1 vial **[POM]** no price available (Hospital only)

- **ANTINEOPLASTIC DRUGS ➤ PLATINUM COMPOUNDS**

### Carboplatin

- **INDICATIONS AND DOSE**
  - Treatment of advanced ovarian cancer and lung cancer (particularly the small cell type)
    - **BY INTRAVENOUS INFUSION**
    - Adult: The dose of carboplatin is determined according to renal function rather than body surface area (consult product literature)

- **INTERACTIONS** ➤ Appendix 1 (platinum compounds).

- **SIDE-EFFECTS**
  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Carboplatin is better tolerated than cisplatin; nausea and vomiting are reduced in severity and nephrotoxicity, neurotoxicity, and ototoxicity are much less of a problem than with cisplatin. It is, however, more myelosuppressive than cisplatin.

### Cisplatin

- **INDICATIONS AND DOSE**
  - Treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer (alone or in combination)
    - **BY INTRAVENOUS INFUSION**
    - Adult: (consult product literature)

- **CAUTIONS**
  - **CAUTIONS, FURTHER INFORMATION**
    - Hydration Cisplatin requires intensive intravenous hydration and treatment may be complicated by severe nausea and vomiting.
Cytotoxic responsive malignancy

Oxaliplatin

**INDICATIONS AND DOSE**
Treatment of metastatic colorectal cancer (in combination with fluorouracil and folinic acid).

**CONTRA-INDICATIONS**
Peripheral neuropathy with functional impairment

**INTERACTIONS** → Appendix 1 (platinum compounds).

**SIDE-EFFECTS**
Alopecia, bone-marrow suppression, extravasation, hyperuricaemia, hypomagnesaemia, myelosuppression, nephrotoxicity, oral mucositis, ototoxicity, peripheral neuropathy, severe nausea, severe vomiting, thromboembolism, tumour lysis syndrome

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

**PREGNANCY**
Avoid (teratogenic and toxic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**RENAL IMPAIRMENT**
Avoid if possible—nephrotoxic.

**MONITORING REQUIREMENTS**
▶ Monitor full blood count.
▶ Monitor audiometry.
▶ Monitor plasma electrolytes.
▶ Nephrotoxic—Monitoring of renal function is essential.

**DIRECTIONS FOR ADMINISTRATION**
Cisplatin is increasingly given in a day care setting.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Cisplatin (Non-proprietary)**
  - Cisplatin 1 mg per 1 ml
    - Cisplatin 50mg/50ml concentrate for solution for infusion vials: 1 vial (Pom) £50.22 (Hospital only) 1 vial (Pom) £50.22-£55.64
    - Cisplatin 10mg/10ml solution for infusion vials: 1 vial (Pom) £5.90 (Hospital only) 1 vial (Pom) £5.90
    - Cisplatin 50mg/50ml solution for infusion vials: 1 vial (Pom) £25.37 (Hospital only) 1 vial (Pom) £25.36-£28.11
    - Cisplatin 10mg/10ml concentrate for solution for infusion vials: 1 vial (Pom) no price available
    - Cisplatin 100mg/100ml concentrate for solution for infusion vials: 1 vial (Pom) £50.22 (Hospital only) 1 vial (Pom) no price available

**ANTINEOPLASTIC DRUGS > PODOPHYLLOTOXIN DERIVATIVES**

**Etoposide**

**INDICATIONS AND DOSE**
Small cell carcinoma of the bronchus, the lymphomas and testicular cancer.

**CONTRA-INDICATIONS**
Peripheral neuropathy with functional impairment

**INTERACTIONS** → Appendix 1 (etoposide).

**SIDE-EFFECTS**
Alopecia, bone-marrow suppression, hyperuricaemia, irritant to tissues, nausea, oral mucositis (more common if given with doxorubicin), thromboembolism, tumour lysis syndrome, vomiting

**CONCEPTION AND CONTRACEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.
**PREN**

**PREGNANCY** Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.

**RENAL IMPAIRMENT** Consider dose reduction — consult local treatment protocol for details.

**DIRECTIONS FOR ADMINISTRATION** Etoposide may be given orally or by slow intravenous infusion, the oral dose being double the intravenous dose. A preparation containing etoposide phosphate can be given by intravenous injection or infusion. Etoposide is usually given daily for 3–5 days and courses should not be repeated more frequently than at intervals of 21 days.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS** 23

- **Vepesid** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Etoposide 50 mg Vepesid 50 mg capsules | 20 capsule [POM] £95.82 (Hospital only)
  - Etoposide 100 mg Vepesid 100 mg capsules | 10 capsule [POM] £87.23 (Hospital only)

**Powder for solution for injection**

- **Etopophos** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Etoposide (as Etoposide phosphate) 100 mg Etopophos 100 mg powder for solution for injection vials | 10 vial [PSM] £261.68 (Hospital only)

**Solution for infusion**

- **Etoposide (Non-proprietary)**
  - Etoposide 20 mg per 1 ml Etoposide 100 mg/5 ml concentrate for solution for infusion vials | 1 vial [POM] no price available (Hospital only) | 1 vial [POM] £11.50 | 10 vial [POM] £115.00
  - Etoposide 500 mg/25 ml concentrate for solution for infusion vials | 1 vial [POM] £50.75 (Hospital only)
  - **Eposin** (medac UK)
    - Etoposide 20 mg per 1 ml Eposin 500 mg/25 ml concentrate for solution for infusion vials | 1 vial [POM] £67.50 (Hospital only)
    - Eposin 100 mg/5 ml concentrate for solution for infusion vials | 1 vial [POM] £13.50 (Hospital only)

**ANTINEOPLASTIC DRUGS**

**TAXANES**

**Cabazitaxel**

*03-Oct-2016*

**INDICATIONS AND DOSE**

Treatment of hormone refractory metastatic prostate cancer in patients who have previously been treated with a docetaxel-containing regimen (in combination with prednisone or prednisolone)

- **BY INTRAVENOUS INFUSION**
- **Adult:** (consult product literature or local protocols)

**CAUTIONS** Avoid in acute porphyrias p. 930

**INTERACTIONS** → Appendix 1 (cabazitaxel).

**SIDE-EFFECTS**

- Common or very common Hypersensitivity reactions

- Frequency not known Abdominal pain · alopecia · anxiety · arthralgia · atrial fibrillation · bone marrow suppression · chest pain · chills · confusion · constipation · cough · dehydration · diarrhoea · dizziness · dry mouth · dry skin · dyspepsia · dyspnoea · electrolyte disturbances · erythema · extravasation · flushing · gastroesophageal reflux · haemorrhoids · headache · hyperglycaemia · hypertension · hyperuricaemia · hypothermia · hypotension · increased lacrimation · malaise · muscle spasm · myalgia · nausea · oedema · oral mucositis · paraesthesia · peripheral neuropathy · rectal haemorrhage · renal disorders (fatal cases of renal failure reported) · sciatica · tachycardia · taste disturbance · thromboembolism · tinnitus ·

tumour lysis syndrome · urinary incontinence · urinary retention · vertigo · vomiting · weight changes

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Hypersensitivity reactions** Routine premedication with a corticosteroid, an antihistamine, and a histamine H₁-receptor antagonist is recommended to prevent severe hypersensitivity reactions.
  - For further information on side-effects, consult product literature.

**CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment (women) and for up to 6 months after treatment (men).

**PREGNANCY** See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Avoid.

**RENAL IMPAIRMENT** Use with caution if creatinine clearance less than 50 mL/minute.

**MONITORING REQUIREMENTS** Monitor electrolytes— correct dehydration.

**DIRECTIONS FOR ADMINISTRATION** Intravenous infusion incompatible with PVC.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (updated August 2016) NICE TA391**
  - Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in patients whose disease has progressed during or after docetaxel chemotherapy, only if the following criteria are met:
    - the patient has an eastern cooperative oncology group (ECOG) performance status of 0 or 1
    - the patient has had 225 mg/m² or more of docetaxel
    - treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles
    - the manufacturer provides cabazitaxel with the discount agreed in the patient access scheme
    - NHS trusts purchase cabazitaxel in accordance with the commercial access agreement, either in vials (at a reduced price to reflect the average cost of waste per patient), or in pre-prepared intravenous infusion bags. Patients currently receiving cabazitaxel that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.

**www.nice.org.uk/TA391**

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**EXCIPIENTS:** May contain Ethanol

- **Jevtana** (Sanofi)
  - Cabazitaxel 40 mg per 1 ml JEVTA V 60 mg/1.5 ml concentrate and solvent for solution for infusion vials | 1 vial [POM] £3,696.00 (Hospital only)
Docetaxel

- **INDICATIONS AND DOSE**
  Adjuvant treatment of operable node-positive and operable node-negative breast cancer (in combination with doxorubicin and cyclophosphamide) | Initial chemotherapy of locally advanced or metastatic breast cancer (with doxorubicin) | Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline or an alkylating drug has failed (monotherapy) | Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline has failed (with capecitabine) | Initial chemotherapy of metastatic breast cancer which overexpresses human epidermal growth factor-2 (with trastuzumab) | Locally advanced or metastatic non-small cell lung cancer where previous chemotherapy has failed | Initial chemotherapy of unresetable, locally advanced or metastatic non-small cell lung cancer (with cisplatin) | Hormone-resistant metastatic prostate cancer (in combination with prednisone or prednisolone) | Initial treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (with cisplatin and fluorouracil) | Induction treatment of locally advanced squamous cell carcinoma of the head and neck (with cisplatin and fluorouracil)

  - **BY INTRAVENOUS INFUSION**
  - **Adult:** (consult product literature or local protocols)

- **CAUTIONS** Avoid in acute porphyrias p. 930 | consult product literature
- **INTERACTIONS** → Appendix 1 (docetaxel).
- **SIDE-EFFECTS** Alopecia | bone-marrow suppression | cystoid macular oedema | extravasation | fat influence | heart failure | hypersensitivity reactions | hyperuricaemia | nausea | oral mucositis | peripheral neurotoxicity | persistent fluid retention (commonly as leg oedema that worsens during treatment) | can be resistant to treatment | severe skin reactions | thrombocytopenia | tumour lysis syndrome | vomiting

  **SIDE-EFFECTS, FURTHER INFORMATION**
  - Hypersensitivity reactions and fluid retention | Pretreatment with dexamethasone by mouth is recommended for reducing fluid retention and hypersensitivity reactions (consult product literature).
  - Consult product literature for monitoring and management of side effects.
- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception for men and women during treatment, and for at least 6 months after stopping treatment in men
- **PREGNANCY** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose according to liver enzymes (consult product literature). Avoid in severe impairment. Monitor liver function in hepatic impairment.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  **NICE technology appraisals (TAs)**
  - **Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (June 2006) NICE TA101**
    Docetaxel is an option for hormone-refractory metastatic prostate cancer and a Karnofsky score of at least 60% | Karnofsky score is a measure of the ability to perform ordinary tasks.
    www.nice.org.uk/TA101
  - **Docetaxel for the adjuvant treatment of early node-positive breast cancer (September 2006) NICE TA109**
    Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (TAC regimen), is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.
    www.nice.org.uk/TA109
  - **Scottish Medicines Consortium (SMC) Decisions**
    The Scottish Medicines Consortium has advised that docetaxel (Taxotere®) in combination with cisplatin and fluorouracil is accepted for restricted use within NHS Scotland for the induction treatment of patients with unresectable (May 2007) and resectable (June 2008) locally advanced squamous cell carcinoma of the head and neck.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for infusion**
  **EXCIPIENTS:** May contain ethanol
  - **Docetaxel (Non-proprietary)**
    Docetaxel 10 mg per 1 ml Docetaxel 80mg/8ml concentrate for solution for infusion vials | 1 vial (POM) £53.75 (Hospital only) | Docetaxel 160mg/16ml concentrate for solution for infusion vials | 1 vial (POM) £109.50 (Hospital only) | Docetaxel 20mg/2ml concentrate for solution for infusion vials | 1 vial (POM) £162.75 (Hospital only) | Docetaxel 20 mg per 1 ml Docetaxel 80mg/4ml concentrate for solution for infusion vials | 1 vial (POM) £53.00 | Docetaxel 160mg/8ml concentrate for solution for infusion vials | 1 vial (POM) no price available | Docetaxel 140mg/7ml concentrate for solution for infusion vials | 1 vial (POM) £90.00 | Docetaxel 20mg/1ml concentrate for solution for infusion vials | 1 vial (POM) £160.00 | Taxotere (Sanofi)
    Taxotere docetaxel 20 mg per 1 ml Taxotere 80mg/4ml concentrate for solution for infusion vials | 1 vial (POM) £50.81 | Taxotere 140mg/7ml concentrate for solution for infusion vials | 1 vial (POM) £72.10 | Taxotere 20mg/1ml concentrate for solution for infusion vials | 1 vial (POM) £154.61 | Taxotere (Sanofi)
    Taxotere docetaxel 20 mg per 1 ml Taxotere 80mg/4ml concentrate for solution for infusion vials | 1 vial (POM) £53.47 (Hospital only) | Taxotere 160mg/8ml concentrate for solution for infusion vials | 1 vial (POM) £1,008.54 (Hospital only) | Taxotere 80mg/4ml concentrate for solution for infusion vials | 1 vial (POM) £504.27 (Hospital only)
Paclitaxel

**DRUG ACTION** Paclitaxel is a member of the taxane group of drugs.

**INDICATIONS AND DOSE**

- Treatment of ovarian cancer (advanced or residual disease following laparotomy) in combination with cisplatin (conventional paclitaxel only)
- Treatment of metastatic ovarian cancer where platinum-containing therapy has failed (conventional paclitaxel only)
- Treatment of locally advanced or metastatic breast cancer (in combination with other cytotoxics or alone if other cytotoxics have failed or are inappropriate) (conventional paclitaxel only)
- Adjuvant treatment of node-positive breast cancer following treatment with anthracycline and cyclophosphamide (conventional paclitaxel only)
- Treatment of non-small cell lung cancer (in combination with cisplatin) when surgery or radiotherapy not appropriate (conventional paclitaxel only)
- Treatment of advanced AIDS-related Kaposis's sarcoma where liposomal anthracycline therapy has failed (conventional paclitaxel only)
- First-line treatment of metastatic adenocarcinoma of the pancreas (in combination with gemcitabine) (conventional paclitaxel only)
- Monotherapy of metastatic breast cancer when first-line treatment has failed and standard, anthracycline-containing therapy is not indicated (albumin-bound paclitaxel only)
- In combination with gemcitabine for the first-line treatment of metastatic adenocarcinoma of the pancreas (albumin-bound paclitaxel only)

**SIDE-EFFECTS**

- Common or very common: Arrhythmia, arthralgia, febrile neutropenia, gastro-intestinal disorders, myalgia, peripheral neuropathy, sensory neuropathy, tachycardia
- Rare: Bradycardia, cardiac arrest, congestive heart failure, left ventricular dysfunction
- Frequency not known: Alopecia, arhythmias (nearly always asymptomatic), asymptomatic hypotension, bone-marrow suppression, bradycardia, cardiac conduction defects, extravasation, hypersensitivity reactions, hyperuricaemia, muscle pain, myelosuppression, nausea, neutropenia, oral mucositis, pneumonia, Stevens-Johnson syndrome, thromboembolism, toxic epidermal necrolysis, tumour lysis syndrome, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Hypersensitivity reactions: Routine premedication with a corticosteroid, an antihistamine and a histamine H₂-receptor antagonist is recommended to prevent severe hypersensitivity reactions; hypersensitivity reactions may occur rarely despite premedication.

**CONCEPTION AND CONTRACEPTION**

Ensure effective contraception during and for at least 6 months after treatment in men or women.

**PREGNANCY**

Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**

Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

Avoid in severe impairment.

**MONITORING REQUIREMENTS**

- Cardiac monitoring should be undertaken, particularly if patients have underlying cardiac disease or previous exposure to anthracyclines.

**CAUTIONS**

Avoid in acute porphyrias p. 930; consult product literature; patients aged over 75 years with metastatic adenocarcinoma of the pancreas.

**INTERACTIONS** ➔ Appendix 1 (paclitaxel).

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Paclitaxel for ovarian cancer (January 2003) NICE TA55
  Either paclitaxel in combination with a platinum compound (cisplatin or carboplatin) or a platinum compound alone are alternatives for the first-line treatment of ovarian cancer (usually following surgery).
  [www.nice.org.uk/TA55](http://www.nice.org.uk/TA55)
- Paclitaxel for the adjuvant treatment of early node-positive breast cancer (September 2006) NICE TA108
  Paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer.
  [www.nice.org.uk/TA108](http://www.nice.org.uk/TA108)
- Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (May 2013) NICE TA284
  Bevacizumab in combination with paclitaxel and carboplatin is not recommended for the first-line treatment of advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).
  [www.nice.org.uk/TA284](http://www.nice.org.uk/TA284)
- Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer (October 2015) NICE TA360
  Albumin-bound paclitaxel (nab-paclitaxel, Abraxane®) with gemcitabine, within its licensed indication, is not recommended for the treatment of previously untreated metastatic adenocarcinoma of the pancreas.
  Patients whose treatment was started before this guidance was published should continue treatment until they and their clinician consider it appropriate to stop.
  [www.nice.org.uk/TA360](http://www.nice.org.uk/TA360)
- Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA389
  Paclitaxel, in combination with platinum or as monotherapy, is recommended as an option for treating recurrent ovarian cancer.
  [www.nice.org.uk/TA389](http://www.nice.org.uk/TA389)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

EXCIPIENTS: May contain Polyoxyl castor oils

- Paclitaxel (Non-proprietary)
  Paclitaxel 6 mg per 1 ml
  Paclitaxel 150mg/25ml concentrate for solution for infusion vials | 1 vial (POD) £504.90–£561.00 (Hospital only) | 1 vial (POD) £300.52
  Paclitaxel 300mg/50ml concentrate for solution for infusion vials | 1 vial (POD) £112.31–£116.05 (Hospital only) | 1 vial (POD) £105.84
  Paclitaxel 300mg/50ml concentrate for solution for infusion vials | 1 vial (POD) £1,009.80–£1,122.00 (Hospital only) | 1 vial (POD) £951.63
  Paclitaxel 100mg/16.7ml concentrate for solution for infusion vials | 1 vial (POD) £336.60–£374.00 (Hospital only) | 1 vial (POD) £317.21

**Powder for suspension for infusion**

**ELECTROLYTES**: May contain Sodium

- Abraxane (Celgene Ltd)
  Abraxane 100 mg
  Abraxane 100mg powder for suspension for infusion vials | 1 vial (POD) £246.00 (Hospital only)
ANTINEOPLASTIC DRUGS > TOPOISOMERASE I INHIBITORS

Irinotecan hydrochloride

- **DRUG ACTION** Irinotecan inhibits topoisomerase I, an enzyme involved in DNA replication.

- **INDICATIONS AND DOSE** Metastatic colorectal cancer in combination with fluorouracil and folinic acid or as monotherapy when treatment containing fluorouracil has failed. Treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer after failure of chemotherapy that has included irinotecan (in combination with cetuximab). First-line treatment of metastatic carcinoma of the colon or rectum (in combination with fluorouracil, folinic acid, and bevacizumab). First-line treatment of metastatic colorectal carcinoma (in combination with capecitabine with or without bevacizumab).

- **CONTRA-INDICATIONS** Bowel obstruction. Chronic inflammatory bowel disease.

- **CAUTIONS** Raised plasma-bilirubin concentration.

- **INTERACTIONS** → Appendix 1 (irinotecan).

- **SIDE-EFFECTS**
  - Uncommon: Interstitial pulmonary disease.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for up to 1 month after treatment in women and up to 3 months after treatment in men.

- **PREGNANCY** Avoid (teratogenic and toxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid if plasma-bilirubin concentration greater than 3 times upper limit of normal range. Monitor closely for neutropenia if plasma-bilirubin concentration 1.5–3 times upper limit of normal range (consult product literature).

- **RENAL IMPAIRMENT** Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS** Monitor respiratory function.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)** Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005) NICE TA93

    A combination of fluorouracil and folinic acid with either irinotecan or oxaliplatin are options for first-line treatment for advanced colorectal cancer. Irinotecan alone or fluorouracil and folinic acid with oxaliplatin are options for patients who require further treatment subsequently. [www.nice.org.uk/TA93](http://www.nice.org.uk/TA93)

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for infusion**

    Irinotecan hydrochloride (Non-proprietary)

    Irinotecan hydrochloride trihydrate 20 mg per 1 ml:

    - Irinotecan 500 mg/25 ml concentrate for solution for infusion vials: £60.15–£65.00 (Hospital only)
    - Irinotecan 40 mg/2 ml concentrate for solution for infusion vials: £49.03–£53.00 (Hospital only)
    - Irinotecan 300 mg/15 ml concentrate for solution for infusion vials: £39.00 (Hospital only)
    - Irinotecan 100 mg/5 ml concentrate for solution for infusion vials: £120.25–£130.00 (Hospital only)
    - Irinotecan £100.62–£123.50

    Campto (Pfizer Ltd)

    Irinotecan hydrochloride trihydrate 20 mg per 1 ml:

    - Campto 100 mg/5 ml concentrate for solution for infusion vials: £130.00 (Hospital only)
    - Campto 40 mg/2 ml concentrate for solution for infusion vials: £53.00 (Hospital only)
    - Campto 300 mg/15 ml concentrate for solution for infusion vials: £390.00 (Hospital only)

- **Topotecan**

  - **DRUG ACTION** Topotecan inhibits topoisomerase I, an enzyme involved in DNA replication.

  - **INDICATIONS AND DOSE** Metastatic ovarian cancer when first-line or subsequent treatment has failed. Treatment of recurrent carcinoma of the cervix, after radiotherapy, and for patients with stage IVB disease (in combination with cisplatin).

    - **BY INTRAVENOUS INFUSION**

      Adult: (consult product literature or local protocols)

    - **Relapsed small-cell lung cancer when retreatment with the first-line regimen is considered inappropriate**

      - **BY INTRAVENOUS INFUSION, OR BY MOUTH**

      Adult: (consult product literature or local protocols)

- **IMPORTANT SAFETY INFORMATION**

  - **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES** See Cytotoxic drugs p. 797.


  - **CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

  - **PREGNANCY** Avoid (teratogenicity and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

  - **BREAST FEEDING** Discontinue breast-feeding.

  - **HEPATIC IMPAIRMENT** Avoid in severe impairment.

  - **RENAL IMPAIRMENT** Reduce dose. Avoid infusion if creatinine clearance less than 30 mL/minute. Avoid oral route if creatinine clearance less than 60 mL/minute.

  - **NATIONAL FUNDING/ACCESS DECISIONS**

    - **NICE technology appraisals (TAs)**

      Topotecan for the treatment of recurrent and stage IVB cervical cancer (October 2009) NICE TA183

      Topotecan in combination with cisplatin is recommended as a treatment option for recurrent or stage IVB cervical cancer in patients who have not previously received cisplatin. [www.nice.org.uk/TA183](http://www.nice.org.uk/TA183)
Topotecan for the treatment of relapsed small-cell lung cancer (November 2009) NICE TA184

Oral topotecan is recommended as an option for treatment in patients with relapsed small-cell lung cancer only if retreatment with the first-line regimen is not considered appropriate, and the combination of cyclophosphamide, doxorubicin and vincristine is contra-indicated.

Intravenous topotecan is not recommended for people with relapsed small-cell lung cancer.

www.nice.org.uk/TA184

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA389

Topotecan is not recommended for treating first recurrence of platinum-sensitive ovarian cancer, recurrent platinum-resistant ovarian cancer, or platinum-refractory ovarian cancer.

Patients currently receiving topotecan should have the option to continue their treatment until they or their clinician consider it appropriate to stop.

www.nice.org.uk/TA389

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2007) that topotecan (Hycamtin®) is accepted for restricted use in combination with cisplatin for treatment of recurrent carcinoma of the cervix after radiotherapy and for stage IVB disease; it is restricted to patients who have not previously received cisplatin treatment.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

- Hycamtin (Novartis Pharmaceuticals UK Ltd)
  - Topotecan (as Topotecan hydrochloride) 1 mg Hycamtin 1mg capsules | 10 capsule £360.00
  - Topotecan (as Topotecan hydrochloride) 250 microgram Hycamtin 0.25mg capsules | 10 capsule £75.00

Solution for infusion

- Topotecan (Non-proprietary)
  - Topotecan (as Topotecan hydrochloride) 1 mg per 1 ml Topotecan 4mg/4ml concentrate for solution for infusion vials | 1 vial £261.55 (Hospital only) | 1 vial no price available | 5 vial £1,453.10 (Hospital only)
  - Topotecan 1mg/1ml concentrate for solution for infusion vials | 1 vial £87.88 (Hospital only) | 1 vial no price available | 5 vial £488.25 (Hospital only)

Powder for solution for infusion

- Hycamtin (Novartis Pharmaceuticals UK Ltd)
  - Topotecan (as Topotecan hydrochloride) 1 mg Hycamtin 1mg powder for concentrate for solution for infusion vials | 1 vial £97.65
  - Topotecan (as Topotecan hydrochloride) 4 mg Hycamtin 4mg powder for concentrate for solution for infusion vials | 1 vial £348.76

- Potactasol (Actavis UK Ltd)
  - Topotecan (as Topotecan hydrochloride) 1 mg Potactasol 1mg powder for concentrate for solution for infusion vials | 1 vial £97.00 (Hospital only)
  - Topotecan (as Topotecan hydrochloride) 4 mg Potactasol 4mg powder for concentrate for solution for infusion vials | 1 vial £290.00 (Hospital only)

Vinblastine sulfate

INDICATIONS AND DOSE

- Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)
  - Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION

Vinblastine is for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 ml minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

CONTRA-INDICATIONS

CONTRA-INDICATIONS, FURTHER INFORMATION

Intrathecal injection contra-indicated.

CAUTIONS

Caution in handling—irritant to tissues

INTERACTIONS

Appendix 1 (vinblastine).

SIDE-EFFECTS

Abdominal pain, alopecia, autonomic neuropathy, constipation, hyperuricaemia, loss of deep tendon reflexes, motor weakness, myelosuppression (dose-limiting), nausea, neurotoxicity, oral mucositis, ototoxicity, peripheral neuropathy, peripheral paraesthesia, severe bronchospasm following administration (more commonly when used in combination with mitomycin-C), severe local irritation (care must be taken to avoid extravasation), thromboembolism, tumour lysis syndrome, vomiting

FURTHER INFORMATION

Neurotoxicity

Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids; it occurs less often with vinblastine than with vincristine.

Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; ototoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced.

Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

CONCEPTION AND CONTRACEPTION

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797

PREGNANCY

Avoid (limited experience suggests fetal harm; teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Dose reduction may be necessary—consult local treatment protocol for details.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Vinblastine sulfate (Non-proprietary)
  - Vinblastine sulfate 1 mg per 1 ml Vinblastine 10mg/10ml solution for injection vials | 5 vial £85.00
Vincristine sulfate

- **INDICATIONS AND DOSE**
  - Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)
  - Adult: (consult local protocol)

**IMPORTANT SAFETY INFORMATION**
Vincristine injections are for **intravenous administration only**. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

- **CONTRA-INDICATIONS**
  - CONTRA-INDICATIONS. FURTHER INFORMATION
  - Intrathecal injection **contra-indicated**.
- **CAUTIONS**
  - Caution in handling—irritant to tissues • neuromuscular disease
- **INTERACTIONS**
  - **Rare** Diarrhoea • inappropriate secretion of antidiuretic hormone • intestinal necrosis • paralytic ileus • seizures • urinary retention
  - **Frequency not known** Abdominal pain • alopecia • autonomic neuropathy • constipation • extravasation • eye disorders • hyperuricaemia • loss of deep tendon reflexes • motor weakness • muscle wasting • myelosuppression (negligible) • nausea • neurotoxicity • oral mucositis • otoxicity • peripheral neuropathy • peripheral paraesthesia • severe bronchospasm following administration (more commonly when used in combination with mitomycin-C) • severe local irritation (care must be taken to avoid extravasation) • thromboembolism • tumour lysis syndrome • vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Neurotoxicity Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids and is a limiting side-effect of vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; otoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced.
  - Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.
- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **PREGNANCY**
  - Avoid (teratogenicity and fetal loss in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **BREAST FEEDING**
  - Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT**
  - Dose reduction may be necessary—consult local treatment protocol for details.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Vincristine sulfate (non-proprietary)**
  - Vincristine sulfate 1 mg per 1 ml Vincristine 1mg/1ml solution for injection vials | 1 vial (POM) £13.47 (Hospital only) | 5 vial (POM) £67.35

Vindesine sulfate

- **INDICATIONS AND DOSE**
  - Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**
Vindesine injections are for **intravenous administration only**. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

- **CONTRA-INDICATIONS**
  - CONTRA-INDICATIONS. FURTHER INFORMATION
  - Intrathecal injection **contra-indicated**.
- **CAUTIONS**
  - Caution in handling—irritant to tissues • neuromuscular disease
- **INTERACTIONS**
  - **Rare** Diarrhoea • autonomic neuropathy • bone-marrow suppression • extravasation • hyperuricaemia • irritant to tissues • myelosuppression (dose-limiting) • nausea • neurotoxicity • oral mucositis • peripheral neuropathy • severe bronchospasm following administration (more commonly when used in combination with mitomycin-C) • severe local irritation (if extravasated) • thromboembolism • tumour lysis syndrome • vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Neurotoxicity Neurotoxicity, usually as peripheral or autonomic neuropathy; it occurs less often with vindesine than with vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; otoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced.
  - Motor weakness can also occur, and increasing motor weakness calls for dose reduction or discontinuation. Recovery from neurotoxic effects is usually slow but complete.
- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **PREGNANCY**
  - Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **BREAST FEEDING**
  - Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT**
  - Dose reduction may be necessary.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Eldisine** (Genus Pharmaceuticals Ltd)
  - Vindesine sulfate 5 mg Eldisine 5mg powder for solution for injection vials | 1 vial (POM) £66.55 (Hospital only)
Vinflunine

**INDICATIONS AND DOSE**

Treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a platinum-containing regimen (monotherapy)

- **Adult:** (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

Vinflunine injections are for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**CONTRA-INDICATIONS**

CONTRA-INDICATIONS, FURTHER INFORMATION

Intrathecal injection contra-indicated.

**CAUTIONS**

Cardiovascular disease - QT-interval prolongation (avoid hypokalaemia)

**INTERACTIONS**

→ Appendix 1 (vinflunine)

Caution with concomitant use of drugs that prolong QT-interval.

**SIDE-EFFECTS**

- **Common or very common**
  - Anorexia • cutaneous reactions • dehydration • diarrhoea • dyspepsia • fatigue • hypertension • hypotension • insomnia • oedema • sweating • tachycardia • thrombosis

- **Uncommon**
  - Increased weight • myocardial infarction • renal failure

- **Frequency not known**
  - Alopecia • autonomic neuropathy • blurred vision • extravasation • hyperuricaemia • inappropriate anti-diuretic hormone secretion • myelosuppression (dose-limiting) • nausea • neurotoxicity • oral mucositis • peripheral neuropathy • QT-interval prolongation • severe bronchospasm following administration (more commonly used when combined with mitomycin-C) • severe local irritation (if extravasated) • thromboembolism • tumour lysis syndrome • vomiting

SIDE-EFFECTS, FURTHER INFORMATION

- Neurotoxicity • Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids and is a limiting side-effect of vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; ototoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced. Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

- **CONCEPTION AND CONTRACEPTION**

Manufacturer advises effective contraception during and for up to 3 months after treatment.

- **PREGNANCY**

Avoid unless essential—teratogenicity and embryotoxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**

Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**

Reduce dose—consult product literature.

- **RENAL IMPAIRMENT**

Reduce dose if creatinine clearance less than 60 mL/minute—consult product literature.

**NATIONAL FUNDING.ACCESS DECISIONS**

NICE technology appraisals (TAs)

- **Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (January 2013) NICE TA272**

Vinflunine is not recommended for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.

www.nice.org.uk/TA272

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Javor (Pierre Fabre Ltd)**

  Vinflunine (as Vinflunine ditartrate) 25 mg per 1 ml Javor 250mg/10ml concentrate for solution for infusion | 1 vial £1.062.50

  Javor 50mg/2ml concentrate for solution for infusion | 1 vial £212.50

**Vinorelbine**

**DRUG ACTION**

Vinorelbine is a semi-synthetic vinca alkaloid.

**INDICATIONS AND DOSE**

Advanced breast cancer | Advanced non-small cell lung cancer

- **BY MOUTH**

  - Adult: 60 mg/m² once weekly for 3 weeks, then increased if tolerated to 80 mg/m² once weekly (max. per dose 160 mg once weekly)

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**

  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

Vinorelbine injections are for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**CONTRA-INDICATIONS**

CONTRA-INDICATIONS, FURTHER INFORMATION

Intrathecal injection contra-indicated.

**CAUTIONS**

Caution in handling—irritant to tissues • ischaemic heart disease

**INTERACTIONS**

→ Appendix 1 (vinorelbine).

**SIDE-EFFECTS**

- **Rare**

  - Pancreatitis

- **Frequency not known**

  - Alopecia • autonomic neuropathy • extravasation • hyperuricaemia • hyponatraemia • inappropriate secretion of antidiuretic hormone • irritant to tissues • motor weakness • myelosuppression (dose-limiting) • nausea • neurotoxicity • oral mucositis • peripheral neuropathy • severe bronchospasm following administration of the vinca alkaloids (more commonly used in combination with mitomycin-C) • severe myelosuppression • severe local irritation (if extravasated) • tumour lysis syndrome • vomiting

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.
local irritation (if extravasated) · thromboembolism · tumour lysis syndrome · vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Neutropenia Neutropenia, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids; it occurs less often with vinorelbine. Patients with neutropenia commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; otoxicity has been reported. If symptoms of neutropenia are severe, doses should be reduced.
- Motor weakness can also occur, and increasing motor weakness calls for dose reduction or discontinuation of these drugs. Recovery from neurotoxic effects is usually slow but complete.
- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for at least 3 months after treatment; men must avoid fathering a child during and for at least 3 months after treatment.
- **PREGNANCY** Avoid unless essential (teratogenicity, and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT**
  - With oral use Reduce oral dose in moderate impairment. Avoid oral use in severe impairment.
  - With intravenous use Reduce intravenous dose in severe impairment. Consult product literature.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>21, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Navelbine (Pierre Fabre Ltd)</strong></td>
<td></td>
</tr>
<tr>
<td>Vinorelbine (as Vinorelbine tartrate) 20 mg</td>
<td>Navelbine 20mg capsules</td>
</tr>
<tr>
<td>Vinorelbine (as Vinorelbine tartrate) 30 mg</td>
<td>Navelbine 30mg capsules</td>
</tr>
<tr>
<td>Vinorelbine (as Vinorelbine tartrate) 80 mg</td>
<td>Navelbine 80mg capsules</td>
</tr>
</tbody>
</table>

**Solution for infusion**

<table>
<thead>
<tr>
<th><strong>Navelbine (Non-proprietary)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml</td>
<td>Vinorelbine 50mg/5ml concentrate for solution for infusion vials</td>
</tr>
<tr>
<td>Vincentine 10mg/1ml concentrate for solution for infusion vials</td>
<td>1 vial</td>
</tr>
<tr>
<td><strong>Navelbine (Pierre Fabre Ltd)</strong></td>
<td></td>
</tr>
<tr>
<td>Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml</td>
<td>Navelbine 10mg/1ml concentrate for solution for infusion vials</td>
</tr>
<tr>
<td>Navelbine 50mg/5ml concentrate for solution for infusion vials</td>
<td>10 vial</td>
</tr>
</tbody>
</table>

**ANTINEOPLASTIC DRUGS > OTHER**

**Arsenic trioxide**

<table>
<thead>
<tr>
<th><strong>INDICATIONS AND DOSE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute promyelocytic leukaemia in patients who have relapsed or failed to respond to previous treatment with a retinoid and chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>BY INTRAVENOUS INFUSION</strong></td>
<td></td>
</tr>
<tr>
<td>Adult: (consult local protocol)</td>
<td></td>
</tr>
</tbody>
</table>

| **CAUTIONS** | Hypokalaemia (correct before treatment) · hypomagnesaemia (correct before treatment) · previous treatment with anthracyclines (increased risk of QT interval prolongation) |
| **INTERACTIONS** | Appendix 1 (arsenic trioxide). Avoid concomitant administration with drugs causing QT interval prolongation. |

**SIDE-EFFECTS**
- **Common or very common** Atrial fibrillation · atrial flutter · diarrhoea · fatigue · haemorrhage · hyperglycaemia · hypokalaemia · leucocyte activation syndrome · musculoskeletal pain · paraesthesia · pleuritic pain · QT interval prolongation
- **Uncommon** Abdominal pain · blurred vision · hypotension · oedema · pneumonia · rash · renal failure · seizures · tachycardia · vasculitis
- **Frequency not known** Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Leucocyte activation syndrome Signs and symptoms of leucocyte activation syndrome include unexplained fever, dyspnoea, weight gain, pulmonary infiltrates, pleural or pericardial effusions, with or without leucocytosis—treatment with high dose corticosteroids, consult product literature.
- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment in men and women.
- **PREGNANCY** Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution—limited information available.
- **RENAI IMPAIRMENT** Manufacturer advises caution—limited information available.
- **MONITORING REQUIREMENTS** ECG required before and during treatment—consult product literature.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

<table>
<thead>
<tr>
<th><strong>Trisenox (Teva UK Ltd)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide 1 mg per 1 ml</td>
<td>Trisenox 10mg/10ml concentrate for solution for infusion ampoules</td>
</tr>
</tbody>
</table>

**Crisantaspase**

**DRUG ACTION** Crisantaspase is the enzyme asparaginase produced by Erwinia chrysanthemi.

**INDICATIONS AND DOSE**
- **Acute lymphoblastic leukaemia**
  - **BY INTRAMUSCULAR INJECTION, OR BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INJECTION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS** History of pancreatitis related to asparaginase therapy.

**SIDE-EFFECTS**
- **Common or very common** Coagulation disorders · confusion · convulsions · diarrhoea · dizziness · drowsiness · headache · lethargy · liver dysfunction · neurotoxicity · pancreatitis
- **Uncommon** Anaphylaxis · changes in blood lipids · hyperglycaemia
- **Rare** CNS depression
- **Very rare** Abdominal pain · hypertension · myalgia
- **Frequency not known** Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**PREGNANCY** Avoid. See also, Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.
Eribulin

**INDICATIONS AND DOSE**
Treatment of locally advanced or metastatic breast cancer when the disease has progressed after treatment with at least 1 chemotherapy regimen for advanced disease

- **BY INTRAVENOUS INJECTION**
  - Adult: Give on day 1 and day 8 of a 21-day cycle, previous therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless the patient is unsuitable for these treatments (consult local protocol)

**CONTRA-INDICATIONS**
- Congenital long QT syndrome

**CAUTIONS**
- Bradyarrhythmias (increased susceptibility to QT-interval prolongation)
- Congestive heart failure (increased susceptibility to QT-interval prolongation)
- Electrolyte disturbances (increased susceptibility to QT-interval prolongation)
- Increased susceptibility to QT-interval prolongation

**INTERACTIONS**
- Caution with concomitant use of drugs that prolong QT-interval.

**SIDE-EFFECTS**
- Alopecia
- Bone-marrow suppression
- Extravasation
- Hyperuricaemia
- Myelosuppression
- Nausea
- Oral mucositis
- Peripheral neuropathy
- QT-interval prolongation
- Thromboembolism
- Tumour lysis syndrome
- Vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
For further information on side effects, consult product literature.

**CONCEPTION AND CONTRACEPTION**
Ensure effective contraception during and for up to 3 months after treatment in men or women.

**PREGNANCY**
Avoid unless essential (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Reduce dose.

**RENAL IMPAIRMENT**
Consider dose reduction if creatinine clearance less than 40 mL/minute.

**MONITORING REQUIREMENTS**
- Monitor for signs of peripheral neuropathy—severe peripheral neurotoxicity requires treatment delay or dose reduction (consult product literature).
- ECG monitoring recommended in patients prescribed concomitant use of drugs that prolong the QT-interval or who are susceptible to QT-interval prolongation.
- Monitor electrolytes periodically.

**NATIONAL FUNDING/ACCESS DECISIONS**
**NICE technology appraisals (TAs)**
- Eribulin for the treatment of locally advanced or metastatic breast cancer (April 2012) NICE TA250
  - Eribulin is not recommended for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease.
  - www.nice.org.uk/TA250

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (March 2016) that eribulin (Halaven®) is accepted for restricted use within NHS Scotland for the treatment of patients with locally advanced or metastatic breast cancer that has progressed after at least two prior chemotherapy regimens for advanced disease, which includes capecitabine if indicated.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **EXCIPIENTS**: May contain Ethanol
- Halaven (Eisai Ltd)
  - Eribulin 44 mg per 1 ml
  - Halaven 0.88mg/2ml solution for injection vials | 1 vial £361.00 (Hospital only)
  - Halaven 1.32mg/3ml solution for injection vials | 1 vial £541.50 (Hospital only)

**Hydroxyurea**
(*Hydroxyurea*)

**INDICATIONS AND DOSE**
Treatment of chronic myeloid leukaemia | Treatment of cancer of the cervix in conjunction with radiotherapy | Polycythaemia

- **BY MOUTH**
  - Adult: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days

**Sickle-cell disease—consult with a specialist centre**

**SIDE-EFFECTS**
- Common or very common
  - Headache
- Reduced sperm count and skin reactions

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises effective contraception before and during treatment.

**PREGNANCY**
Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment, unless used for malignant conditions.

**RENAL IMPAIRMENT**
In sickle-cell disease, reduce initial dose by 50% if eGFR less than 60 mL/minute/1.73 m². In sickle-cell disease, avoid if eGFR less than 30 mL/minute/1.73 m².

- Use with caution in malignant disease.

**IMPORTANT SAFETY INFORMATION**
**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 797.

**CAUTIONS**
- Leg ulcers (review treatment if cutaneous vasculitic ulcerations develop)

**INTERACTIONS**
- Appendix 1 (hydroxyurea).

**SIDE-EFFECTS**
- Common or very common
  - Headache
- Myelosuppression
- Skin reactions
- Rare
  - Aminorrhoea (in sickle-cell disease)
  - Fever (in sickle-cell disease)

**FURTHER INFORMATION**
See Cytotoxic drugs 2016 p. 833

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (March 2016) that eribulin (Halaven®) is accepted for restricted use within NHS Scotland for the treatment of patients with locally advanced or metastatic breast cancer that has progressed after at least two prior chemotherapy regimens for advanced disease, which includes capecitabine if indicated.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **EXCIPIENTS**: May contain Ethanol
- Halaven (Eisai Ltd)
  - Eribulin 44 mg per 1 ml
  - Halaven 0.88mg/2ml solution for injection vials | 1 vial £361.00 (Hospital only)
  - Halaven 1.32mg/3ml solution for injection vials | 1 vial £541.50 (Hospital only)
Mitotane

**DRUG ACTION** Mitotane selectively inhibits the activity of the adrenal cortex, necessitating corticosteroid replacement therapy.

**INDICATIONS AND DOSE**
Symptomatic treatment of advanced or inoperable adrenocortical carcinoma

- **BY MOUTH**
- Adult: Initially 2–3 g daily in 2–3 divided doses adjusted according to plasma-concentration monitoring, in severe illness initial dose can be increased up to 6 g daily; reduce dose or interrupt treatment if signs of toxicity, discontinue if inadequate response after 3 months

**MONITORING REQUIREMENTS**
- Monitor renal and hepatic function before and during treatment.
- Monitor full blood count before treatment, and repeatedly throughout use; in sickle-cell disease monitor every 2 weeks for the first 2 months and then every 2 months thereafter (or every 2 weeks if on maximum dose).
- Patients receiving long-term therapy for malignant disease should be monitored for secondary malignancies.

**PATIENT AND CARER ADVICE**
Patients receiving long-term therapy with hydroxycarbamide should be advised to protect skin from sun exposure.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

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<thead>
<tr>
<th>Tablet</th>
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<tbody>
<tr>
<td>&lt;b&gt;Siklos&lt;/b&gt; (Nordic Pharma Ltd)</td>
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<tr>
<td>&lt;b&gt;Hydroxycarbamide 1 gram&lt;/b&gt;</td>
<td>Siklos 1000mg tablets</td>
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<td>Hydroxycarbamide 100 mg</td>
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<th>Capsule</th>
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<td>Hydroxycarbamide (Non-proprietary)</td>
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<tr>
<td>Hydroxycarbamide 500 mg Hydroxycarbamide 500mg capsules</td>
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<td>Hydrea (Bristol-Myers Squibb Pharmaceuticals Ltd)</td>
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<td>Hydroxycarbamide 500 mg Hydrea 500mg capsules</td>
<td>100 capsule</td>
<td>£10.47 DT price = £12.11</td>
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**SIDE-EFFECTS**
- Common or very common: Anaemia · anaorexia · asthenia · ataxia · cognitive impairment · confusion · diarrhoea · dizziness · drowsiness · endocrine side effects · epigastric discomfort · gastro-intestinal disturbances · gynaecomastia · headache · hypercholesterolaemia · hypertriglyceridaemia · hypogonadism · leucopenia · liver disorders · movement disorder · myasthenia · nausea · neuropathy · neurotoxicity · paraesthesia · prolonged bleeding time · rash · thrombocytopenia · thyroid disorders · vomiting
- Rare: Flushing · haematuria · haemorrhagic cystitis · hypersalivation · hypertension · hypouricaemia · ocular disorders · postural hypotension · proteinuria · pyrexia · visual disturbances

**CAUTIONS**
- Avoid in acute porphyrias p. 930 · risk of accumulation in overweight patients

**INTERACTIONS** → Appendix 1 (mitotane).

**RENNAL IMPAIRMENT**
- Plasma-mitotane concentration for optimum response ~14–20 mg/litre.
- Monitor plasma-mitotane concentration—consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION**
Corticosteroid replacement therapy
Corticosteroid replacement therapy is necessary with treatment with mitotane. The dose of glucocorticoid should be increased in case of shock, trauma, or infection.

**PREGNANCY**
Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
- Avoid in severe impairment. Manufacturer advises caution in mild to moderate impairment; monitoring of plasma-mitotane concentration is recommended.

**RENAI IMPAIRMENT**
- Avoid in severe impairment. Manufacturer advises caution in mild to moderate impairment; monitoring of plasma-mitotane concentration is recommended.

**MONITORING REQUIREMENTS**
- Plasma-mitotane concentration for optimum response ~14–20 mg/litre.
- Monitor plasma-mitotane concentration—consult product literature.

**SIDE-EFFECTS**
- Frequency not known: Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**Panobinostat**

**DRUG ACTION** Panobinostat is a histone deacetylase inhibitor, which promotes cell-cycle arrest and apoptosis of tumour cells via multiple pathways.

**INDICATIONS AND DOSE**
Treatment of relapsed or refractory multiple myeloma (in combination with bortezomib and dexamethasone), in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent

- **BY MOUTH**
- Adult 18–74 years: 20 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 8 cycles. Patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks), for doses of dexamethasone and bortezomib, or dose adjustment due to side-effects—consult product literature
- Adult 75 years and over: 20 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 8 cycles. Patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks),

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**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 797.

**CAUTIONS** Avoid in acute porphyrias p. 930 · risk of accumulation in overweight patients

**INTERACTIONS** → Appendix 1 (mitotane).

**SIDE-EFFECTS**
- Common or very common: Anaemia · anaorexia · asthenia · ataxia · cognitive impairment · confusion · diarrhoea · dizziness · drowsiness · endocrine side effects · epigastric discomfort · gastro-intestinal disturbances · gynaecomastia · headache · hypercholesterolaemia · hypertriglyceridaemia · hypogonadism · leucopenia · liver disorders · movement disorder · myasthenia · nausea · neuropathy · neurotoxicity · paraesthesia · prolonged bleeding time · rash · thrombocytopenia · thyroid disorders · vomiting
- Rare: Flushing · haematuria · haemorrhagic cystitis · hypersalivation · hypertension · hypouricaemia · ocular disorders · postural hypotension · proteinuria · pyrexia · visual disturbances

**RENNAL IMPAIRMENT**
- Plasma-mitotane concentration for optimum response ~14–20 mg/litre.
- Monitor plasma-mitotane concentration—consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION**
Corticosteroid replacement therapy
Corticosteroid replacement therapy is necessary with treatment with mitotane. The dose of glucocorticoid should be increased in case of shock, trauma, or infection.

**PREGNANCY**
Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
- Avoid in severe impairment. Manufacturer advises caution in mild to moderate impairment; monitoring of plasma-mitotane concentration is recommended.

**RENAI IMPAIRMENT**
- Avoid in severe impairment. Manufacturer advises caution in mild to moderate impairment; monitoring of plasma-mitotane concentration is recommended.

**MONITORING REQUIREMENTS**
- Plasma-mitotane concentration for optimum response ~14–20 mg/litre.
- Monitor plasma-mitotane concentration—consult product literature.

**SIDE-EFFECTS**
- Frequency not known: Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**Panobinostat**

**DRUG ACTION** Panobinostat is a histone deacetylase inhibitor, which promotes cell-cycle arrest and apoptosis of tumour cells via multiple pathways.

**INDICATIONS AND DOSE**
Treatment of relapsed or refractory multiple myeloma (in combination with bortezomib and dexamethasone), in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent

- **BY MOUTH**
- Adult 18–74 years: 20 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 8 cycles. Patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks), for doses of dexamethasone and bortezomib, or dose adjustment due to side-effects—consult product literature
- Adult 75 years and over: 20 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 8 cycles. Patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks),
alternatively initially 15 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 1 cycle, increased if tolerated to 20 mg once daily, for 7 subsequent cycles, patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks), lower dose may be used for the first cycle depending on patient’s condition and co-morbidities, for doses of dexamethasone and bortezomib, or dose adjustment due to side-effects—consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
Reduce dose to 10 mg with concomitant use of potent CYP3A4 inhibitors (such asitraconazole, ketoconazole, posaconazole, ritonavir, saquinavir, and telithromycin); if the potent CYP3A4 inhibitor is to be continued, consider increasing the dose to 15 mg if tolerated. Avoid potent CYP3A4 inhibitors if possible in patients taking a reduced panobinostat dose due to side-effects.

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

- **CAUTIONS** Coagulation disorders · elderly · QT-interval prolongation · risk factors for QT-interval prolongation

- **INTERACTIONS** → Appendix 1 (panobinostat). Contra-indicated with concomitant use of drugs that prolong the QT-interval. Avoid concurrent use of potent CYP3A4 inhibitors in patients with hepatic impairment.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal distension · abdominal pain · abnormal hepatic function · anaemia · atrial fibrillation · bradycardia · chilblains · cough · decreased appetite · dehydration · diarrhoea · dizziness · dry mouth · dysgeusia · dyspepsia · dyspnoea · electrolyte disturbances · epistaxis · erythema · fatigue · flatulence · fluid retention · gastritis · haemorrhage (may lead to haemorrhagic shock) · headache · hyperglycaemia · hypertension · hypoalbuninaemia · hypotension (including orthostatic) · hypothyroidism · insomnia · joint swelling · leucopenia · lymphopenia · nausea · neutropenia · palpitations · pancytopenia · peripheral oedema · QT-interval prolongation · rash · renal failure · respiratory failure · skin lesions · syncope · tachycardia · thrombocytopenia · tremor · urinary incontinence · vomiting · wheezing
  - **Uncommon** Colitis · myocardial infarction

- **SIDE-EFFECTS, FURTHER INFORMATION**

- **SIDE-EFFECTS** are reported when used in combination with bortezomib and dexamethasone.

- **Gastro-intestinal disorders** Manufacturer advises that patients are treated with anti-diarrhoeals, or any medicines used for diarrhoea. Patients are treated with anti-diarrhoeals, or any medicines used for diarrhoea. Patients are treated with anti-diarrhoeals, or any medicines used for diarrhoea.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises exclude pregnancy before starting treatment in women of child-bearing potential, and ensure highly effective contraception used during treatment and for 3 months after last dose. Women using hormonal contraceptives should also use a barrier method of contraception. Highly effective contraception also required for men and their female partners during treatment and for 6 months after last dose.

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—absence of data in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises reduce initial dose to 15 mg during the first treatment cycle in mild impairment—dose may be increased to 20 mg based on patient tolerability; reduce initial dose to 10 mg during the first treatment cycle in moderate impairment—dose may be increased to 15 mg based on patient tolerability. Manufacturer advises frequent monitoring of hepatic function in mild and moderate impairment, particularly during the dose escalation phase; avoid in severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor full blood count before treatment, then frequently during treatment; reduce dose or interrupt treatment if thrombocytopenia or neutropenia occur—consult product literature.
  - Manufacturer advises monitor ECG before treatment and repeat periodically before each treatment cycle; QTCF should be <480 milliseconds before treatment initiation—consult product literature.
  - Manufacturer advises monitor electrolytes before treatment and periodically as clinically indicated, especially in patients with diarrhoea; monitor thyroid and pituitary function (free T4 and TSH) as clinically indicated; monitor hepatic function before treatment and regularly during treatment as clinically indicated.
  - Manufacturer advises monitor patients over 65 years more frequently, especially for thrombocytopenia and gastrointestinal toxicity.

- **PATIENT AND CARER ADVICE**

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**
  - Panobinostat for treating multiple myeloma after at least 2 previous treatments (January 2016) NICE TA380

  Panobinostat, in combination with bortezomib and dexamethasone, is recommended as an option for treatment relapsed or refractory multiple myeloma in patients who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent when the manufacturer provides panobinostat with the discount agreed in the patient access scheme.

  www.nice.org.uk/TA380

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**

  CAUTIONARY AND ADVISORY LABELS 25

  - **Farydak** (Novartis Pharmaceuticals UK Ltd) ▼
    - Panobinostat (as Panobinostat lactate anhydrous) 10 mg Farydak 10mg capsules | 6 capsule [POM] £3,492.00
    - Panobinostat (as Panobinostat lactate anhydrous) 15 mg Farydak 15mg capsules | 6 capsule [POM] £3,492.00
    - Panobinostat (as Panobinostat lactate anhydrous) 20 mg Farydak 20mg capsules | 6 capsule [POM] £4,656.00
Procarbazine

- **DRUG ACTION** Procarbazine is a mild monoamine-oxidase inhibitor.

### INDICATIONS AND DOSE

**Hodgkin’s Lymphoma**

- **BY MOUTH**
- Adult: (consult local protocol)

### IMPORTANT SAFETY INFORMATION

#### RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 797.

- **CONTRA-INDICATIONS** Pre-existing severe leucopenia - pre-existing severe thrombocytopenia
- **CAUTIONS** Cardiovascular disease - cerebrovascular disease - epilepsy - phaeochromocytoma - procarbazine is a mild monoamine oxidase inhibitor (dietary restriction is rarely considered necessary)
- **INTERACTIONS** → Appendix 1 (procarbazine). Alcohol ingestion may cause a disulfiram-like reaction.
- **SIDE-EFFECTS**
  - Common or very common: Loss of appetite
  - Frequency not known: Alopecia - bone-marrow suppression - hypersensitivy rash (discontinue treatment) - hyperuricaemia - jaundice - myelosuppression - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting
- **CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **PREGNANCY** Avoid (teratogenic in animal studies and isolated reports in humans). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Reduce dose and increase dosing interval if creatinine clearance less than 65 mL/minute (consult product literature). Avoid if creatinine clearance less than 25 mL/minute.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **Tomudex** (Hospira UK Ltd)
    - Raltitrexed 2 mg Tomudex 2mg powder for solution for infusion vials | 1 vial [POD] £148.75

### RETINOID AND RELATED DRUGS

#### Bexarotene

- **DRUG ACTION** Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. Bexarotene can cause regression of cutaneous T-cell lymphoma.

### INDICATIONS AND DOSE

Skin manifestations of cutaneous T-cell lymphoma refractory to previous systemic treatment

- **BY MOUTH**
- Adult: Initially 300 mg/m² once daily, adjusted according to response, to be taken with a meal

### IMPORTANT SAFETY INFORMATION

#### RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 797.

- **CONTRA-INDICATIONS** History of pancreatitis - hypervitaminosis A - uncontrolled hyperlipidaemia - uncontrolled hypothyroidism
- **CAUTIONS** Avoid in acute porphyrias p. 930 - hyperlipidaemia - hypothyroidism
- **INTERACTIONS** → Appendix 1 (bexarotene).
- **SIDE-EFFECTS** Alopecia - bone-marrow suppression - headache - hyperlipidaemia - hyperuricaemia - hypothyroidism - immunosuppression - leucopenia - myelosuppression - nausea - oral mucositis - pruritus - rash - thromboembolism - tumour lysis syndrome - vomiting

### ALLERGY AND CROSS-SENSITIVITY

Caution—hypersensitivity to retinoids.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for at least 1 month after treatment in men and women.
- **PREGNANCY** Avoid. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Avoid.

### NATIONAL FUNDING/ACCESS DECISIONS

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (November 2002) that bexarotene is recommended for restricted use...
as a second-line treatment for patients with advanced cutaneous T-cell lymphoma.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - Targretin (Teva UK Ltd)

**SIDE-EFFECTS**


**SIDE-EFFECTS, FURTHER INFORMATION**

- Retinoid acid syndrome
- Fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural effusion, hyperleucocytosis, hypotension, oedema, weight gain, hepatic, renal and multi-organ failure requires immediate treatment—consult product literature.

**CONCEPTION AND CONTRACEPTION**

Effective contraception must be used for at least 1 month before oral treatment, during treatment and for at least 1 month after stopping (oral progestogen-only contraceptives not considered effective).

**PREGNANCY**

Teratogenic. See Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**

Avoid (discontinue breast-feeding).

**HEPATIC IMPAIRMENT**

Reduce dose to 25 mg/m².

**RENAL IMPAIRMENT**

Reduce dose to 25 mg/m².

**MONITORING REQUIREMENTS**

Monitor haematological and coagulation profile, liver function, serum calcium and plasma lipids before and during treatment.

**PRESCRIBING AND DISPENSING INFORMATION**

Tretinoin is the acid form of vitamin A.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - Tretinoin (Non-proprietary)
  - Tretinoin 10 mg  Tretinoin 10mg capsules | 100  capsule

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### 2.1 Cytotoxic drug-induced side effects

#### ANTIDOTES AND CHELATORS ▶ IRON CHELATORS

**Dexrazoxane**

- **DRUG ACTION**
  - Dexrazoxane is an iron chelator.

**INDICATIONS AND DOSE**

**Cardoxane**

Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin treatment in advanced or metastatic breast cancer patients who have received a prior cumulative dose of 300 mg/m² of doxorubicin or a prior cumulative dose of 540 mg/m² of epirubicin when further anthracycline treatment is required

- **BY INTRAVENOUS INFUSION**
  - Adult: Administer 10 times the doxorubicin-equivalent dose or 10 times the epirubicin-equivalent dose, dose to be given 30 minutes before anthracycline administration

**Savene**

**Anthracycline extravasation**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 1 g/m² daily (max. per dose 2 g) for 2 days, then 500 mg/m² for 1 day, first dose to be given as soon as possible and within 6 hours after injury

**CAUTIONS**

- Myelosuppression (effects may be additive to those of chemotherapy)

**Cardoxane**

- Manufacturer advises caution in patients with heart failure, myocardial infarction in previous 12 months, symptomatic valvular heart disease, uncontrolled angina—no information available

**INTERACTIONS**

- Appendix 1 (dextrazoxane).

**SIDE-EFFECTS**

**Cardoxane**

- **Common or very common**
  - Anorexia - asthenia - diarrhoea - dizziness - dry mouth - dysphonia - erythema - infection - malaise - nausea - oedema - paraesthesia - peripheral neuropathy - stomatitis - syncope - vomiting

- **Uncommon**
  - Abdominal pain - acute myeloid leukaemia - constipation - cough - dyspepsia - headache - lymphoedema - nail disorder - reduced ejection fraction - tachycardia - thromboembolism (when given with cytotoxic drugs)

- **Frequency not known**
  - Alopecia - anaemia - blood disorders - fatigue - injection-site reactions - leucopenia - phlebitis - pruritus - pyrexia - thrombocytopenia

**Savene**

- **Common or very common**

- **Uncommon**
  - Drowsiness - myalgia - thromboembolism (when given with cytotoxic drugs) - weight loss

**CONCEPTION AND CONTRACEPTION**

Ensure effective contraception during and for at least 3 months after treatment in men and women.

- **PREGNANCY**
  - Avoid unless essential (toxicity in animal studies).

- **BREAST FEEDING**
  - Discontinue breast-feeding.
Keratinocyte growth factors

Breast feeding

Pregnancy

Side-effects

Drug action

Medicinal forms

Detoxifying drugs

Palifermin

Drug action

Indications and dose

Management of oral mucositis in patients with haematological malignancies receiving myeloblastic radiochemotherapy with autologous haematopoietic stem-cell support

BY INTRAVENOUS INJECTION

Adult: 60 micrograms/kg once daily for 3 doses (third dose given 24–48 hours before myeloblastic therapy) then 3 further doses at least 24 hours after myeloblastic therapy, and more than 4 days after most recent palifermin injection, starting on the same day as (but after) stem-cell infusion

Side-effects

Arthralgia • discoloration of the tongue • erythema • fever • oedema • oral paraesthesia • pruritus • rash • skin hyperpigmentation • taste disturbance • thickening of the tongue

Pregnancy

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

Breast feeding

Manufacturer advises avoid—no information available.

Indications and dose

Cytotoxic induced urothelial toxicity

BY MOUTH, OR BY INTRAVENOUS INJECTION

Adult: Dose to be calculated according to oxazophosphorine (cyclophosphamide or ifosfamide) treatment (consult product literature)

Side-effects

Common or very common

Colic • depression • diarrhoea • fatigue • headache • hypotension • irritability • joint pains • limb pains • nausea • rash • tachycardia • vomiting

Rare

Hypersensitivity reactions (more common in patients with auto-immune disorders)

Allergy and cross-sensitivity

Contra-indicated if history of hypersensitivity to thiol-containing compounds.

Pregnancy

Not known to be harmful. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

Effect on laboratory tests

False positive urinary ketones. False positive or false negative urinary erythrocytes.

Directions for administration

For oral administration of the injection, contents of ampoule are taken in a flavoured drink such as orange juice or cola which may be stored in a refrigerator for up to 24 hours in a sealed container.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

Mesna (Non-proprietary)

Mesna 400 mg Mesna 400mg tablets | 10 tablet £134.30–£134.40

Mesna 600 mg Mesna 600mg tablets | 10 tablet £190.60

Solution for injection

Mesna (Non-proprietary)

Mesna 100 mg per 1 ml Mesna 18/18ml solution for injection ampoules | 15 ampoule £441.15

Mesna 400mg/4ml solution for injection ampoules | 5 ampoule no price available | 15 ampoule £201.15

Vitamins and trace elements

Folinic acid

Indications and dose

Prevention of methotrexate-induced adverse effects

BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION

Adult: 15 mg every 6 hours for 24 hours, to be started usually 12–24 hours after start of methotrexate infusion, dose may be continued by mouth, consult local treatment protocol for further information

Suspected methotrexate overdosage

BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION

Adult: Initial dose equal to or exceeding dose of methotrexate, to be given at a maximum rate of 160 mg/minute, consult poisons information centres for advice on continuing management

Adjuvant to fluorouracil in colorectal cancer

BY SLOW INTRAVENOUS INJECTION

Adult: (consult product literature)
Levofolinic acid

**DRUG ACTION** Levofolinic acid is an isomer of folinic acid.

**INDICATIONS AND DOSE**

Prevention of methotrexate-induced adverse effects

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Usual dose 7.5 mg every 6 hours for 10 doses, usually started 12–24 hours after beginning of methotrexate infusion

Suspected methotrexate overdosage

- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: Initial dose at least 50% of the dose of methotrexate, intravenous infusion to be administered at a maximum rate of 160 mg/minute, consult poisons information centres for advice on continuing management

Adjunct to fluorouracil in colorectal cancer

- **BY SLOW INTRAVENTOUS INJECTION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS** Intrathecal injection

**CAUTIONS** Avoid simultaneous administration of methotrexate - not indicated for pernicious anaemia or other megaloblastic anaemias caused by vitamin B12 deficiency

**INTERACTIONS** → Appendix 1 (folates).

**SIDE-EFFECTS**

- Rare Agitation (after high doses) - depression (after high doses) - insomnia (after high doses) - pyrexia (after parenteral use)

**PREGNANCY** Not known to be harmful; benefit outweighs risk.

**BREAST FEEDING** Presence in milk unknown but benefit outweighs risk.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.

www.nice.org.uk/TA212

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Folinic acid (Non-proprietary)**
  - Folinic acid (as Calcium folinate) 7.5 mg per 1 ml Calcium folinate 15mg/2ml solution for injection ampoules | 5 ampoule Pom £38.99 – £39.00 DT price = £38.99
  - Folinic acid (as Calcium folinate) 10 mg per 1 ml Calcium folinate 50mg/5ml solution for injection vials | 1 vial Pom £20.00 (Hospital only) | 1 vial Pom £20.00
  - Calcium folinate 300mg/30ml solution for injection vials | 1 vial Pom £100.00 (Hospital only) | 1 vial Pom £100.00
  - Calcium folinate 100mg/10ml solution for injection vials | 1 vial Pom £37.50 (Hospital only) | 1 vial Pom £37.50
  - Folinic acid (as Disodium folinate) 50 mg per 1 ml Disodium folinate 50mg/1ml solution for injection vials | 1 vial Pom £24.70
  - Disodium folinate 200mg/4ml solution for injection vials | 1 vial Pom £80.40
  - Refolinon (Pfizer Ltd) Folinic acid (as Calcium folinate) 3 mg per 1 ml Refolinon 30mg/10ml solution for injection ampoules | 5 ampoule Pom £23.12
  - Sodiofolin (medac UK) Folinic acid (as Disodium folinate) 50 mg per 1 ml Sodiofolin 400mg/8ml solution for injection vials | 1 vial Pom £126.25

2.1a Hyperuricaemia associated with cytotoxic drugs

Other drugs used for Hyperuricaemia associated with cytotoxic drugs: Allopurinol, p. 980 - Febuxostat, p. 981

**DETOXIFYING DRUGS** Urate oxidases

**Rasburicase**

**INDICATIONS AND DOSE**

Prophylaxis and treatment of acute hyperuricaemia, before and during initiation of chemotherapy, in patients with haematological malignancy and high tumour burden at risk of rapid lysis

- **BY INTRAVENOUS INFUSION**
  - Adult: 200 micrograms/kg once daily for up to 7 days according to plasma-urate acid concentration

**CONTRA-INDICATIONS** G6PD deficiency

**CAUTIONS** Atopic allergies
Hormone responsive malignancy

3 Hormone responsive malignancy

Breast cancer

Description of condition

Breast cancer is the most common form of malignancy in women. The causes of breast cancer are complex and there are several risk factors. Established risk factors include age, early onset of menstruation, late menopause, greater age at first completed pregnancy, and a family history. The use of oral contraceptives and postmenopausal HRT are also associated with a small excess risk.

Non-invasive breast cancer, also known as ductal carcinoma in situ, is when the cancer remains localised in the ducts. However, in most cases, the cancer is invasive at the time of diagnosis, which means that malignant cells are liable to spread beyond the immediate area of the tumour. Invasive breast cancer, where malignant cells spread beyond the ducts, can be defined as early breast cancer (operable, primary, stage I/II), locally advanced disease (inoperable local, stage III) and advanced disease (metastatic, stage IV).

Aims of treatment

Reducing mortality, increasing progression-free and disease-free survival and improving quality of life are the main aims of the available treatments for breast cancer and are dependant on the stage of the disease.

Surgery and radiotherapy aim to remove the tumour mass, while adjuvant drug therapy aims to reduce the risk of recurrence and the risk of developing invasive disease. Advanced breast cancer is not curable and treatment aims to achieve remission, to prolong the disease free survival, to relieve symptoms and improve quality of life.

Treatment

The course of the disease and the therapeutic approach vary depending on the characteristics of the cancer; factors such as patient age and menopausal status, tumour size and grade, involvement of axillary lymph nodes or skin, and presence of hormone receptors within the tumour may inform the extent and aggressiveness of the disease. The management of patients with breast cancer involves surgery, radiotherapy, drug therapy, or a combination of these.

Early and locally advanced breast cancer

For operable breast cancer, primary treatment is surgical using breast-conserving surgery or mastectomy, followed by adjuvant therapy to eradicate the micrometastases that cause relapses. Radiotherapy is recommended after breast conserving surgery, as it reduces local recurrence rates. It is also used after mastectomy if there is a high risk of recurrence.

Drug therapy can be used after surgery (adjuvant therapy) or may be offered before surgery (neoadjuvant therapy) to achieve local tumour downsizing in order to make breast-conserving surgery possible. The choice of adjuvant therapy is determined by the safety and efficacy of the drugs, the oestrogen-receptor status, and the human epidermal growth factor 2 (HER2) status of the primary tumour.

Adjuvant chemotherapy or radiotherapy should be considered for all patients, irrespective of age, and it should be started as soon as clinically possible within 31 days of surgery.

A high-dose anthracycline-based chemotherapy regimen is usually preferred to a low-dose anthracycline-based regimen or to a non-anthracycline-based regimen. Choice of chemotherapy regimen is usually guided by local policy, Clinical Cancer Networks, and funding arrangements.

Adjuvant anthracycline-taxane combination chemotherapy should be considered in patients where the additional benefit outweighs risks. For patients with lymph node-positive breast cancer, docetaxel p. 826 can be added as part of an adjuvant chemotherapy regimen; paclitaxel p. 827 is not recommended.

Following surgery, tamoxifen p. 848, alone or in combination with chemotherapy, can be given to premenopausal women with oestrogen-receptor-positive early invasive breast cancer. If chemotherapy has not been selected, tamoxifen can be used in combination with ovarian ablation or suppression. Tamoxifen is not recommended for non-invasive (ductal carcinoma in situ) early breast cancer. Premenopausal women with oestrogen-receptor-positive breast cancer who decline chemotherapy may benefit from treatment with goserelin p. 675 or ovarian ablation.

For postmenopausal women with oestrogen-receptor-positive early invasive breast cancer, not considered to be low risk, an aromatase inhibitor, such as anastrozole p. 849 or letrozole p. 850, is first-line therapy. Tamoxifen is an alternative if an aromatase inhibitor is not tolerated or is contra-indicated. An aromatase inhibitor should be given as initial adjuvant therapy for 5 years, or by switching to an aromatase inhibitor after 2–3 years of tamoxifen for a total of 5 years. Postmenopausal women who have already received tamoxifen for 5 years may be considered for extended therapy (5 years) with letrozole.

Adjuvant trastuzumab p. 795 is recommended as an option in patients with HER2 positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy. Trastuzumab should not be given concurrently with anthracycline-containing regimens (because of the risk of congestive heart failure) but it may be given either concurrently with taxane-based regimens or sequentially.

Advanced breast cancer

Treatment of advanced breast cancer depends on the patient’s drug history, disease severity, and oestrogen receptor and HER2 status.

For the majority of patients with oestrogen-receptor-positive advanced breast cancer, endocrine therapy is first-line treatment. Aromatase inhibitors, such as anastrozole, letrozole and exemestane p. 850, may be offered to patients...
with no previous history of endocrine treatment or in those previously treated with tamoxifen.

Tamoxifen should be considered as first-line treatment for pre- and perimenopausal women with oestrogen-receptor-positive breast cancer not previously treated with tamoxifen. Ovarian suppression is used in pre- and perimenopausal women who have had disease progression despite treatment with tamoxifen.

In patients with advanced breast cancer that is imminent life-threatening or with visceral organ involvement, which requires early relief of symptoms, an anthracycline-based chemotherapy regimen is the preferred treatment. If anthracyclines are not suitable, the alternative is docetaxel monotherapy as first-line treatment, vinorelbine p. 831 or capecitabine p. 811 as second-line treatment or, for third-line treatment, whichever of the two drugs was not used second line. Gemcitabine p. 815 in combination with paclitaxel is recommended for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel with capecitabine are also considered appropriate.

Trastuzumab is recommended for the treatment of HER2-positive advanced breast cancer. It is used in combination with paclitaxel in those who have not received chemotherapy for metastatic breast cancer and as monotherapy for patients who have received at least two chemotherapy regimens for metastatic breast cancer (see trastuzumab National funding/access decisions).

Lapatinib p. 870 in combination with an aromatase inhibitor, fulvestrant p. 848, trastuzumab emtansine p. 796, and toremifene p. 849 are all licensed for use in patients with metastatic breast cancer, however their use is not recommended (see drug monographs for Indications and National funding/access decisions).

The gonadorelin analogue, goserelin is licensed for advanced breast cancer in pre- and perimenopausal women suitable for hormone manipulation. Some progesterone preparations, such as medroxyprogesterone acetate p. 741, norethisterone p. 699, megestrol acetate p. 847 are also licensed for the treatment of breast cancer (see drug monographs).

The use of bisphosphonates in patients with metastatic breast cancer may reduce pain and prevent skeletal complications of bone metastases.

Familial breast cancer

Chemoprevention may be an option for patients who have been identified as having a high or moderate risk of developing breast cancer. The decision whether to consider or offer either tamoxifen p. 848 or raloxifene hydrochloride p. 689 [unlicensed indications] for 5 years is dependent on menopausal status and past history or risk of developing thromboembolic disease or endometrial cancer.

Tamoxifen [unlicensed indication] is recommended for pre- and postmenopausal women with or without uterus. Raloxifene hydrochloride [unlicensed indication] is recommended only for postmenopausal women with a uterus. Neither, tamoxifen nor raloxifene should be given to patients at high risk of developing breast cancer who have had a bilateral mastectomy.

Breast cancer in men

Breast cancer in men is rare. Although, not fully understood, risk factors may be associated with sex hormone metabolism, including those acquired through liver disease or testicular trauma, environmental risk factors such as industrial exposure to heat, and genetic predisposition. Treatment is similar to that for women involving surgery, radiotherapy, drug therapy, or a combination of these.

Useful Resources


Hormone responsive malignancy

Prostate Cancer

Description of condition

Prostate cancer is the most common form of cancer affecting men. The main risk factors are age (most cases being diagnosed in men over 65 years of age), ethnicity (more common in black African-Caribbean men), and a familial component. Prostate cancer is usually slow-growing and asymptomatic at diagnosis, however, the presenting symptoms of advanced disease are usually urinary outflow obstruction, or pelvic or back pain due to bone metastases. Treatment decisions are guided by baseline prostate specific antigen (PSA) levels, tumour grade (Gleason score), the stage of the tumour, the patient’s life expectancy (based on age and comorbid conditions), treatment morbidity, and patient preference.

Aims of treatment

In early or locally advanced prostate cancer, radical treatment aims to eliminate the malignancy. In metastatic disease, drug therapy is aimed at prolonging survival and reducing symptoms.

Drug treatment

Treatment options for patients with prostate cancer include active monitoring, radical prostatectomy, external beam radiotherapy, and brachytherapy. Hormone therapy (androgen deprivation or anti-androgens) is the primary treatment for metastatic prostate cancer, but is also increasingly being used for patients with locally advanced, non-metastatic disease.

In patients with localised prostate cancer, the choice of treatment is guided by whether the disease is considered low, intermediate, or high risk according to the Gleason score, the serum PSA level, and the tumour stage.

Localised or locally advanced prostate cancer

In patients with low-risk localised prostate cancer, and those at intermediate risk who decline radical treatments (prostatectomy or radiotherapy), active monitoring is a suitable option. This involves close monitoring to avoid unnecessary treatment until disease progression occurs (or until the patient requests treatment). In patients with intermediate-risk or high-risk localised prostate cancer (when there is a realistic prospect of long-term disease control) and in those with locally advanced disease, radical prostatectomy or radical radiotherapy should be offered. Other treatment options include a combination of radical radiotherapy and androgen deprivation therapy, consisting of 6 months of androgen deprivation therapy before, during or after radiotherapy. Pelvic radiotherapy should be considered in those with locally advanced prostate cancer who have a higher than 15% risk of pelvic lymph node involvement and are to receive neoadjuvant hormonal therapy.

Androgen deprivation therapy involves the use of a luteinising hormone-releasing hormone (LHRH) agonist (buserelin p. 674, goserelin p. 575, leuprorelin acetate p. 676, or triptorelin p. 677), or bilateral orchidectomy, which removes the supply of endogenous hormone. Androgen deprivation therapy may be continued for up to 3 years in patients with high-risk localised prostate cancer.
Patients should be informed about the side-effects of treatment, particularly urinary and sexual dysfunction, loss of fertility, radiation-induced enteropathy, and hot flushes. Although there is limited evidence, intermittent therapy may be considered for patients who are having long-term androgen deprivation therapy, to reduce drug toxicity. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment with androgen deprivation therapy and prophylactic anti-androgen therapy (such as cyproterone acetate p. 704) may be added.

Medroxyprogesterone acetate p. 741 [unlicensed indication] can be used, initially for up to 10 weeks, to manage troublesome hot flushes caused by long-term androgen suppression; cyproterone acetate is an alternative if medroxyprogesterone acetate is not effective or not tolerated.

Patients who experience a reduction in libido and loss of sexual function should have access to specialist erectile dysfunction services and be considered for treatment with a phosphodiesterase type-5 inhibitor.

Osteoporosis and fatigue may also be a problem with androgen deprivation therapy. A bisphosphonate can be offered to men who have osteoporosis; denosumab p. 670 is an alternative if bisphosphonates are not appropriate. Gynaecomastia can occur with long-term (6 months) bicalutamide p. 843 treatment. Prophylactic radiotherapy (within the first month of treatment), or weekly tamoxifen p. 848 [unlicensed indication], if radiotherapy is unsuccessful, can be considered.

**Metastatic prostate cancer**

Bilateral orchidectomy should be offered to all patients with metastatic prostate cancer as an alternative to continuous LHRH agonist treatment. Anti-androgen monotherapy with bicalutamide [unlicensed indication] can be offered to those who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function. However, if satisfactory sexual function is not maintained, stop bicalutamide and start androgen deprivation therapy.

Abiraterone (in combination with prednisone p. 623 or prednisolone p. 622) and enzalutamide p. 843 are both recommended as options for the treatment of castration-resistant metastatic prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel p. 826–containing chemotherapy regimen.

In patients who develop hormone-relapsed metastatic tumour, chemotherapy with docetaxel can be used. It is recommended to stop the treatment with docetaxel after 10 cycles, or if severe adverse events occurred, or if there is evidence of disease progression.

Abiraterone acetate (in combination with prednisone or prednisolone) is also recommended as an option for treating metastatic hormone-relapsed prostate cancer in patients who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated.

In patients with hormone-relapsed prostate cancer, a corticosteroid, such as dexamethasone p. 618, can be offered as third line therapy, after androgen deprivation therapy and anti-androgen therapy.

**Useful Resources**


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**Other drugs used for Hormone responsive malignancy**

Ethinylenestradiol, p. 694

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## ANTINEOPLASTIC DRUGS > ANTI-ANDROGENS

### Abiraterone acetate

**INDICATIONS AND DOSE**

Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel-containing chemotherapy regimen (in combination with prednisone or prednisolone). Metastatic castration-resistant prostate cancer in patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (in combination with prednisone or prednisolone).

- **BY MOUTH**
  - Adult: 1 g once daily, for dose of concurrent prednisone or prednisolone—consult product literature

**CAUTIONS**

Diabetes (increased risk of hyperglycaemia—monitor blood sugar frequently) • history of cardiovascular disease

**CAUTIONS, FURTHER INFORMATION**

- Cardiovascular disease Correct hypertension and hypokalaemia before treatment (if significant risk of congestive heart failure, such as history of cardiac failure, uncontrolled hypertension or cardiac events, consult product literature for management and increased monitoring).

**INTERACTIONS**

Appendix 1 (abiraterone).

- Caution with concurrent chemotherapy—safety and efficacy not established.
- Caution with concomitant use of drugs known to be associated with myopathy or rhabdomyolysis.

**SIDE-EFFECTS**

- Common or very common Angina • arrhythmia • atrial fibrillation • diarrhoea • dyspepsia • fractures • haematuria • heart failure • hepatotoxicity • hypertension • hypertriglyceridaemia • hypokalaemia • peripheral oedema • rash • sepsis • tachycardia • urinary tract infection

- Uncommon Adrenal insufficiency • myopathy • rhabdomyolysis

**RARE**

Allergic alveolitis

**CONCEPTION AND CONTRACEPTION**

Men should use condoms if their partner is pregnant, and use condoms in combination with another effective contraceptive method if their partner is of child-bearing potential—risk to the foetus.

**HEPATIC IMPAIRMENT**

Use with caution in moderate impairment and only if benefit clearly outweighs risk. Avoid in severe impairment.

**RENAL IMPAIRMENT**

Use with caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Monitor blood pressure, serum potassium concentration, and fluid balance before treatment, and at least monthly during treatment—consult product literature for management of hypertension, hypokalaemia and oedema.

- Monitor liver function before treatment, then every 2 weeks for the first 3 months of treatment, then monthly thereafter—interrupt treatment if serum alanine aminotransferase or aspartate aminotransferase greater than 5 times the upper limit (consult product literature for details of restarting treatment at a lower dose) and discontinue permanently if 20 times the upper limit.
**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (June 2012) NICE TA259
  Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer only if:
  - their disease has progressed on or after one docetaxel-containing chemotherapy regimen, and
  - the manufacturer provides abiraterone with the discount agreed in the patient access scheme.
  Patients currently receiving abiraterone in combination with prednisone or prednisolone whose disease does not meet the first criteria should be able to continue therapy until they and their clinician consider it appropriate to stop.
  [www.nice.org.uk/TA259](http://www.nice.org.uk/TA259)
- Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (April 2016) NICE TA387
  Abiraterone, in combination with prednisone or prednisolone, is recommended as an option for treating metastatic hormone-relapsed prostate cancer in patients who have mild or no symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated. In addition, the manufacturer is required to rebate the cost of abiraterone from the 11th month until the end of treatment for patients who remain on treatment for more than 10 months.
  [www.nice.org.uk/TA387](http://www.nice.org.uk/TA387)

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (July 2012) that abiraterone (Zytiga®), in combination with prednisone or prednisolone, is accepted for restricted use within NHS Scotland for the treatment of metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with docetaxel-containing chemotherapy regimen, and have received only one prior chemotherapy regimen.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS**
  23
  - **Zytiga** (Janssen-Cilag Ltd)
  - **Abiraterone acetate 250 mg** Zytiga 250mg tablets | 28 tablet [PoM] £2,930.00

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**Bicalutamide**

**INDICATIONS AND DOSE**
Locally advanced prostate cancer at high risk of disease progression either alone or as adjuvant treatment to prostatectomy or radiotherapy | Locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention inappropriate

**BY MOUTH**
- Adult: 150 mg once daily

**Advanced prostate cancer, in combination with gonadorelin analogue or surgical castration**

**BY MOUTH**
- Adult: 50 mg once daily, to be started at the same time as surgical castration or at least 3 days before gonadorelin therapy

**CAUTIONS** Risk of photosensitivity—avoid excessive exposure to UV light and sunlight

**INTERACTIONS**
- Appendix 1 (bicalutamide).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain · alopecia · anaemia · asthenia · breast tenderness · chest pain · cholestasis · constipation · decreased appetite · decreased libido · depression · dizziness · dry skin · dyspepsia · flatulence · gynaecomastia · haematuria · hepatotoxicity · hirsutism · hot flushes · impotence · jaundice · nausea · oedema · pruritus · rash · somnolence · weight gain
- **Uncommon** Angioedema · hypersensitivity reactions · interstitial lung disease · urticaria
- **Rare** Hepatic failure · photosensitivity reactions
- **HEPATIC IMPAIRMENT** Increased accumulation possible in moderate to severe impairment— manufacturer advises caution.

**MONITORING REQUIREMENTS** Consider periodic liver function tests.

**PATIENT AND CARER ADVICE**
Risk of photosensitivity Patients should be advised to consider the use of sunscreen.

**MEDICAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **Bicalutamide (Non-proprietary)**
  - **Bicalutamide 50 mg** Bicalutamide 50mg tablets | 28 tablet [PoM] £128.00 DT price = £1.89
  - **Bicalutamide 150 mg** Bicalutamide 150mg tablets | 28 tablet [PoM] £240.00 DT price = £4.36
  - **Casodex** (AstraZeneca UK Ltd)
  - **Bicalutamide 50 mg** Casodex 50mg tablets | 28 tablet [PoM] £119.79 DT price = £1.89
  - **Bicalutamide 150 mg** Casodex 150mg tablets | 28 tablet [PoM] £240.00 DT price = £4.36

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**Enzalutamide**

**INDICATIONS AND DOSE**
Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after docetaxel therapy

**BY MOUTH**
- Adult: 160 mg once daily, for dose adjustments due to side-effects, consult product literature

**CAUTIONS**
Alcoholism · bradycardia · brain injury · brain metastases · brain tumours · history of QT-interval prolongation · history or risk of seizure · recent cardiovascular disease · risk factors for QT-interval prolongation · stroke · uncontrolled hypertension

**INTERACTIONS**
- Appendix 1 (enzalutamide).
  Caution with concurrent use of medication which may lower seizure threshold.
  Caution with concurrent chemotherapy—safety and efficacy not established.
  Caution with concomitant use of drugs that prolong QT interval.

**SIDE-EFFECTS**
- **Common or very common** Anxiety · cognitive disorder · dry skin · falls · fractures · headache · hot flush · hypertension · memory impairment · neutropenia · pruritus · visual hallucinations
- **Uncommon** Leucopenia · seizure

**CONCEPTION AND CONTRACEPTION**
Men should use condoms during treatment and for 3 months after stopping treatment if their partner is pregnant, and use condoms in combination with another effective contraceptive method if their partner is of child-bearing potential—toxicity in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Caution in severe impairment—no information available.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (January 2016) NICE TA377
      Enzalutamide is recommended as an option for treating metastatic hormone–relapsed prostate cancer in patients who have mild or no symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated, and only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. www.nice.org.uk/TA377
    - Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (July 2014) NICE TA316
      Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone–relapsed prostate cancer in adults only if, their disease has progressed during or after docetaxel-containing chemotherapy, and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. This guidance does not cover the use of enzalutamide for metastatic hormone–relapsed prostate cancer previously treated with abiraterone. www.nice.org.uk/TA316
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - CAUTIONARY AND ADVISORY LABELS 25
      - Xtandi (Astellas Pharma Ltd) ▼
        - Enzalutamide 40 mg Xtandi 40mg capsules | 112 capsule
          £2,734.67
  - **Flutamide**
    - **INDICATIONS AND DOSE**
      - Advanced prostate cancer | Metastatic prostate cancer refractory to gonadorelin analogue therapy (monotherapy)
        - **BY MOUTH**
          - Adult: 250 mg 3 times a day
    - **CAUTIONS** Avoid excessive alcohol consumption - avoid in acute porphyrias p. 950 - cardiac disease (oedema reported)
    - **INTERACTIONS** → Appendix 1 (flutamide).
    - **HEPATIC IMPAIRMENT** Use with caution (hepatotoxic).
    - **MONITORING REQUIREMENTS** Liver function tests, monthly for first 4 months, periodically thereafter and at the first sign or symptom of liver disorder (e.g. pruritus, dark urine, persistent anorexia, jaundice, abdominal pain, unexplained influenza-like symptoms).
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Flutamide (Non-proprietary)
      - Flutamide 250 mg Flutamide 250mg tablets | 84 tablet
      - £106.25 DT price = £106.22

### Diethylstilbestrol
(Stilboestrol)
- **INDICATIONS AND DOSE**
  - Breast cancer in postmenopausal women
    - **BY MOUTH**
      - Adult: 10–20 mg daily
  - **Prostate cancer**
    - **BY MOUTH**
      - Adult: 1–3 mg daily
  - **CAUTIONS** Cardiovascular disease
  - **SIDE-EFFECTS** Arterial thrombosis - bone pain (in breast cancer) - feminising effects in men - fluid retention - gynaecomastia - hypercalcaemia (in breast cancer) - impotence - jaundice - nausea - sodium retention with oedema - thromboembolism - venous thrombosis - withdrawal bleeding
  - **PREGNANCY** In first trimester, high doses associated with vaginal carcinoma, urogenital abnormalities, and reduced fertility in female offspring. Increased risk of hypospadias in male offspring.
  - **HEPATIC IMPAIRMENT** Avoid. Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin–Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Diethylstilbestrol (Non-proprietary)
      - Diethylstilbestrol 1 mg Diethylstilbestrol 1mg tablets | 28 tablet
        - £123.00 DT price = £120.32
      - Diethylstilbestrol 5 mg Diethylstilbestrol 5mg tablets | 28 tablet
        - £185.00–£208.00 DT price = £208.00

### PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > ANTI-GONADOTROPHIN-RELEASING HORMONES
- **Degarelix**
  - **INDICATIONS AND DOSE**
    - Advanced hormone-dependent prostate cancer
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: Initially 240 mg, to be administered as 2 injections of 120 mg, then 80 mg every 28 days, dose to be administered into the abdominal region
  - **CAUTIONS** Diabetes - susceptibility to QT-interval prolongation
  - **INTERACTIONS** Avoid concomitant use of drugs that prolong QT interval.
  - **SIDE-EFFECTS**
    - Common or very common Asthenia - dizziness - drowsiness - headache - hot flushes - influenza-like symptoms - injection-site reactions - insomnia - nausea - night sweats - sweating - weight gain
    - Uncommon Abdominal discomfort - alopecia - anaemia - anorexia - anxiety - atrio-ventricular block - constipation -
depression · diarrhoea · dry mouth · fainting ·
gynaecomastia · hypersensitivity reactions · hypertension ·
micturition urgency · musculoskeletal pain · oedema ·
pelvic pain · prostatitis · QT-interval prolongation · rash ·
renal impairment · sexual dysfunction · testicular pain ·
tinnitus · urticaria · vomiting

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.

- **RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.

- **MONITORING REQUIREMENTS** Monitor bone density.

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solution for injection**
  - **Firmagon** (Ferring Pharmaceuticals Ltd)
    - Degarelix (as Degarelix acetate) 80 mg Firmagon 80mg powder and solution for solution for injection vials | 1 vial £129.37
    - Degarelix (as Degarelix acetate) 120 mg Firmagon 120mg powder and solution for solution for injection vials | 2 vial £260.00

### Pituitary and Hypothalamic Hormones and Analogues

#### Somatostatin analogues, malignant disease

**Overview**

Lanreotide below, octreotide p. 846 and pasireotide p. 847 are analogues of the hypothalamic release-inhibiting hormone somatostatin. Lanreotide and octreotide are indicated for the relief of symptoms associated with neuroendocrine (particularly carcinoid) tumours and acromegaly. Additionally, lanreotide is licensed for the treatment of thyroid tumours and octreotide is also licensed for the prevention of complications following pancreatic surgery. Lanreotide (Somatuline Autogel®) is also licensed for the treatment of unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded. Octreotide long-acting depot injection is licensed for treatment of advanced neuroendocrine tumours of the midgut, or treatment where primary origin is not known but non-midgut sites of origin have been excluded. Octreotide may also be valuable in reducing vomiting in palliative care and in stopping variceal bleeding [unlicensed indication]—see also vasopressin p. 613 and terlipressin acetate p. 85. Pasireotide is licensed for the treatment of Cushing’s disease when surgery has failed or is inappropriate.

### Somatostatin analogues

- **CAUTIONS** Diabetes mellitus (antidiabetic requirements may be reduced) · insulinoma (increased depth and duration of hypoglycaemia may occur—observe patients and monitor blood glucose levels when initiating treatment and changing doses) · may cause growth hormone-secreting pituitary tumour expansion during treatment (causing serious complications)

- **SIDE-EFFECTS**
  - **Rare** Pancreatitis (shortly after administration)
  - **Frequency not known** Abdominal pain · anorexia · bloating · diarrhoea · flatulence · gallstones (after long-term treatment) · gastro-intestinal disturbances · hyperglycaemia (with chronic administration) · hypoglycaemia · impaired postprandial glucose tolerance (with chronic administration) · irritation at the injection site · nausea · pain at the injection site · steatorrhoea · vomiting

### Monitoring Requirements

- **MONITORING REQUIREMENTS**
  - Monitor for signs of tumour expansion (e.g. visual field defects).
  - Ultrasound examination of the gallbladder is recommended before treatment and at intervals of 6–12 months during treatment.

### Directions for Administration

- **Adults**
  - **BY INTRAMUSCULAR INJECTION**
    - Initially 60 mg every 28 days, adjusted according to response, (consult product literature), for patients treated previously with somatostatin analogue, consult product literature for initial dose, dose to be given in the gluteal region
  - **BY DEEP SUBCUTANEOUS INJECTION**
    - Adult: 120 mg every 28 days

### Acromegaly (if somatostatin analogue not given previously)

- **BY DEEP SUBCUTANEOUS INJECTION**
  - Adult: Initially 60–120 mg every 28 days, adjusted according to response, dose to be given in the gluteal region

### Neuroendocrine (particularly carcinoid) tumours

- **BY DEEP SUBCUTANEOUS INJECTION**
  - Adult: 120 mg every 28 days

### Unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded

- **BY DEEP SUBCUTANEOUS INJECTION**
  - Adult: 120 mg every 28 days

### Acromegaly and neuroendocrine (particularly carcinoid) tumours

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 30 mg every 14 days, increased to 30 mg every 7–10 days, adjusted according to response

### Thyroid tumours

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 30 mg every 14 days, increased to 30 mg every 10 days, adjusted according to response

- **CAUTIONS**
  - Cardiac disorders (including bradycardia) · patients with carcinoid tumours—exclude the presence of an obstructive intestinal tumour before treatment

- **INTERACTIONS**
  - Appendix 1 (lanreotide).

- **SIDE-EFFECTS**
  - **Common or very common** Alopecia · biliary dilatation · bradycardia · constipation · dizziness · dyspepsia · headache · lethargy · malaise · musculoskeletal pain · myalgia · raised bilirubin
  - **Uncommon** Hot flushes · insomnia
  - **Rare** Hypothyroidism

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises caution—no information available.

- **MONITORING REQUIREMENTS** Monitor for hypothyroidism when clinically indicated.
**846 Hormone responsive malignancy**

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### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Somatuline Autogel (Ipsen Ltd)**
  - Lanreotide (as Lanreotide acetate) 120 mg per 1 ml Somatuline Autogel 60mg/0.5ml solution for injection pre-filled syringes with safety system | 1 pre-filled disposable injection (PfM) £55.00
  - Lanreotide (as Lanreotide acetate) 180 mg per 1 ml Somatuline Autogel 90mg/0.5ml solution for injection pre-filled syringes with safety system | 1 pre-filled disposable injection (PfM) £73.00
  - Lanreotide (as Lanreotide acetate) 240 mg per 1 ml Somatuline Autogel 120mg/0.5ml solution for injection pre-filled syringes with safety system | 1 pre-filled disposable injection (PfM) £93.00

- **Powder and solvent for suspension for injection**
  - Somatuline LA (Ipsen Ltd)
    - Lanreotide (as Lanreotide acetate) 30 mg Somatuline LA 30mg powder and solvent for suspension for injection vials | 1 vial (PfM) £22.00

### Indications and Dose

**Symptoms associated with carcinoid tumours with features of carcinoid syndrome, VIPomas, glucagonomas**

- **By subcutaneous injection**
  - Adult: Initially 50 micrograms 1–2 times a day, adjusted according to response; increased to 200 micrograms 3 times a day, higher doses may be required exceptionally; maintenance doses are variable; in carcinoid tumours, discontinue after 1 week if no effect, if rapid response required, initial dose may be given by intravenous injection (with ECG monitoring and after dilution)

**Acromegaly, short-term treatment before pituitary surgery or long-term treatment in those inadequately controlled by other treatment or until radiotherapy becomes fully effective**

- **By subcutaneous injection**
  - Adult: 100–200 micrograms 3 times a day, discontinue if no improvement within 3 months

**Prevention of complications following pancreatic surgery**

- **By subcutaneous injection**
  - Adult: (consult product literature)

**Test dose before use of depot preparation**

- **By subcutaneous injection**
  - Adult: Test dose 50–100 micrograms for 1 dose, test dose should be given if subcutaneous octreotide not previously given

**Acromegaly | Neuroendocrine (particularly carcinoid) tumour adequately controlled by subcutaneous octreotide**

- **By deep intramuscular injection using depot injection**
  - Adult: Initially 20 mg every 4 weeks for 3 months then adjusted according to response, increased if necessary up to 30 mg every 4 weeks, to be administered into the gluteal muscle, for acromegaly, start depot 1 day after the last dose of subcutaneous octreotide, for neuroendocrine tumours, continue subcutaneous octreotide for 2 weeks after first dose of depot octreotide

**Advanced neuroendocrine tumours of the midgut, or tumours of unknown primary origin where non-midgut sites of origin have been excluded**

- **By deep intramuscular injection using depot injection**
  - Adult: 30 mg every 4 weeks

**Reduce intestinal secretions in palliative care | Reduce vomiting due to bowel obstruction in palliative care**

- **By continuous subcutaneous infusion**
  - Adult: 0.25–0.5 mg/24 hours (max. per dose 0.75 mg/24 hours), occasionally doses higher than the maximum are sometimes required

### Interactions

- **Appendix 1 (octreotide).**

### Side-effects

- **Alopecia | arrhythmias | biliary colic (associated with abrupt withdrawal of subcutaneous octreotide) | bradycardia | dehydration | dizziness | dyspnoea | headache | hepatitis | pancreatitis (associated with abrupt withdrawal of subcutaneous octreotide) | rash**

### Further Information

- **Gastro-intestinal side-effects** Administering non-depot injections of octreotide between meals and at bedtime may reduce gastro-intestinal side-effects.

### Conception and Contraception

- **Effective contraception required during treatment.**

### Pregnancy

- **Possible effect on fetal growth; manufacturer advises use only if potential benefit outweighs risk.**

### Breast Feeding

- **Manufacturer advises avoid—present in milk in animal studies.**

### Hepatic Impairment

- **Adjustment of maintenance dose of non-depot preparations may be necessary in patients with liver cirrhosis.**

### Monitoring Requirements

- **Monitor thyroid function on long-term therapy.**
- **Monitor liver function.**
- **With intravenous use ECG monitoring required with intravenous administration.**

### Treatment Cessation

- **Avoid abrupt withdrawal of short-acting subcutaneous octreotide (associated with biliary colic and pancreatitis).**

### Directions for Administration

- **For intravenous injection or intravenous infusion, dilute with Sodium Chloride 0.9% to a concentration of 10–50%.**

### Prescribing and Dispensing Information

- **Palliative care**

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Octreotide (Non-proprietary)**
  - Lanreotide (as Octreotide acetate) 50 microgram per 1 ml Octreotide 50micrograms/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PfM) £15.85–£18.85 DT price = £18.85
  - Octreotide 50micrograms/1ml solution for injection ampoules | 5 ampoule (PfM) £14.85–£18.60
  - Octreotide 50micrograms/1ml solution for injection vials | 5 vial (PfM) £14.87–£22.00 DT price = £22.00
  - Octreotide (as Octreotide acetate) 100 microgram per 1 ml Octreotide 100micrograms/1ml solution for injection ampoules | 5 ampoule (PfM) £29.99–£32.65 DT price = £27.97
  - Octreotide 100micrograms/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PfM) £28.90–£32.90
  - Octreotide 100micrograms/1ml solution for injection vials | 5 vial (PfM) £27.37–£32.65
  - Octreotide (as Octreotide acetate) 200 microgram per 1 ml Octreotide 1mg/5ml solution for injection vials | 1 vial (PfM) £65.00–£69.66
  - Octreotide (as Octreotide acetate) 500 microgram per 1 ml Octreotide 500micrograms/1ml solution for injection vials | 5 vial (PfM) £139.43–£169.00
  - Sandostatin (Novartis Pharmaceuticals UK Ltd)
    - Octreotide (as Octreotide acetate) 50 microgram per 1 ml Sandostatin 50micrograms/1ml solution for injection ampoules | 5 ampoule (PfM) £14.87
    - Octreotide (as Octreotide acetate) 100 microgram per 1 ml Sandostatin 100micrograms/1ml solution for injection ampoules | 5 ampoule (PfM) £27.97 DT price = £27.97
Octreotide (as Octreotide acetate) 200 microgram per 1 ml Sandostatin 1mg/5ml solution for injection vials | 1 vial | £55.73
Octreotide (as Octreotide acetate) 500 microgram per 1 ml Sandostatin 500micrograms/1ml solution for injection ampoules | 5 ampoule | £135.47 DT price = £135.47

Powder and solvent for suspension for injection
- Sandostatin LAR (Novartis Pharmaceuticals UK Ltd) Octreotide (as Octreotide acetate) 10 mg Sandostatin LAR 10mg powder and solvent for suspension for injection vials | 1 vial | £549.11
Octreotide (as Octreotide acetate) 20 mg Sandostatin LAR 20mg powder and solvent for suspension for injection vials | 1 vial | £799.33
Octreotide (as Octreotide acetate) 30 mg Sandostatin LAR 30mg powder and solvent for suspension for injection vials | 1 vial | £998.41

Pasireotide

- INDICATIONS AND DOSE
  Cushing’s disease when surgery has failed or is inappropriate
    - BY SUBCUTANEOUS INJECTION
    - Adult: Initially 600 micrograms twice daily for 2 months, then increased if necessary to 900 micrograms twice daily, consider discontinuation if no response within 2 months, for dose adjustment due to side effects—consult product literature

- CAUTIONS
  Cardiac disorders (including bradycardia) - susceptibility to QT-interval prolongation (including electrolyte disturbances)

- INTERACTIONS
  Appendix 1 (pasireotide). Caution with concomitant use of drugs that prolong QT interval.

- SIDE-EFFECTS
  Adrenal insufficiency - alopecia - anaemia - arthralgia - bradycardia - decreased appetite - fatigue - headache - hyperglycaemia - hypotension - myalgia - pruritus - QT-interval prolongation

- PREGNANCY
  Avoid—toxicity in animal studies.

- BREAST FEEDING
  Avoid—present in milk in animal studies.

- HEPATIC IMPAIRMENT
  Reduce initial dose to 300 micrograms twice daily (increased if necessary after 2 months to max. 600 micrograms twice daily) in moderate impairment. Avoid in severe impairment.

- MONITORING REQUIREMENTS
  - Monitor liver function before treatment and after one week, and periodically thereafter.
  - Monitor ECG and electrolytes in patients susceptible to QT-prolongation before treatment, after one week, and periodically thereafter.
  - Diabetes mellitus: In diabetic patients, assess glycaemic status before treatment, weekly for the first 2–3 months of treatment, periodically thereafter, and 3 months after treatment is complete.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Solution for injection
  - Signifor (Novartis Pharmaceuticals UK Ltd) Pasireotide (as Pasireotide diasparte) 300 microgram per 1 ml Signifor 0.3mg/1ml solution for injection ampoules | 60 ampoule | £2,800.00
  Pasireotide (as Pasireotide diasparte) 600 microgram per 1 ml Signifor 0.6mg/1ml solution for injection ampoules | 60 ampoule | £3,240.00
  Pasireotide (as Pasireotide diasparte) 900 microgram per 1 ml Signifor 0.9mg/1ml solution for injection ampoules | 60 ampoule | £3,240.00

  Powder and solvent for suspension for injection
  - Signifor (Novartis Pharmaceuticals UK Ltd) Pasireotide (as Pasireotide pamoate) 20 mg Signifor 20mg powder and solvent for suspension for injection vials | 1 vial | £2,300.00
  Pasireotide (as Pasireotide pamoate) 40 mg Signifor 40mg powder and solvent for suspension for injection vials | 1 vial | £2,300.00
  Pasireotide (as Pasireotide pamoate) 60 mg Signifor 60mg powder and solvent for suspension for injection vials | 1 vial | £2,300.00

PROGESTOGENS

Megestrol acetate

- INDICATIONS AND DOSE
  Treatment of breast cancer
  - BY MOUTH
  - Adult: 160 mg once daily

- CONTRA-INDICATIONS
  Acute porphyrias p. 930 - breast cancer (unless progestogens are being used in the management of this condition) - genital cancer (unless progestogens are being used in the management of this condition) - history during pregnancy of idiopathic jaundice - history during pregnancy of pemphigoid gestations - history during pregnancy of severe pruritus - history of liver tumours - severe arterial disease - undiagnosed vaginal bleeding

- CAUTIONS
  Asthma - cardiac dysfunction - conditions that may worsen with fluid retention - diabetes (progestogens can decrease glucose tolerance—monitor patient closely) - epilepsy - history of depression - hypertension - migraine - susceptibility to thromboembolism (particular caution with high dose)

- INTERACTIONS
  Appendix 1 (progestogens).

- SIDE-EFFECTS
  Acne - adrenal insufficiency - alopecia - anaphylactoid reactions - anaphylactoid reactions - angina - bloating - breast - carpal tunnel syndrome - change in libido - constipation - Cushing’s syndrome - depression - diarrhoea - dizziness - drowsiness - fluid retention - headache - hirsutism - indigestion - insomnia - jaundice - loss of vision during treatment (discontinue treatment if papilloedema or retinal vascular lesions) - menstrual disturbances - nausea - premenstrual-like syndrome - pruritus - rash - skin reactions - tumour flare (with or without hypercalcaemia) - urinary frequency - urticaria - vomiting - weight change - weight gain

- PREGNANCY
  Avoid. Reversible feminisation of male fetuses reported in animal studies. Risk of hypospadias in male fetuses and masculinisation of female fetuses.

- BREAST FEEDING
  Discontinue breast-feeding.

- HEPATIC IMPAIRMENT
  Manufacturer advises caution in severe impairment.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension

  Tablet
  - Megestrol acetate (Non-proprietary) Megestrol acetate 40 mg Megestrol 40mg tablets | 100 tablet no price available
  - Megace (Swedish Orphan Biovitrum Ltd) Megace 160 mg Megace 160mg tablets | 30 tablet | £19.52 DT price = £19.52
  Oral suspension
  - Megestrol acetate (Non-proprietary) Megestrol acetate 40 mg per 1 ml Megestrol 200mg/5ml oral suspension | 240 ml | no price available | 480 ml | no price available
3.1 Hormone responsive breast cancer

**ANTINEOPLASTIC DRUGS > ANTI-OESTROGENS**

### Fulvestrant

- **INDICATIONS AND DOSE**
  - Treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy
  - **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 500 mg every 2 weeks for the first 3 doses, then 500 mg every month, to be administered into the buttock

- **SIDE-EFFECTS**
  - Common or very common: Anorexia, asthenia, back pain, diarrhoea, headache, hot flushes, hypertension, injection-site reactions, nausea, rash, urinary tract infections, venous thromboembolism, vomiting
  - Uncommon: Leucorrhea, vaginal candidiasis, vaginal haemorrhage

- **PREGNANCY**
  - Manufacturer advises avoid—increased incidence of fetal abnormalities and death in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution if creatinine clearance less than 30 mL/minute—no information available.

- **DIRECTIONS FOR ADMINISTRATION**
  - 500 mg dose should be administered as one 250-mg injection (slowly over 1–2 minutes) into each buttock.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - Faslodex (AstraZeneca UK Ltd)
    - Fulvestrant 50 mg per 1 ml Faslodex 250mg/5ml solution for injection pre-filled syringes | 2 pre-filled disposable injection (POM) £522.41

### Tamoxifen

- **DRUG ACTION**
  - An anti-oestrogen which induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; choriocarcinoma is sometimes used as an adjunct in the treatment of female infertility.

- **INDICATIONS AND DOSE**
  - Pre- and perimenopausal women with oestrogen-receptor-positive breast cancer not previously treated with tamoxifen
    - **BY MOUTH**
    - Adult: 20 mg daily
  - Anovulatory infertility
    - **BY MOUTH**
    - Adult: Initially 20 mg daily on days 2, 3, 4 and 5 of cycle, if necessary the daily dose may be increased to 40 mg then 80 mg for subsequent courses; if cycles irregular, start initial course on any day, with subsequent course starting 45 days later or on day 2 of cycle if menstruation occurs

  - **CONTRA-INDICATIONS**
    - Treatment of infertility contra-indicated if personal or family history of idiopathic venous thromboembolism or genetic predisposition to thromboembolism

  - **CAUTIONS**
    - Porphyria

  - **INTERACTIONS**
    - Rare: Angioedema, bullous pemphigoid, cholestasis, fatty liver, hepatitis, hypersensitivity reactions, hypertriglyceridaemia, interstitial pneumonitis, neutropenia, Stevens-Johnson syndrome.

  - **Frequency not known**
    - Alopecia, anaemia, cataracts, corneal changes, decreased platelet counts, endometrial changes, gastrointestinal disturbances, headache, hot flushes, hypercalcaemia if bony metastases, increased risk of thromboembolic events, especially when used with cytotoxics, leucopenia, light-headedness, liver enzyme changes, occasional cystic ovarian swellings in premenopausal women, occasionally oedema, pancreatitis, pruritus vulvae, rash, retinopathy, suppression of menstruation in some premenopausal women, thrombocytopenia, thromboembolic events, tumour flare, uterine fibroids, vaginal bleeding, vaginal discharge, visual disturbances

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Endometrial changes: Increased endometrial changes, including hyperplasia, polyps, cancer, and uterine sarcoma reported; prompt investigation required if abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and pelvic pain or pressure in those receiving (or who have received) tamoxifen.

  - Risk of thromboembolism: Tamoxifen can increase the risk of thromboembolism particularly during and immediately after major surgery or periods of immobility (consider interrupting treatment to initiate anticoagulant measures).

  - **CONCEPTION AND CONTRACEPTION**
    - Unless being used in the treatment of female infertility, effective contraception must be used during treatment and for 2 months after stopping. Patients being treated for infertility should be warned that there is a risk of multiple pregnancy (rarely more than twins).

  - **PREGNANCY**
    - Avoid—possible effects on fetal development.

  - **BREAST FEEDING**
    - Suppresses lactation. Avoid unless potential benefit outweighs risk.

  - **PATIENT AND CARER ADVICE**
    - Endometrial changes: Patients should be informed of the risk of endometrial cancer and told to report relevant symptoms promptly. Thromboembolism: Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness and any pain in the calf of one leg.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Tablet**
  - Tamoxifen (Non-proprietary) 10 mg Tamoxifen 10mg tablets | 30 tablet (POM) £61.12 DT price = £37.81
  - Tamoxifen (as Tamoxifen citrate) 20 mg Tamoxifen 20mg tablets | 30 tablet (POM) £13.00 DT price = £2.73
  - Tamoxifen (as Tamoxifen citrate) 40 mg Tamoxifen 40mg tablets | 30 tablet (POM) £54.75 DT price = £33.47

  **Oral suspension**
  - Tamoxifen (Non-proprietary) 2 mg per 1 ml Tamoxifen 10mg/5ml oral suspension | 150 ml (POM) no price available
Toremifene

**INDICATIONS AND DOSE**
Hormone-dependent metastatic breast cancer in postmenopausal women
- **BY MOUTH**
- Adult: 60 mg daily

**CONTRA-INDICATIONS**
- Bradycardia, electrolyte disturbances (particularly uncorrected hypokalaemia), endometrial hyperplasia, heart failure with reduced left-ventricular ejection fraction, history of arrhythmias, QT prolongation

**CAUTIONS**
- Avoid in acute porphyrias

**INTERACTIONS**
- Avoid concomitant administration of drugs that prolong QT interval

**SIDE-EFFECTS**
- Common or very common: Depression, dizziness, fatigue, hot flushes, nausea, oedema, rash, sweating, vaginal bleeding, vaginal discharge, vomiting
- Uncommon: Anorexia, constipation, dyspnoea, endometrial hypertrophy, headache, increased weight, insomnia, thromboembolic events
- Very rare: Alopecia, jaundice, transient corneal opacity
- Frequency not known: Hypercalcaemia (especially if bone metastases and usually at beginning of treatment)

**SIDE-EFFECTS, FURTHER INFORMATION**
- Endometrial changes: Increased endometrial changes, including hyperplasia, polyps and cancer reported. Abnormal vaginal bleeding including menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

**PREGNANCY**
- Avoid.

**BREAST FEEDING**
- Avoid.

**HEPATIC IMPAIRMENT**
- Elimination decreased in hepatic impairment—avoid if severe.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Fareston** (Orion Pharma (UK) Ltd)
- **Toremifene (as Toremifene citrate) 60 mg** Fareston 60 mg tablets
  - 30 tablet [P on M] £29.08

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**HORMONE ANTAGONISTS AND RELATED AGENTS**

**Anastrozole**

**INDICATIONS AND DOSE**
- Adjuvant treatment of oestrogen-receptor-positive early invasive breast cancer in postmenopausal women
- Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy
- Advanced breast cancer in postmenopausal women which is oestrogen-receptor-positive or responsive to tamoxifen
- **BY MOUTH**
- Adult: 1 mg daily

**CONTRA-INDICATIONS**
- Not for premenopausal women

**CAUTIONS**
- Susceptibility to osteoporosis

**SIDE-EFFECTS**
- Very rare: Allergic reactions, anaphylaxis, angioedema
- Frequency not known: Anorexia, arthralgia, arthritis, asthenia, bone fractures, bone pain, cutaneous vasculitis, diarrhoea, drowsiness, hair thinning, headache, hot flushes, nausea, rash, slight increases in total cholesterol levels, Stevens-Johnson syndrome, vaginal bleeding, vaginal dryness, vomiting

**PREGNANCY**
- Avoid.

**BREAST FEEDING**
- Avoid.

**HEPATIC IMPAIRMENT**
- Avoid in moderate to severe impairment.

**RENAL IMPAIRMENT**
- Avoid if creatinine clearance less than 20 ml/minute.

**PRE-TREATMENT SCREENING**
- Laboratory test for menopause if doubt.

**MONITORING REQUIREMENTS**
- Osteoporosis: Assess bone mineral density before treatment and at regular intervals.

**PATIENT AND CARER ADVICE**
- Asthenia and drowsiness may initially affect ability to drive or operate machinery.

**NATIONAL FUNDING/ACCESS DECISIONS**

**ARIMIDEX®**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (August 2005 and October 2006) that anastrozole (Arimidex®) is accepted for restricted use within NHS Scotland, within the licensed indications, for early breast cancer and early invasive breast cancer.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Anastrozole (Non-proprietary)**
- **Anastrozole 1 mg** Anastrozole 1mg tablets
  - 28 tablet [P on M] £65.13 DT price = £1.19
- **Arimidex** (AstraZeneca UK Ltd)
- **Anastrozole 1 mg** Arimidex 1mg tablets
  - 28 tablet [P on M] £68.56 DT price = £1.19
**Exemestane**

- **INDICATIONS AND DOSE**
  Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy | Advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed
  - **BY MOUTH**
  - **Adult:** 25 mg daily

- **CONTRA-INDICATIONS**
  Not indicated for premenopausal women

- **INTERACTIONS**
  → Appendix 1 (exemestane).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain | alopecia | anorexia | constipation | depression | dizziness | dyspepsia | fatigue | headache | hot flushes | insomnia | nausea | rash | vomiting
  - **Uncommon** Asthenia | drowsiness | peripheral oedema
  - **Rare** Leucopenia | thrombocytopenia

- **PREGNANCY**
  Avoid.

- **BREAST FEEDING**
  Avoid.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution.

- **RENAL IMPAIRMENT**
  Manufacturer advises caution.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  Scottish Medicines Consortium (SMC) Decisions
  The Scottish Medicines Consortium has advised (October 2005) that exemestane (Aromasin®) is accepted for restricted use within NHS Scotland as an adjuvant treatment in postmenopausal women with oestrogen-receptor-positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  **CAUTIONARY AND ADVISORY LABELS**
  21
  - Exemestane (Non-proprietary)
    - Exemestane 25 mg | Exemestane 25mg tablets | 30 tablet | POM
    - £88.80 DT price = £5.75 | 90 tablet | POM
      - no price available
  - Aromasin (Pfizer Ltd)
    - Exemestane 25 mg | Aromasin 25mg tablets | 30 tablet | POM
      - £88.80 DT price = £5.75

- **Letrozole**

  - **INDICATIONS AND DOSE**
    First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer | Adjuvant treatment of oestrogen-receptor-positive invasive early breast cancer in postmenopausal women | Advanced breast cancer in postmenopausal women (naturally or artificially induced menopause) in whom another anti-oestrogen therapy has failed | Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received standard adjuvant tamoxifen therapy for 5 years | Neo-adjuvant treatment in postmenopausal women with localised hormone-receptor-positive, human epidermal growth factor-2 negative breast cancer where chemotherapy is not suitable and surgery not yet indicated
    - **BY MOUTH**
    - **Adult:** 2.5 mg daily

  - **CONTRA-INDICATIONS**
    Not indicated for premenopausal women

  - **CAUTIONS**
    Susceptibility to osteoporosis

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain | alopecia | anorexia | appetite increase | arthralgia | bone fracture | constipation | depression | diarrhoea | dizziness | dry skin | dyspepsia | fatigue | headache | hot flushes | hypercholesterolaemia | hypertension | increased sweating | musculoskeletal pain | nausea | osteoporosis | peripheral oedema | rash | vaginal bleeding | vomiting | weight changes
  - **Uncommon** Anxiety | arthritis | blurred vision | breast pain | cardiac events | cataract | cerebrovascular events | cough | dysaesthesia | dyspnoea | eye irritation | general oedema | insomnia | leucopenia | memory impairment | mucosal dryness | palpitation | pruritus | pyrexia | stomatitis | tachycardia | taste disturbance | thrombophlebitis | tumour pain | urinary frequency | urinary-tract infection | urticaria | vaginal discharge
  - **Rare** Arterial thrombosis | pulmonary embolism
  - **Frequency not known** Hepatitis | toxic epidermal necrolysis

- **CONCEPTION AND CONTRACEPTION**
  Manufacturer advises effective contraception required until postmenopausal status fully established (return of ovarian function reported in postmenopausal women).

- **PREGNANCY**
  Avoid (isolated cases of birth defects reported).

- **BREAST FEEDING**
  Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in severe impairment.

- **RENAL IMPAIRMENT**
  Manufacturer advises caution if creatinine clearance less than 10 ml/minute.

- **MONITORING REQUIREMENTS**
  Osteoporosis | Assess bone mineral density before treatment and at regular intervals.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Letrozole (Non-proprietary)
    - Letrozole 2.5 mg | Letrozole 2.5mg tablets | 14 tablet | POM
      - £49.90 DT price = £1.32 | 28 tablet | POM
      - £73.24
  - Femara (Novartis Pharmaceuticals UK Ltd)
    - Letrozole 2.5 mg | Femara 2.5mg tablets | 30 tablet | POM
      - £90.92

**4 Immunotherapy responsive malignancy**

**IMMUNOSTIMULANTS**

**INTERFERONS**

- **Interferon alfa**

  - **DRUG ACTION**
    Interferon alfa has shown some antitumour effect in certain lymphomas and solid tumours.

  - **INDICATIONS AND DOSE**
    **INTRONA® PEN**
    Chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine) | Haemat cell leukaemia | Follicular lymphoma | Lymph or liver metastases of carcinoid tumour | Chronic hepatitis B | Chronic hepatitis C | Adjunct to surgery in malignant melanoma | Maintenance of remission in multiple myeloma
    - **BY SUBCUTANEOUS INJECTION**
    - **Adult:** (consult local protocol)
INTRONA® VIALS
Chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine) | Hairy cell leukaemia | Follicular lymphoma | Lymph or liver metastases of carcinoid tumour | Chronic hepatitis B | Chronic hepatitis C | Adjunct to surgery in malignant melanoma | Maintenance of remission in multiple myeloma
BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INFUSION
Adult: (consult local protocol)

ROFERON-A®
Chronic myelogenous leukaemia | Hairy cell leukaemia | Chronic hepatitis B | Chronic hepatitis C | Adjunct to surgery in malignant melanoma | AIDS-related Kaposi’s sarcoma | Advanced renal cell carcinoma | Progressive cutaneous T-cell lymphoma | Follicular non-Hodgkin’s lymphoma
BY SUBCUTANEOUS INJECTION
Adult: (consult local protocol)

**CONTRA-INDICATIONS**
CONTRA-INDICATIONS, FURTHER INFORMATION
For contra-indications consult product literature and local treatment protocol.

**CAUTIONS**
CAUTIONS, FURTHER INFORMATION
For cautions consult product literature and local treatment protocol.

**INTERACTIONS** → Appendix 1 (interferons).

**SIDE-EFFECTS**
Common or very common | Anorexia | diarrhoea | influenza-like symptoms | lethargy | nausea
Frequency not known | Alopecia | arrhythmias | cardiovascular problems | coma (usually with high doses in the elderly) | confusion | depression | hepatotoxicity | hyperglycaemia | hypersensitivity reactions | hypertension | hypertriglyceridaemia (sometimes severe) | hypotension | myelosuppression (particularly affecting granulocyte counts) | nephrotoxicity | ocular side-effects | palpitation | psoriasiform rash | seizures (usually with high doses in the elderly) | suicidal behaviour | thyroid abnormalities
SIDE-EFFECTS, FURTHER INFORMATION
Consult product literature and local treatment protocols for information on side-effects.

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment—consult product literature.

**PREGNANCY** Avoid unless potential benefit outweighs risk (toxicity in animal studies).

**BREAST FEEDING** Unlikely to be harmful.

**HEPATIC IMPAIRMENT** Avoid in severe hepatic impairment. Close monitoring required in mild to moderate hepatic impairment.

**RENAL IMPAIRMENT** Avoid in severe renal impairment. Close monitoring required in mild to moderate renal impairment.

**MONITORING REQUIREMENTS** Monitoring of liver concentration is recommended.

**DIRECTIONS FOR ADMINISTRATION**
ROFERON-A® | Roferon-A® injection for subcutaneous injection.
INTRONA® VIALS | IntronA® injection vials for subcutaneous injection or intravenous infusion.

**NATIONAL FUNDING/ACCESS DECISIONS**
NICE technology appraisals (TAs)
PEGinterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200
Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa.
www.nice.org.uk/TA200

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for Injection**
EXCIPIENTS: May contain Benzyl alcohol

Interferon alfa-2b 10 mega u per 1 ml IntronA 10 million units/1 ml solution for injection vials | 1 vial (Pfizer) $103.94
Interferon alfa-2b 15 mega u per 1 ml IntronA 15 million units/1 ml solution for injection multidose pens | 1 pre-filled disposable injection (Pfizer) $74.83
Interferon alfa-2b 25 mega u per 1 ml IntronA 25 million units/1 ml solution for injection multidose vials | 1 vial (Pfizer) $249.45

Roferon-A (Roche Products Ltd)
Interferon alfa-2a 6 mega u per 1 ml Roferon-A 3 million units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pfizer) $14.20
Interferon alfa-2a 9 mega u per 1 ml Roferon-A 4.5 million units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pfizer) $21.29
Interferon alfa-2a 12 mega u per 1 ml Roferon-A 6 million units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pfizer) $42.57

**Interferon gamma-1b**
(Immune interferon)

**INDICATIONS AND DOSE**
To reduce the frequency of serious infection in chronic granulomatous disease
BY SUBCUTANEOUS INJECTION
Adult: 50 micrograms/m² 3 times a week
To reduce the frequency of serious infection in severe malignant osteoporosis
BY SUBCUTANEOUS INJECTION
Adult: 50 micrograms/m² 3 times a week

**CAUTIONS**
Arrhythmias - cardiac disease - congestive heart failure - ischaemia - seizure disorders (including seizures associated with fever)

**INTERACTIONS** → Appendix 1 (interferons).
Avoid simultaneous administration of foreign proteins including immunological products (risk of exaggerated immune response).

**SIDE-EFFECTS**
Common or very common | Abdominal pain | arthralgia | chills | depression | diarrhoea | fatigue | fever | headache | injection-site reactions | myalgia | nausea | rash | vomiting
Rare | Confusion | systemic lupus erythematosus
Frequency not known | Neutropenia | proteinuria | raised liver enzymes | thrombocytopenia
IMMUNOSTIMULANTS  >  INTERLEUKINS

**Aldesleukin**

- **DRUG ACTION** Aldesleukin produces tumour shrinkage in a small proportion of patients, but it has not been shown to increase survival.

- **INDICATIONS AND DOSE**
  
  **Metastatic renal cell carcinoma (specialist use only)**
  
  - By subcutaneous injection, or by intravenous infusion
  
  - Adult: (consult product literature)

- **UNLICENSED USE**
  
  Aldesleukin is not licensed for use in patients in whom all three of the following prognostic factors are present: performance status of Eastern Cooperative Oncology Group of 1 or greater, more than one organ with metastatic disease sites, and a period of less than 24 months between initial diagnosis of primary tumour and date of evaluation of treatment.

- **CONTRA-INDICATIONS**
  
  **CONTRA-INDICATIONS, FURTHER INFORMATION** Consult product literature for information about aldesleukin contra-indications.

- **CAUTIONS**
  
  **CAUTIONS, FURTHER INFORMATION** Consult product literature for information about aldesleukin cautions.

- **INTERACTIONS** → Appendix 1 (aldesleukin).

- **SIDE-EFFECTS**
  
  - Common or very common Bone-marrow toxicity · CNS toxicity · hepatic toxicity · renal toxicity · thyroid toxicity
  
  - Frequency not known Alopecia · bone-marrow suppression · extravasation · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

  **SIDE-EFFECTS, FURTHER INFORMATION** Also consult product literature.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment in men and women.

- **PREGNANCY** Use only if potential benefit outweighs risk (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING** Discontinue breast-feeding.

- **DIRECTIONS FOR ADMINISTRATION** Aldesleukin is now rarely given by intravenous infusion because of an increased risk of capillary leak syndrome, which can cause pulmonary oedema and hypotension.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for injection**
  
  - **Proleukin** (Novartis Pharmaceuticals UK Ltd)
    
    Aldesleukin 18 mega u Proleukin 18 million powder for solution for injection vials | 1 vial (POD) £112.00 | 10 vial (POD) £1,036.00

**IMMUNOSTIMULANTS  >  OTHER**

**Bacillus Calmette-Guérin**

- **DRUG ACTION** Bacillus Calmette-Guérin is a live attenuated strain derived from *Mycobacterium bovis*.

- **INDICATIONS AND DOSE**
  
  Bladder instillation for the treatment of primary or recurrent bladder carcinoma and for the prevention of recurrence following transurethral resection

  - By intravesical instillation
  
  - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  
  - Fever of unknown origin · HIV infection · impaired immune response · severe haematuria · tuberculosis · urinary-tract infection

- **CAUTIONS**
  
  - Bladder injury (delay administration until mucosal damage healed) · traumatic catheterisation (delay administration until mucosal damage healed) · urethral injury (delay administration until mucosal damage healed)

- **SIDE-EFFECTS**
  
  - Rare Arthralgia · bladder contracture · hypersensitivity reactions · orchitis · rash · renal abscess · transient urethral obstruction
  
  - Frequency not known Cystitis · dysuria · fever · haematuria · influenza-like syndrome · malaise · ocular symptoms · systemic BCG infection (with fatalities)—consult product literature · urinary frequency

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Avoid.

- **PRE-TREATMENT SCREENING** Screen for active tuberculosis (contra-indicated if tuberculosis confirmed).

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Powder for reconstitution for installation**
  
  - ImmuCyst (Alliance Pharmaceuticals Ltd)
    
    Connaught strain Bacillus of Calmette-Guérin 81 mg ImmuCyst 81 mg powder for reconstitution for installation vials | 1 vial (POD) £118.73 (Hospital only)
  
  - OncoTICE (Merck Sharp & Dohme Ltd)
    
    TICE strain Bacillus of Calmette-Guérin 12.5 mg OncoTICE 12.5 mg powder for reconstitution for installation vials | 1 vial (POD) £71.61 (Hospital only)

**Histamine dihydrochloride**

- **INDICATIONS AND DOSE**
  
  Maintenance therapy, in combination with aldesleukin, in patients with acute myeloid leukaemia in first remission

  - By subcutaneous injection
  
  - Adult: (consult local protocol)

- **CONTRA-INDICATIONS**
  
  **CONTRA-INDICATIONS, FURTHER INFORMATION** Consult product literature for information about histamine dihydrochloride contra-indications.
Mifamurtide

**INDICATIONS AND DOSE**

Treatment of high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection (in combination with chemotherapy)

- **BY INTRAVENOUS INFUSION**
  - Adult: Infusion to be given over 1 hour (consult product literature or local protocols)

**UNLICENSED USE**

Not licensed for use in patients over 30 years of age at initial diagnosis.

**CAUTIONS**

Asthma—consider prophylactic bronchodilator therapy; chronic obstructive pulmonary disease—consider prophylactic bronchodilator therapy; history of autoimmune disease; history of collagen disease; history of inflammatory disease

**INTERACTIONS**

- Appendix 1 (mifamurtide).

**SIDE-EFFECTS**

Abdominal pain; alopecia; anaemia; anorexia; anxiety; blurred vision; confusion; constipation; cough; depression; diarrhoea; dizziness; drowsiness; dry skin; dyspepsia; dyspnoea; dysuria; epistaxis; flushing; gastro-intestinal disturbances; granulocytopenia; haematuria; haemoptysis; headache; hearing loss; hypertension; hypoaesthesia; hypokalaemia; hypotension; insomnia; leucopenia; musculoskeletal pain; nausea; oedema; palpitations; paraesthesia; phlebitis; pleural effusion; pollakiuria; rash; respiratory disorders; sweating; tachycardia; tachypnoea; thrombocytopenia; tinnitus; tremor; vertigo; vomiting

**CONCEPTION AND CONTRACEPTION**

Effective contraception required.

**PREGNANCY**

Avoid.

**BREAST FEEDING**

Avoid—no information available.

**HEPATIC IMPAIRMENT**

Use with caution—no information available.

**RENAL IMPAIRMENT**

Use with caution—no information available.

**MONITORING REQUIREMENTS**

- Monitor renal function, hepatic function and clotting parameters.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (Tas)

- Mifamurtide for the treatment of osteosarcoma (October 2011) NICE TA235

Mifamurtide in combination with postoperative multi-agent chemotherapy is recommended (within its licensed indication), as an option for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults and when mifamurtide is made available at a reduced cost to the NHS under the patient access scheme.

www.nice.org.uk/TA235

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

Lenalidomide

**DRUG ACTION**

Lenalidomide is an immunomodulating drug with anti-neoplastic, anti-angiogenic, and pro-erythropoietic properties.

**INDICATIONS AND DOSE**

Multiple myeloma (newly diagnosed) in patients not eligible for transplant, given in combination with dexamethasone until disease progression

- **BY MOUTH**
  - Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature

Multiple myeloma (newly diagnosed) in patients not eligible for transplant, given in combination with melphalan and prednisone followed by maintenance monotherapy

- **BY MOUTH**
  - Adult: 10 mg once daily for 21 consecutive days of repeated 28-day cycles for up to 9 cycles, for doses of melphalan and prednisone, and dose adjustments due to side-effects, consult product literature

Multiple myeloma in patients who have received at least one prior therapy, given in combination with dexamethasone

- **BY MOUTH**
  - Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature
Treatment of transfusion-dependent anaemia due to low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other treatment options are insufficient or inadequate

- **BY MOUTH**
  - Adult: 10 mg once daily for 21 consecutive days of repeated 28-day cycles, for dose adjustments due to side-effects, consult product literature

- **CAUTIONS**
  - High tumour burden—risk of tumour lysis syndrome
  - Patients with risk factors for myocardial infarction

- **CAUTIONS, FURTHER INFORMATION**
  - Thromboembolism
  - Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised and thromboprophylaxis should be considered in patients with multiple risk factors.

- **SECONDARY MALIGNANCY**
  - Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

- **INTERACTIONS**
  - Appendix 1 (lenalidomide).
  - Use caution with concomitant drugs that increase the risk of thromboembolism.

- **SIDE-EFFECTS**
  - **Common or very common**
    - Abdominal pain
    - Anaemia
    - Arrhythmias
    - Arthralgia
    - Ataxia
    - Atrial fibrillation
    - Bacterial infections
    - Bradycardia
    - Cardiac failure
    - Cataract
    - Cerebrovascular events
    - Chest pain
    - Cholestasis
    - Constipation
    - Decreased appetite
    - Deep vein thrombosis
    - Dehydration
    - Depression
    - Diarrhoea
    - Dizziness
    - Dry mouth
    - Dyspnoea
    - Epilepsy
    - Electrolyte disturbances
    - Falls
    - Flu-like illness
    - Fungal infections
    - Haematoma
    - Haematuria
    - Haemorrhagic disorders
    - Headache
    - Hearing disturbances
    - Hyperglycaemia
    - Hyperhidrosis
    - Hypertension
    - Hypothyroidism
    - Insomnia
    - Iron-overload
    - Leukopenia
    - Malaise
    - Mood changes
    - Musculoskeletal disorders
    - Myalgia
    - Myocardial infarction
    - Nausea
    - Oedema
    - Peripheral neuropathy
    - Pneumonia
    - Pruritus
    - Pulmonary embolism
    - Pyrexia
    - Rash
    - Renal failure
    - Respiratory distress
    - Respiratory tract infections
    - Sepsis
    - Severe neutropenia
    - Sexual dysfunction
    - Sinusitis
    - Skin disorders
    - Stomatitis
    - Syncope
    - Tachycardia
    - Taste disturbances
    - Thrombocytopenia
    - Tremor
    - Urinary incontinence
    - Urinary retention
    - Vasculitis
    - Viral infections
    - Visual disturbances
    - Vomiting
  - **Uncommon**
    - Acquired Fanconi syndrome
    - Angioedema
    - Blindness
    - Caecitis
    - Clotting disorders
    - Colitis
    - Haemolytic anaemia
    - Hepatic failure
    - Ischaemia
    - Secondary malignancies
  - **Rare**
    - Stevens-Johnson syndrome
    - Toxic epidermal necrolysis
    - Tumour lysis syndrome
  - **Frequency not known**
    - Cholestatic hepatitis
    - Cyclofosfamide hepatitis
    - Interstitial pneumonitis
    - Leukocytoclastic vasculitis
    - Pancreatitis
    - Toxic hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Rash
  - If rash occurs, treatment should be discontinued and only restarted following appropriate clinical evaluation.
  - Discontinue permanently if angioedema, exfoliative or bullous rash, or Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected.
  - For information on side effects consult product literature.

- **CONCEPTION AND CONTRACEPTION**
  - For women of childbearing potential, pregnancy must be excluded before starting treatment with lenalidomide (perform pregnancy test on initiation or within 3 days prior to initiation).
  - Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

- **PREGNANCY**
  - Important: teratogenic risk. Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis.

- **BREAST FEEDING**
  - Discontinue breast-feeding—no information available.

- **RENAL IMPAIRMENT**
  - Reduce dose in moderate to severe impairment—consult product literature.

- **MONITORING REQUIREMENTS**
  - Monitor full blood count (including differential white cell count, platelet count, haemoglobin, and haematocrit) and liver function before treatment, then every week for the first 8 weeks, then monthly thereafter (reduce dose or interrupt treatment if neutropenia, thrombocytopenia or impaired liver function develop—consult product literature).
  - Monitor for arterial or venous thromboembolism (if thromboembolic event occurs, discontinue lenalidomide and treat with standard anticoagulation therapy; lenalidomide may be restarted with continued anticoagulation therapy once thromboembolic event resolved—consult product literature).

- **Monitor thyroid function.**

- **Monitor signs and symptoms of peripheral neuropathy.**

- **Monitor visual ability regularly (risk of cataract).**

- **Hepatic disorders**
  - Liver function should be monitored particularly when there is history of, or concurrent viral liver infection, or when lenalidomide is combined with drugs known to be associated with liver dysfunction (e.g. paracetamol).

**PRESCRIBING AND DISPENSING INFORMATION**

- Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a completed Prescription Authorisation Form.

- **PATIENT AND CARER ADVICE**
  - Thromboembolism
  - Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.
  - Neutropenia and thrombocytopenia
  - Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop.

  - **Patient advice required around conception and contraception**
    - **Pregnancy and contraception**
      - Patient counselling is advised for lenalidomide capsules (pregnancy and contraception).

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**
  - Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (September 2014) NICE TA322
    - Lenalidomide is recommended as an option, within its marketing authorisation, for treating transfusion-dependent anaemia caused by low-or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, with the following condition:
    - the drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than
Lenalidomide for the treatment of multiple myeloma (June 2009) NICE TA171

Lenalidomide in combination with dexamethasone is an option for the treatment of multiple myeloma in patients who have received two or more prior therapies. The drug cost of lenalidomide will be met by the manufacturer for patients who remain on treatment for more than 26 cycles.

www.nice.org.uk/TA171

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (April 2010) that lenalidomide, in combination with dexamethasone, is accepted for restricted use within NHS Scotland for patients with multiple myeloma who have received at least two prior therapies and (March 2014) for those who have received prior treatment with bortezomib and for whom thalidomide has not been tolerated or is contra-indicated.

The Scottish Medicines Consortium has advised (December 2015) that lenalidomide is accepted for restricted use within NHS Scotland for patients with previously untreated multiple myeloma who are not eligible for transplant and when thalidomide-containing regimens are unsuitable.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

- Revlimid (Celgene Ltd)
- Lenalidomide 2.5 mg: Revlimid 2.5 mg capsules | 21 capsule POM £3,426.00
- Lenalidomide 5 mg: Revlimid 5 mg capsules | 21 capsule POM £3,570.00
- Lenalidomide 7.5 mg: Revlimid 7.5 mg capsules | 21 capsule POM £3,675.00
- Lenalidomide 10 mg: Revlimid 10 mg capsules | 21 capsule POM £3,780.00
- Lenalidomide 15 mg: Revlimid 15 mg capsules | 21 capsule POM £3,965.00
- Lenalidomide 20 mg: Revlimid 20 mg capsules | 21 capsule POM £4,163.50
- Lenalidomide 25 mg: Revlimid 25 mg capsules | 21 capsule POM £4,368.00

Pomalidomide

DRUG ACTION

Pomalidomide is structurally related to thalidomide and has immunomodulatory properties and direct anti-myeloma tumoricidal activity.

INDICATIONS AND DOSE

Treatment of relapsed and refractory multiple myeloma in patients who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and who have had disease progression during the last treatment (in combination with dexamethasone)

- BY MOUTH
  - Adult: 4 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone and dose adjustment due to side effects—consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B REACTIVATION

An EU wide review has concluded that pomalidomide can cause hepatitis B reactivation; the MHRA recommends to establish hepatitis B virus status in all patients before initiation of treatment.

CAUTIONS

- Cardiac disease • cardiac risk factors • hepatitis B infection • high tumour burden—risk of tumour lysis syndrome • interstitial lung disease—discontinue if suspected • peripheral neuropathy

CAUTIONS, FURTHER INFORMATION

- Thromboembolism Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised. Thromboprophylaxis should be considered, particularly in patients with additional risk factors.

- Second primary malignancy Patients should be carefully evaluated before and during treatment with pomalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

- Hepatitis B infection The MHRA advises that those with a history of hepatitis B infection should be closely monitored for signs and symptoms of active infection throughout treatment; expert advice should be sought for patients who test positive for active infection.

INTERACTIONS • Appendix 1 (pomalidomide).

Use caution with concomitant drugs that increase the risk of bleeding or thromboembolism.

SIDE-EFFECTS

- Common or very common Anaemia • bone pain • cardiac failure • confusion • constipation • cough • decreased appetite • diarrhoea • dizziness • dyspnoea • febrile neutropenia • hyperkaemia • hypotension • impaired consciousness • interstitial lung disease • leucopenia • malaise • muscle spasms • nasopharyngitis • nausea • neutropenia • neutropenic sepsis • pelvic pain • peripheral neuropathy • peripheral oedema • pneumonia • pruritus • pyrexia • rash • renal failure • respiratory tract infection • thrombocytopenia • thromboembolic events • tremor • urinary retention • vertigo • vomiting

- Uncommon Hepatitis

- Frequency not known Atrial fibrillation • hepatitis B reactivation • pulmonary oedema

CONCEPTION AND CONTRACEPTION

For women of child-bearing potential, pregnancy must be excluded before starting treatment with pomalidomide (perform pregnancy test on initiation or within 3 days prior to initiation).

Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

PREGNANCY

Important: teratogenic risk.

BREAST FEEDING

Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises caution—no information available.

RENAL IMPAIRMENT

Manufacturer advises caution—no information available.

MONITORING REQUIREMENTS

- Manufacturer advises monitor full blood count before treatment, then every week for the first 8 weeks, then monthly thereafter (reduce dose or interrupt treatment if neutropenia or thrombocytopenia develop—consult product literature).

- Manufacturer advises monitor for arterial or venous thromboembolism.

- Manufacturer advises monitor for signs and symptoms of cardiac failure.

- Manufacturer advises monitor for acute onset or
Immune system and malignant disease

CAUTIONS
- Manufacturer advises monitor liver function for 6 months after initiation, then as clinically indicated.

PRESCRIBING AND DISPENSING INFORMATION
- Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a completed Prescription Authorisation Form.

PATIENT AND CARER ADVICE
- Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.
- Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop.

Patient advice required around conception and contraception
- Patient counselling is advised for pomalidomide capsules (pregnancy and contraception).

NATIONAL FUNDING/ACCESS DECISIONS
- NICE technology appraisals (TAs)
  - Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (March 2015) NICE TA338
  - Pomalidomide, in combination with dexamethasone, is not recommended for the treatment of relapsed and refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.
  - www.nice.org.uk/TA338

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Capsule
- CAUTIONARY AND ADVISORY LABELS 3, 25
- CAUTIONS, FURTHER INFORMATION
- Thromboembolism Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised. Thromboprophylaxis is recommended for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors.
- Second primary malignancy Patients should be carefully evaluated before and during treatment with thalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instigated as indicated.
- Peripheral neuropathy Patients with pre-existing peripheral neuropathy should not be treated with thalidomide unless the potential clinical benefits outweigh the risk.

SIDE-EFFECTS
- Common or very common Anaemia · asthenia · bradycardia · cardiac failure · confusion · constipation · deep vein thrombosis · depression · dizziness · dry mouth · dysaesthesia · dyspepsia · dyspnoea · interstitial lung disease · leucopenia · lymphopenia · neutropenia · paraesthesia · peripheral neuropathy · peripheral oedema · pneumonia · pulmonary embolism · pyrexia · skin reactions · Stevens-Johnson syndrome · syncope · thrombocytopenia · tremor · vomiting
- Frequency not known Atrial fibrillation · atrioventricular block · cerebrovascular events · convulsions · gastrointestinal haemorrhage · gastrointestinal perforation · hearing loss · hepatic disorders · hypothyroidism · intestinal obstruction · menstrual disorders · myocardial infarction · renal failure · second primary malignancy · sexual dysfunction · toxic epidermal necrolysis · worsening of Parkinson’s disease symptoms

SIDE-EFFECTS, FURTHER INFORMATION
- Rash If rash occurs, treatment should be discontinued and only restarted following appropriate clinical evaluation.
- Peripheral neuropathy If symptoms suggestive of peripheral neuropathy develop (such as paraesthesia, abnormal coordination, or weakness) dose reduction, dose interruption, or treatment discontinuation may be necessary—consult product literature.

CONCEPTION AND CONTRACEPTION
- For women of child-bearing potential, pregnancy must be excluded before starting treatment with thalidomide (perform pregnancy test on initiation or within 3 days prior to initiation).
- Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

PREGNANCY
- Important: teratogenic risk.

BREAST FEEDING
- Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
- Caution in severe impairment—no information available.

RENAL IMPAIRMENT
- Caution in severe impairment—no information available.

MONITORING REQUIREMENTS
- Monitor white blood cell count (including differential count) and platelet count (reduce dose or interrupt treatment if neutropenia or thrombocytopenia develop—consult product literature).

Monitor for arterial or venous thromboembolism.

Thalidomide
- DRUG ACTION
  - Thalidomide has immunomodulatory and anti-inflammatory activity.

INDICATIONS AND DOSE
- First-line treatment for untreated multiple myeloma, in patients aged 65 years and over, or for those not eligible for high-dose chemotherapy (for example, patients with significant co-morbidity such as cardiac risk factors) in combination with melphalan and prednisolone
  - BY MOUTH
    - Adult 18–75 years: 200 mg once daily for 6–week cycle for a maximum of 12 cycles, dose to be taken at bedtime
    - Adult 76 years and over: 100 mg once daily for 6–week cycle for a maximum of 12 cycles, dose to be taken at bedtime

CAUTIONS
- High tumour burden—risk of tumour lysis syndrome · patients aged 76 years and over—increased risk of serious side-effects
Photodynamic therapy responsive malignancy

5 Photodynamic therapy responsive malignancy

PHOTOSENSITISERS

Porfimer sodium

- **DRUG ACTION** Porfimer sodium accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect.

- **INDICATIONS AND DOSE** Photodynamic therapy of non-small cell lung cancer and obstructing oesophageal cancer
  - **BY SLOW INTRAVENOUS INJECTION**
  - **Adult:** (consult product literature)

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 · broncho-oesophageal fistula · tracheo-oesophageal fistula

- **SIDE-EFFECTS** Alopecia · bone-marrow suppression · constipation · extravasation · hyperuricaemia · nausea · oral mucositis · photosensitivity (sunscreens offer no protection) · thromboembolism · tumour lysis syndrome · vomiting

- **PREGNANCY** Manufacturer advises avoid unless essential.

- **BREAST FEEDING** No information available—manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Avoid in severe impairment.

- **PATIENT AND CARER ADVICE** Photosensitivity Avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days.

- **MEDICAL FORMS**
  - **Powder for solution for injection**
    - **Porfimer sodium 15 mg** Photofrin 15mg powder for solution for injection vials | 1 vial (£POM) no price available (Hospital only)
    - **Porfimer sodium 75 mg** Photofrin 75mg powder for solution for injection vials | 1 vial (£POM) no price available (Hospital only)

Temoporfin

- **DRUG ACTION** Temoporfin accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect.

- **INDICATIONS AND DOSE** Photodynamic therapy of advanced head and neck squamous cell carcinoma refractory to, or unsuitable for, other treatments
  - **BY SLOW INTRAVENOUS INJECTION**
  - **Adult:** (consult product literature)

- **CONTRA-INDICATIONS** Acute porphyrias p. 930 · concomitant photosensitising treatment · diseases exacerbated by light · elective surgery · ophthalmic slit-lamp examination for 30 days after administration

- **INTERACTIONS** → Appendix 1 (temoporfin).

- **SIDE-EFFECTS** Alopecia · blistering · bone-marrow suppression · constipation · dysphagia · erythema · extravasation · facial pain · giddiness · haemorrhage · hyperpigmentation · hyperuricaemia · injection site pain · nausea · oedema · oral mucositis · photosensitivity (sunscreens ineffective) · scarring · skin necrosis · thromboembolism · trismus · tumour lysis syndrome · vomiting

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises avoid pregnancy for at least 3 months after treatment.

- **PREGNANCY** Toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING** Manufacturer advises avoid breastfeeding for at least 1 month after treatment—no information available.

- **PATIENT AND CARER ADVICE** Photosensitivity Avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 15 days after administration. Avoid prolonged exposure of injection site arm to direct sunlight for 6 months after administration. If extravasation occurs protect area from light for at least 3 months.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for injection**
    - **Photofrin (Axcyan Pharma Inc)**
      - **Porfimer sodium 15 mg** Photofrin 15mg powder for solution for injection vials | 1 vial (£POM) no price available (Hospital only)
      - **Porfimer sodium 75 mg** Photofrin 75mg powder for solution for injection vials | 1 vial (£POM) no price available (Hospital only)

Porfimer sodium (Roche)

- **Cautions**
  - Photosensitivity
  - Avoid in severe impairment.
  - Avoid in severe impairment.
  - Photosensitivity
  - Avoid in severe impairment.
  - Avoid in severe impairment.
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  - Avoid in severe impairment.
6 Targeted therapy responsive malignancy

**ANTINEOPLASTIC DRUGS > PROTEIN KINASE INHIBITORS**

### Afatinib

#### DRUG ACTION
Afatinib is a protein kinase inhibitor.

#### INDICATIONS AND DOSE
Treatment of locally advanced or metastatic non-small-cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, in patients who have not previously been treated with EGFR tyrosine kinase inhibitor

- **BY MOUTH**
  - Adult: 40 mg once daily; increased if tolerated to up to 50 mg once daily, dose increase may be considered after 3 weeks at initial dose; consult product literature for details on dosing and dose adjustment due to side effects

#### IMPORTANT SAFETY INFORMATION

##### RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 797.

- **CAUTIONS**
  - Cardiac risk factors - conditions which may affect left ventricular ejection fraction - consider cardiac monitoring, including assessment of left ventricular ejection fraction, at baseline and during treatment - diarrhea - protracted management recommended (consult product literature) - exposure to sun (protect skin from exposure to sun) - history of keratitis - new pulmonary symptoms (including dyspnea, cough, fever) - interrupt treatment until interstitial lung disease is excluded - severe dry eyes - signs and symptoms of keratitis - promptly refer to ophthalmologist for assessment - signs and symptoms of skin reaction - treat promptly and interrupt afatinib treatment if severe or if Stevens-Johnson syndrome suspected (consult product literature) - ulcerative keratitis - use of contact lenses - worsening pulmonary symptoms (including dyspnea, cough, fever) - interrupt treatment until interstitial lung disease is excluded

- **INTERACTIONS**
  - Appendix 1 (afatinib).

- **SIDE-EFFECTS**
  - Common or very common
    - Acne
    - Conjunctivitis
    - Cystitis
    - Decreased appetite
    - Dehydration
    - Diarrhea
    - Dry eyes
    - Dry skin
    - Dysgeusia
    - Dyspepsia
    - Epistaxis
    - Hand-foot syndrome
    - Hypokalaemia
    - Muscle spasms
    - Paronychia
    - Pruritus
    - Pyrexia
    - Rash (see Cautions)
    - Renal failure
    - Rhinorrhea
    - Weight loss
  - Uncommon
    - Interstitial lung disease - keratitis
  - Frequency not known
    - Alopecia
    - Bone-marrow suppression
    - Hyperuricaemia
    - Nausea
    - Oral mucositis
    - Thromboembolism
    - Tumour lysis syndrome
    - Vomiting

- **CONCEPTION AND CONTRACEPTION**
  - Ensure effective contraception during and for at least one month after treatment in women of childbearing potential.

- **PREGNANCY**
  - Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Monitor hepatic function regularly and consult product literature for dose adjustment in worsening liver function. Manufacturer advises avoid in severe hepatic impairment.

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid in severe renal impairment.

- **DIRECTIONS FOR ADMINISTRATION**
  - Tablets should be taken whole on an empty stomach. Food should not be consumed for at least 3 hours before and at least 1 hour after each dose.
  - Giotrif™ tablets may be dispersed in approximately 100 mL of noncarbonated water by stirring occasionally for up to 15 minutes (must not be crushed). The dispersion should be swallowed immediately, and the glass rinsed with the same volume of water which should also be swallowed. The dispersion can also be administered via a gastric tube.

- **PATIENT AND CARER ADVICE**
  - Patient counselling advised (administration).
  - Driving and skilled tasks
    - Ocular adverse reactions may affect performance of skilled tasks e.g. driving.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**
  - Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (April 2014) NICE TA310
  - Afatinib is recommended as an option, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer in adults:
    - whose tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation, and
    - who have not previously had an EGFR-TK inhibitor, and
    - if the manufacturer provides afatinib with the discount agreed in the patient access scheme.
    - www.nice.org.uk/TA310

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS**
  - 25
  - **Giotrif** (Boehringer Ingelheim Ltd) ▼
    - Afatinib 20 mg Giotrif 20mg tablets | 28 tablet £2,023.28
    - Afatinib 30 mg Giotrif 30mg tablets | 28 tablet £2,023.28
    - Afatinib 40 mg Giotrif 40mg tablets | 28 tablet £2,023.28
    - Afatinib 50 mg Giotrif 50mg tablets | 28 tablet £2,023.28

### Axitinib

#### DRUG ACTION
Axitinib is a tyrosine kinase inhibitor.

#### INDICATIONS AND DOSE
Treatment of advanced renal cell carcinoma following failure of previous treatment with sunitinib or a cytokine (aldesleukin or interferon alfa)

- **BY MOUTH**
  - Adult: (consult product literature)

#### IMPORTANT SAFETY INFORMATION

##### RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 797.

- **CONTRA-INDICATIONS**
  - Recent active gastrointestinal bleeding - untreated brain metastases
**CAUTIONS** Hypertension (blood pressure should be well-controlled before starting and monitored during treatment)

**INTERACTIONS** → Appendix 1 (axitinib).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain · anal fistula · arthralgia · asthenia · cerebral haemorrhage · constipation · cough · decreased appetite · dehydration · diarrhoea · dizziness · dry skin · dysgeusia · dyspepsia · dysphonia · dyspnoea · erythema · fatigue · flatulence · gastrointestinal haemorrhage · gastro-intestinal perforation · haemoptysis · haemorrhage · haemorrhoids · hand-foot syndrome · headache · hypercalcaemia · hyperkalaemia · hypertension · hyperthyroidism · hypothyroidism · myalgia · proteinuria · pruritus · rash · renal failure · tinnitus · weight loss
- **Uncommon** Hypertensive crisis · polycythaemia · posterior reversible encephalopathy syndrome
- **Frequency not known** Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION** Effective contraception required during and for up to 1 week after treatment.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**HEPATIC IMPAIRMENT** Reduce starting dose in moderate impairment. Avoid in severe impairment—no information available.

**MONITORING REQUIREMENTS**
- Monitor for thyroid dysfunction.
- Monitor haemoglobin or haematocrit before and during treatment.
- Monitor for symptoms of gastro-intestinal perforation.
- Monitor for symptoms of fistula.
- Monitor for proteinuria before and during treatment.
- Monitor liver function before and during treatment.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- **Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment (February 2015)**
  NICE TA333
  Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme. [www.nice.org.uk/TA333](http://www.nice.org.uk/TA333)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

- **Inlyta (Pfizer Ltd)**
  - **Axitinib 1 mg** Inlyta 1mg tablets | 56 tablet PBM £703.40 (Hospital only)
  - **Axitinib 3 mg** Inlyta 3mg tablets | 56 tablet PBM £2,110.20 (Hospital only)
  - **Axitinib 5 mg** Inlyta 5mg tablets | 56 tablet PBM £3,517.00 (Hospital only)
  - **Axitinib 7 mg** Inlyta 7mg tablets | 56 tablet PBM £4,923.80 (Hospital only)

**INDICATIONS AND DOSE**

**Treatment of chronic, accelerated and blast phase Philadelphia chromosome-positive chronic myeloid leukaemia, in those previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not clinically appropriate**

- **BY MOUTH**
  - Adult: 500 mg once daily, consult product literature for dose adjustment due to side effects, or incomplete haematologic response by week 8, or incomplete cytogenetic response by week 12

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS**

An EU wide review has concluded that bosutinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

**CAUTIONS** Cardiac disease · hepatitis B infection · history of pancreatitis—hold treatment if lipase elevated and abdominal symptoms occur · history of QT prolongation—monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment · recent cardiac event—monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment · risk factors for QT prolongation—monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment · significant gastrointestinal disorder

**CONCEPTION, FURTHER INFORMATION**

- Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

**INTERACTIONS** → Appendix 1 (bosutinib).

Caution with concomitant use of drugs that prolong the QT interval (monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain · abnormal liver function · acne · arthralgia · biochemical disturbances · cough · decreased appetite · dehydration · diarrhoea · dizziness · dysgeusia · dysphonia · electrolyte disturbances · gastritis · headache · hepatotoxicity · infection · malaise · myalgia · oedema · pericardial effusion · pleural effusion · pruritus · pyrexia · QT prolongation · rash · renal failure · renal impairment · urticaria
- **Uncommon** Gastric haemorrhage · pancreatitis · pericarditis · pulmonary hypertension · pulmonary oedema · respiratory failure · tinnitus
- **Frequency not known** Alopecia · bone-marrow suppression · hepatic failure (fatal cases reported) · hepatitis · hepatitis B reactivation · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment in women.

**PREGNANCY** Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Caution—no information available.
MONITORING REQUIREMENTS
- Manufacturer advises monitor liver function before treatment initiation, then monthly for the first 3 months and thereafter as clinically indicated—consult product literature for management of raised transaminases.
- Manufacturer advises monitor full blood count weekly for the first month and then monthly thereafter or as clinically indicated.
- Manufacturer advises monitor for signs and symptoms of fluid retention (including pericardial effusion, pleural effusion and pulmonary oedema).

NATIONAL FUNDING/ACCESS DECISIONS
- NICE technology appraisals (TAs)
  - Bosutinib for previously treated chronic myeloid leukaemia (August 2016) NICE TA401
    Bosutinib is recommended as a treatment option, within its marketing authorisation, for chronic, accelerated and blast phase Philadelphia–chromosome-positive CML in adults, when:
    - they have previously been treated with 1 or more tyrosine kinase inhibitor, and
    - imatinib, nilotinib and dasatinib are not appropriate, and
    - the manufacturer provides bosutinib with the discount agreed in the patient access scheme.
    www.nice.org.uk/TA401

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 21
- Bosulif (Pfizer Ltd) ▼
  - Bosutinib 100 mg Bosulif 100mg tablets | 28 tablet POM £859.17 (Hospital only)
  - Bosutinib 500 mg Bosulif 500mg tablets | 28 tablet POM £3,436.67 (Hospital only)

DRUG ACTION
Bosutinib is an inhibitor of several protein kinases.

INDICATIONS AND DOSE
Treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma
- BY MOUTH
  - Adult: 140 mg once daily, for dose adjustment or treatment interruption due to side effects, consult product literature (closely monitor for first 8 weeks of therapy)

IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 797.

CONTRA-INDICATIONS
Reversible Posterior Leukoencephalopathy Syndrome

CAUTIONS
Hypertension—discontinue treatment if uncontrolled despite medical intervention - palmar-plantar erythrodyssasia syndrome—consider treatment interruption if severe and restart at a lower dose when resolved to grade 1 • patients at increased risk of fistulas—consult product literature • patients at increased risk of gastro-intestinal perforation—consult product literature • patients at increased risk of intra-abdominal abscess—consult product literature • patients at risk of haemorrhage (including tumour involvement of the trachea or bronchi)—discontinue if symptoms develop • patients at risk of thromboembolic events including myocardial infarction—discontinue if symptoms develop • risk of osteonecrosis of the jaw • susceptibility to QT-interval prolongation (e.g. cardiac disease, electrolyte disturbances, bradycardia, concomitant use of drugs that prolong the QT interval)—monitor ECG and electrolytes periodically

CAUTIONS, FURTHER INFORMATION
- Elective surgery Withhold treatment for at least 28 days before elective surgery and restart only if adequate wound healing—discontinue in patients with wound healing complications requiring medical intervention.
- Risk of osteonecrosis of the jaw Discontinue treatment at least 28 days before elective invasive dental procedures—monitor for symptoms before and during treatment and discontinue if osteonecrosis develops.

INTERACTIONS ▶ Appendix 1 (cabozantib), Caution with concomitant use of drugs which increase the risk of osteonecrosis of the jaw e.g. bisphosphonates. Caution with concomitant use of drugs that prolong the QT interval.

SIDE-EFFECTS
- Common or very common Abdominal pain • abnormal hair growth • abscess • acne • alopecia • anal fissure • anxiety • arthralgia • aspiration • atrial fibrillation • blurred vision • chelitis • chills • cholelithiasis • constipation • decreased appetite • dehydration • depression • diarrhoea • dizziness • dry skin • dysgeusia • dyspepsia • dysphagia • dysuria • erythema • face oedema • folliculitis • fungal infection • gastrointestinal perforation • gastrointestinal haemorrhage • glossodynia • haematuria • haemorrhoids • hair colour changes • headache • hyperbilirubinaemia • hyperkeratosis • hypertension • hypoaIbuminaemia • hypocalcaemia • hypokalaemia • hypophosphataemia • hypotension • hypothyroidism • impaired wound healing • lymphopenia • mucosal inflammation • muscle spasms • musculoskeletal chest pain • nausea • neumonia • non-gastro-intestinal fistula • oropharyngeal pain • osteonecrosis of jaw • pallor • palmar-plantar erythrodyssasia syndrome • pancreatitis • paraesthesia • peripheral coldness • peripheral neuropathy • platelet disorders • pneumonia • proteinuria • pulmonary embolism • rash • respiratory tract haemorrhage • skin exfoliation • skin hypopigmentation • stomatitis • tinnitus • tremor • venous thrombosis • vomiting
- Uncommon Hypoacusia • acute renal failure • amniunorrhoea • angina • arterial thrombosis • aspergillosis • ataxia • atelectasis • cataract • conjunctivitis • cyst • delirium • facial pain • gastro-intestinal fistula • hepatic encephalopathy • loss of consciousness • oesophagitis • pharyngeal oedema • pneumonitis • posterior reversible encephalopathy syndrome • rhadomyolysis • skin ulcer • speech disorder • supraventricular tachycardia • telangiectasia • transient ischaemic attack • vaginal haemorrhage
- Frequency not known Bone-marrow suppression • hyperuricaemia • oral mucositis • thromboembolism • tumour lysis syndrome

CONCEPTION AND CONTRACEPTION
Patients and their sexual partners must use effective contraception (in addition to barrier method) during treatment and for at least 4 months after the last dose.

PREGNANCY
Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

BREAST FEEDING
Manufacturer advises discontinue breast-feeding during treatment and for at least 4 months after the last dose.

HEPATIC IMPAIRMENT
Manufacturer advises avoid.

RENAL IMPAIRMENT
Manufacturer advises caution in renal impairment. Avoid in severe impairment.

MONITORING REQUIREMENTS
Monitor urine protein regularly and discontinue if nephrotic syndrome develops.

Cabozantinib

DRUG ACTION
Cabozantinib is an inhibitor of several protein kinases.

INDICATIONS AND DOSE
Treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma
- BY MOUTH
  - Adult: 140 mg once daily, for dose adjustment or treatment interruption due to side effects, consult product literature (closely monitor for first 8 weeks of therapy)
Patient and carer advice
Food should not be consumed for at least 2 hours before and at least 1 hour after each dose.

Driving and skilled tasks
Fatigue and weakness may affect performance of skilled tasks e.g. driving.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Cabozantinib (non-proprietary)
  - Cabozantinib (as Cabozantinib s-malate) 20 mg
  - Cabozantinib (as Cabozantinib s-malate) 40 mg

Capsule
- Cometriq
  - Cabozantinib (as Cabozantinib s-malate) 20 mg
  - Cabozantinib (as Cabozantinib s-malate) 80 mg

Patient and carer advice

Drug action
Ceritinib is a tyrosine kinase inhibitor, with particular activity against anaplastic lymphoma kinase (ALK).

Indications and dose
Treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously treated with crizotinib
- By mouth
- Adult: 750 mg once daily, dose should be taken at the same time every day, temporary dose interruption or dose reduction may be required based on tolerability—consult product literature; discontinue treatment if patient unable to tolerate at least 300 mg daily

Dose adjustments due to interactions
Consider reducing the dose by one third (rounded to the nearest multiple of the 150 mg dosage form) if concomitant use of potent inhibitors of CYP3A4 (e.g. itraconazole, ketoconazole, posaconazole, ritonavir, saquinavir, telithromycin, or voriconazole) is unavoidable.

Important safety information
Risks of incorrect dosing of oral-anticancer medicines
See Cytotoxic drugs p. 797.

Contra-indications
Congenital long QT syndrome

Cautions
- Diabetes mellitus - history or susceptibility to QT-interval prolongation

Cautions, further information
- QT-interval prolongation
  - QT-interval prolongation has been observed in clinical studies, which may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsades de pointes) or sudden death. Risk factors include pre-existing bradycardia, other relevant pre-existing cardiac disease or electrolyte disturbances; manufacturer advises to monitor ECG and electrolytes periodically.

Interactions
- Appendix 1 (ceritinib)
  - Caution with concomitant use of drugs that prolong the QT-interval.

Side-effects
- Common or very common
  - Abdominal pain, anaemia, bradycardia, constipation, decreased appetite, diarrhoea, dyspepsia, dysphagia, fatigue, gastro-oesophageal reflux disease, hyperglycaemia, hypophosphataemia, nausea, pericarditis, pneumonitis, QT-interval prolongation, rash, renal failure, renal impairment, visual disorders, vomiting
- Uncommon
  - Hepatotoxicity, pancreatitis

Side-effects, further information
- Gastro-intestinal effects
  - Manufacturer advises monitor for signs of gastro-intestinal toxicity and consider dose reduction or discontinuation of treatment.
- Interstitial lung disease
  - Manufacturer advises monitor patients who exhibit pulmonary symptoms and consider dose reduction or discontinuation of treatment.

Conception and contraception
Manufacturer recommends effective contraception in women of childbearing potential during treatment and for up to 3 months after discontinuation of treatment.

Pregnancy
- Manufacturer advises avoid unless essential—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

Breast feeding
- Manufacturer advises avoid—no information available.

Hepatic impairment
- Manufacturer advises avoid in moderate to severe impairment—no information available but extensively metabolised by the liver.

Renal impairment
- Manufacturer advises caution in severe impairment—no information available.

Monitoring requirements
- Manufacturer advises to monitor fasting blood glucose concentration prior to initiation of treatment and periodically thereafter. Also monitor for amylase and lipase elevations periodically during treatment. Consider dose reduction, interruption or discontinuation of treatment if outside of normal range.
  - In addition, manufacturer advises measure baseline liver function, then monitor every 2 weeks for the first month and monthly thereafter; consider discontinuation if severe changes in liver function occur—increased risk of hepatotoxicity. Monitor heart rate and blood pressure regularly; consider dose reduction or discontinuation if bradycardia is reported—consult product literature.

Directions for administration
Capsules should be taken on an empty stomach—no food should be eaten for 2 hours before or after dose.

Patient and carer advice
- Patients and carers should be counselled on the administration of capsules.

Missed doses
If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks
Manufacturer advises patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of fatigue and vision disorders.

National funding/access decisions
NICE technology appraisals (Tas)
- Ceritinib for previously treated anaplastic lymphoma kinase-positive non small cell lung cancer (June 2016) NICE TA395
  - Ceritinib is recommended, within its marketing authorisation, as an option for treating advanced anaplastic lymphoma kinase-positive non-small cell lung cancer in adults previously treated with crizotinib; only if the manufacturer provides the discount agreed in the patient access scheme.
  - www.nice.org.uk/guidance/ta395
**862 Targeted therapy responsive malignancy**

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS** 25
- **EXCIPIENTS:** May contain Gelatin, propylene glycol
- **Zykadia** (Novartis Pharmaceuticals UK Ltd)
- **Ceritinib 150 mg**
  - Zykadia 150mg capsules  | 150 capsule  **PO**
  - £4,923.45

**Crizotinib**
- **DRUG ACTION**
  - Crizotinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**
- Treatment of previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer
  - **BY MOUTH**
  - Adult: 250 mg twice daily, for dose adjustments due to side-effect, consult product literature

**IMPORTANT SAFETY INFORMATION**
- **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
  - See Cytotoxic drugs p. 797.
  - **MHRA/CHM ADVICE (NOVEMBER 2015): RISK OF CARDIAC FAILURE**
  - Severe, sometimes fatal cases of cardiac failure have been reported in patients treated with crizotinib. The MHRA has issued the following advice:
    - Monitor all patients for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention)
    - Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur

**CAUTIONS FURTHER INFORMATION**
- History of diverticulitis (risk of gastrointestinal perforation—discontinue treatment if gastrointestinal perforation occurs) - metastases of gastrointestinal tract (risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs) - patients with susceptibility to QT-prolongation (including bradycardia, history of cardiac disease, concomitant use of drugs that prolong QT interval, and electrolyte disturbances)—periodic renal monitoring required - risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs - vision disorders reported—consider full ophthalmological evaluation if vision disorder worsens or persists

**CAUTIONS, FURTHER INFORMATION**
- **FATAL INTERSTITIAL LUNG DISEASE AND PNEUMONITIS**
  - Fatal interstitial lung disease and pneumonitis reported (monitor patients with pulmonary symptoms, withdraw treatment if suspected, and permanently discontinue treatment if diagnosed).

**INTERACTIONS**
- Appendix 1 (crizotinib).
  - Caution with concomitant use of drugs that prolong QT interval—periodic renal monitoring required.
  - Caution with concomitant use of drugs which may cause gastrointestinal perforation—discontinue treatment if gastrointestinal perforation occurs.

**SIDE-EFFECTS**
- **Frequency not known**
  - Alopecia - hyperuricaemia - oral mucositis - thromboembolism - tumour lysis syndrome

**PREGNANCY**
- Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**
- Avoid—no information available.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
- Reduce dose to 250 mg once daily in severe impairment not requiring peritoneal dialysis or hemodialysis, may be increased to 200 mg twice daily after at least 4 weeks, based on individual assessment of safety and tolerability.

**MONITORING REQUIREMENTS**
- Monitor liver function once a week during the first 2 months of treatment, then at least monthly thereafter and as clinically indicated. Monitor ECG and electrolytes (correct if abnormal) in all patients before starting treatment, then periodically and as clinically indicated thereafter. Monitor for signs and symptoms of treatment emergent bradycardia (including syncope, dizziness and hypotension)—monitor blood pressure and heart rate regularly.

**PATIENT AND CARER ADVICE**
- Counsel all patients on the early signs and symptoms of gastrointestinal perforation—advice to seek immediate medical attention.

**Driving and skilled tasks**
- Symptomatic bradycardia (including syncope, dizziness and hypotension), vision disorder and fatigue may affect performance of skilled tasks (e.g. driving or operating machinery).

**NATIONAL FUNDING/ACCESS DECISIONS**
- **NICE technology appraisals (TAs)**
  - **Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (September 2013) NICE TA296**
  - Crizotinib is **not** recommended within its marketing authorisation, for treating adults with previously treated anaplastic-lymphoma-kinase-positive advanced non-small-cell lung cancer.
  - **www.nice.org.uk/TA296**

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS** 25
  - **Xalkori** (Pfizer Ltd)
  - **Crizotinib 200 mg**
    - Xalkori 200mg capsules  | 60 capsule  **PO**
    - £4,689.00 (Hospital only)
  - **Crizotinib 250 mg**
    - Xalkori 250mg capsules  | 60 capsule  **PO**
    - £4,689.00 (Hospital only)
### Dabrafenib

**DRUG ACTION** Dabrafenib is a BRAF kinase inhibitor.

**INDICATIONS AND DOSE**

**Monotherapy for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation**

- **BY MOUTH**
  - Adult: 150 mg every 12 hours, for dose adjustments due to side effects consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**CONTRA-INDICATIONS**

- BRAF wild-type melanoma • long QT syndrome • uncorrectable electrolyte abnormalities (including magnesium)

**CAUTIONS**

- Pyrexia (interrupt treatment if ≥38.5°C and assess for signs and symptoms of infection—consult product literature)

**INTERACTIONS**

- Contra—indicated with concomitant use of drugs that prolong the QT interval.

**SIDE-EFFECTS**

- Common or very common
  - Acrochordon • arthralgia • basal cell carcinoma • chills • constipation • cough • cutaneous squamous cell carcinoma • decrease in left ventricular ejection fraction • decreased appetite • diarrhoea • dry skin • erythema • hand-foot syndrome • headache • hyperglycaemia • hyperkeratosis • hypophosphataemia • influenza-like symptoms • keratosis • malaise • myalgia • papilloma • pruritus • pyrexia • rash • skin lesions

- Uncommon
  - Nephritis • new primary melanoma • pancreatitis • panniculitis • QT-interval prolongation • renal failure • uveitis

- Frequency not known
  - Alopecia • bone-marrow suppression • hyperuricaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Pancreatitis
  - Promptly investigate signs and symptoms of pancreatitis—consult product literature.

**CONCEPTION AND CONTRACEPTION**

- Effective non-hormonal contraception required during and for one month after treatment in women of childbearing potential.

**PREGNANCY**

- Manufacturer advises caution in the establishment of pregnancy before treatment in women of childbearing potential.

**BREAST FEEDING**

- Manufacturer advises caution in breast feeding.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in moderate to severe impairment. Additional monitoring of ECG and electrolytes required in hepatic impairment—consult product literature.

**RENAL IMPAIRMENT**

- Manufacturer advises caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Assess for cutaneous squamous cell carcinoma and new primary melanoma before treatment, monthly during treatment, and for 6 months after discontinuation or until initiation of alternative treatment.

- Assess and monitor for non-cutaneous secondary or recurrent malignancy before, during, and for 6 months after discontinuation or until initiation of alternative treatment—consult product literature.

- Monitor serum creatinine and other signs of renal failure—consult product literature and interrupt dose as appropriate.

- Monitor for ophthalmologic reactions including uveitis and iritis.

- Monitor ECG and electrolytes (including magnesium) before and one month after treatment initiation and after each dose modification—consult product literature if abnormalities occur.

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks
  - Ocular adverse reactions and fatigue may affect performance of skilled tasks e.g. driving.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (Tas)**
  - Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (October 2014) NICE TA321
  - Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the manufacturer provides dabrafenib with the discount agreed in the patient access scheme. www.nice.org.uk/TA321

- **Scottish Medicines Consortium (SMC) Decisions**
  - The Scottish Medicines Consortium has advised (February 2015) that dabrafenib (Tafinlar®) is accepted for restricted use within NHS Scotland for the treatment of unresectable or metastatic BRAFV600 mutation-positive melanoma in patients who have received no prior therapy.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 23, 25
    - **Tafinlar** (Novartis Pharmaceuticals UK Ltd)
      - Dabrafenib (as Dabrafenib mesilate) 75 mg capsules
        - 28 capsule (£33.33 Hospital only)
      - Dabrafenib (as Dabrafenib mesilate) 50 mg capsules
        - 28 capsule (£43.00 Hospital only)

**Dasatinib**

**DRUG ACTION** Dasatinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

**Chronic phase chronic myeloid leukaemia (consult product literature for details)**

- **BY MOUTH**
  - Adult: 100 mg once daily, then increased if necessary up to 140 mg once daily

**Accelerated and blast phase chronic myeloid leukaemia (consult product literature for details) Acute lymphoblastic leukaemia (consult product literature for details)**

- **BY MOUTH**
  - Adult: 140 mg once daily, then increased if necessary up to 180 mg once daily

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS**

An EU wide review has concluded that dasatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

**CAUTIONS**

- Hepatitis B infection • risk of cardiac dysfunction (monitor closely) • susceptibility to QT-interval prolongation (correct hypokalaemia or hypomagnesaemia before starting treatment)

**CAUTIONS, FURTHER INFORMATION**

- Pulmonary arterial hypertension
  - Patients should be evaluated for signs and symptoms of underlying cardiopulmonary
Erlotinib

**DRUG ACTION** Erlotinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

Treatment of locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy. Monotherapy for maintenance treatment of locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of platinum-based chemotherapy.

BY MOUTH

- Adult: 150 mg once daily
- Treatment of metastatic pancreatic cancer (in combination with gemcitabine)

**BY MOUTH**

- Adult: 100 mg once daily

**IMPORTANT SAFETY INFORMATION**

**EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)**

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**CAUTIONS**

- **CAUTIONS, FURTHER INFORMATION**
  - Smoking: Dose adjustment may be necessary if smoking started or stopped during treatment.
  - **INTERACTIONS** → Appendix 1 (erlotinib).
  - Caution with concomitant use with hepatotoxic drugs—monitor liver function.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, anorexia, conjunctivitis, depression, diarrhoea, dry skin, dyspepsia, fatigue, flatulence, headache, neuropathy, pruritus, rigor

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864 Targeted therapy responsive malignancy
Uncommon  Eyelash changes - gastro-intestinal perforation - interstitial lung disease—discontinue if unexplained symptoms such as dyspnoea, cough or fever occur

Rare  Hepatic failure

Very rare  Corneal perforation - corneal ulceration - Stevens-Johnson syndrome - toxic epidermal necrolysis

Frequency not known  Alopecia - bone-marrow suppression - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

CONCEPTION AND CONTRACEPTION  Effective contraception required during and for at least 2 weeks after treatment.

Pregnancy  Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

Breast feeding  Manufacturer advises avoid—no information available.

Hepatic impairment  Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment. Monitor liver function in pre-existing liver disease.

Renal impairment  Manufacturer advises avoid in severe impairment.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)

Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (June 2011) NICE TA227
Erlotinib monotherapy is not recommended for maintenance treatment in patients with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy. www.nice.org.uk/TA227

Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (June 2012) NICE TA258
Erlotinib is recommended as an option in patients for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer if:
- they test positive for the epidermal growth factor tyrosine kinase (EGFR-TK) mutation and
- the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012). www.nice.org.uk/TA258

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (December 2015) NICE TA374
Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in patients with tumours of unknown epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation status, only if all of the following criteria are met:
- the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA,
- the treating clinician considers that the tumour is very unlikely to be EGFR-TK mutation-positive,
- the patient's condition responds to the first 2 cycles of treatment with erlotinib, and,
- the manufacturer provides erlotinib with the discount agreed in the patient access scheme.

Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in patients with tumours that are EGFR-TK mutation-negative.

Patients who are already receiving erlotinib should continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA374

Everolimus

Drug action  Everolimus is a protein kinase inhibitor.

Indications and dose
Afinitor®
Treatment of advanced renal cell carcinoma when the disease has progressed despite treatment with vascular endothelial growth factor-targeted therapy/ Treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin | Treatment of hormone-receptor-positive, human epidermal growth factor-2 (HER-2) negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor

By mouth
Adult: 10 mg once daily

Certican®
Liver transplantation

By mouth
Adult: Initially 1 mg twice daily, to be started approximately 4 weeks after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Renal transplantation | Heart transplantation

By mouth
Adult: Initially 750 micrograms twice daily, to be started as soon as possible after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Votubia®
Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

By mouth
Adult: (consult product literature)

Renal angiomyolipoma associated with tuberous sclerosis complex

By mouth
Adult: (consult product literature)

Important safety information
Risks of incorrect dosing of oral anti-cancer medicines
See Cytotoxic drugs p. 797.

Caution
History of bleeding disorders

Interactions  Appendix 1 (everolimus), Caution with concomitant use of drugs that increase risk of bleeding.

Side-effects
Common or very common  Abdominal pain - anorexia - arthralgia - asthenia - chest pain - convulsions - dehydration - diarrhoea - dry mouth - dysphagia - electrolyte disturbance - epistaxis - eyelid oedema - fatigue
Immune system and malignant disease

Everolimus for the second-line treatment of advanced renal cell carcinoma (April 2011) NICE TA219
Everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma.
www.nice.org.uk/TA219

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (August 2013) NICE TA295
Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating postmenopausal women with advanced human epidermal growth factor receptor 2 (HER2) negative hormone-receptor-positive breast cancer that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor.
www.nice.org.uk/TA295

• Frequency not known
  • Alopecia
  • Bone-marrow suppression
  • Haemorrhage
  • Hepatitis B reactivation
  • Hyperuricaemia
  • Nausea
  • Oral mucositis
  • Thromboembolism
  • Tumour lysis syndrome
  • Vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Reduce dose or discontinue if severe side-effects occur—consult product literature.

• CONCEPTION AND CONTRACEPTION
  Effective contraception must be used during and for up to 8 weeks after treatment.

• PREGNANCY
  Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

• BREAST FEEDING
  Manufacturer advises avoid.

• HEPATIC IMPAIRMENT
  Consult product literature.

• MONITORING REQUIREMENTS
  For Certican®, manufacturer advises pre-dose (“trough”) whole blood everolimus concentration should be 3–8 nanograms/mL; monitoring should be performed every 4–5 days (using chromatographic assay) after initiation or dose adjustment until 2 consecutive stable concentrations; monitor patients with hepatic impairment taking concomitant strong CYP3A4 inducers and inhibitors when switching formulation, and/or if concomitant ciclosporin dose is reduced.

  • Monitor blood-glucose concentration, serum-triglycerides and serum-cholesterol before treatment and periodically thereafter.

  • Monitor renal function before treatment and periodically thereafter.

• DIRECTIONS FOR ADMINISTRATION

  VOTUBIA® Tablets may be dispersed in approximately 30 mL of water by gently stirring, immediately before drinking. After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed.

• PATIENT AND CARER ADVICE

  Pneumonitis
  Non-infectious pneumonitis reported. Patients should be advised to seek urgent medical advice if new or worsening respiratory symptoms occur.

• NATIONAL FUNDING/ACCESS DECISIONS

  NICE technology appraisals (TAs)

  ▶ Everolimus for preventing organ rejection in liver transplantation (July 2015) NICE TA348
  Everolimus (Certican®) is not recommended within its marketing authorisation for preventing organ rejection in patients who have undergone a liver transplant. Patients currently receiving everolimus for this indication should have the option to continue treatment until they and their clinician consider it appropriate to stop.

  www.nice.org.uk/TA348

  ▶ Afinitor®

  Scottish Medicines Consortium (SMC) Decisions

  The Scottish Medicines Consortium has advised (April 2012) that everolimus (Afinitor®) is accepted for restricted use within NHS Scotland for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin (pNET) in adults with progressive disease.

  ▶ MEDICINAL FORMS

  There can be variation in the licensing of different medicines containing the same drug.

  Tablet

  CAUTIONARY AND ADVISORY LABELS 25

  ▶ Afinitor (Novartis Pharmaceuticals UK Ltd)
  Everolimus 2.5 mg Afinitor 2.5mg tablets | 30 tablet (PO)
  £1,200.00
  Everolimus 5 mg Afinitor 5mg tablets | 30 tablet (PO) £2,250.00
  Everolimus 10 mg Afinitor 10mg tablets | 30 tablet (PO) £2,673.00

  ▶ Certican (Novartis Pharmaceuticals UK Ltd)
  Everolimus 250 microgram Certican 0.25mg tablets | 60 tablet (PO) £148.50
  Everolimus 500 microgram Certican 0.5mg tablets | 60 tablet (PO) £297.00
  Everolimus 750 microgram Certican 0.75mg tablets | 60 tablet (PO) £445.50

  ▶ Votubia (Novartis Pharmaceuticals UK Ltd)
  Everolimus 2.5 mg Votubia 2.5mg tablets | 30 tablet (PO) £1,200.00
  Everolimus 5 mg Votubia 5mg tablets | 30 tablet (PO) £2,250.00
  Everolimus 10 mg Votubia 10mg tablets | 30 tablet (PO) £2,970.00

Geftinib

• DRUG ACTION

  Gefitinib is a tyrosine kinase inhibitor.

• INDICATIONS AND DOSE

  Treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor

  ▶ BY MOUTH

  ▶ Adult: 250 mg once daily

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

RISKS OF INCORRECT DOING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 797.
Ibrutinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

**Treatment of relapsed or refractory mantle cell lymphoma**

- **By mouth**
  - Adult: 560 mg once daily, for dose adjustments due to side effects consult product literature

**Treatment of chronic lymphocytic leukaemia, in patients who have received at least one prior therapy, or as first-line treatment in patients with 1p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy**

- **By mouth**
  - Adult: 420 mg once daily, for dose adjustments due to side effects consult product literature

**Treatment of relapsed or refractory mantle cell lymphoma (reduced dose for patients taking concomitant moderate or potent CYP3A4 inhibitors)**

- **By mouth**
  - Adult: 140 mg once daily, for dose adjustments due to side effects consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

Reduce dose in patients taking concomitant potent CYP3A4 inhibitors (such as cobicistat, clarithromycin, darunavir boosted with ritonavir, indinavir, itraconazole, ketoconazole, ritonavir, saquinavir, telithromycin, and voriconazole) or moderate CYP3A4 inhibitors (such as amiodarone, aprepitant, azanavir, ciprofloxacin, crizotinib, diltiazem, dronedaron, erythromycin, fluconazole, fosamprenavir, imatinib, and verapamil); alternatively temporarily stop ibrutinib if the potent CYP3A4 inhibitor is only required for 7 days or less. Avoid concomitant use with these drugs unless unavoidable.

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**CAUTIONS**

- Family history of congenital short QT syndrome
- Increased lymphocytes—increased risk of leukostasis, consider withholding treatment temporarily and monitor closely—patients at risk from further shortening of QTc interval—personal history of congenital short QT syndrome—risk of haemorrhagic events— withholding ibrutinib treatment for at least 3 to 7 days before and after surgery depending on risk of bleeding

**INTERACTIONS**

- Appendix 1 (ibrutinib).

Avoid concomitant use of drugs that increase risk of bleeding

**SIDE-EFFECTS**

- Common or very common Arthralgia, atrial fibrillation, blurred vision, bruising, constipation, dehydration, diarrhoea, dizziness, dry mouth, epistaxis, haemorrhage, headache, hypertension, interstitial lung disease, nausea, oral mucositis, rash, rhinitis, sinusitis, Steven Johnson syndrome, thrombocytopenia, vomiting.

- Uncommon Corneal erosion, pancreatitis.

- Rare Hepatitis, toxic epidermal necrolysis.

**FREQUENCY NOT KNOWN**

- Allopecia, bone marrow suppression, hyperuricaemia, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting.

**SIDE-EFFECTS**

- Common or very common Acne, anorexia, asthma, blepharitis, conjunctivitis, diarrhoea, dry eye, dry mouth, dry skin, epistaxis, haematuria, interstitial lung disease—discontinue if confirmed—nail disorder—proteinuria, pruritus, pyrexia, rash, skin reactions.

**CONCEPTION AND CONTRACEPTION**

Manufacturer advises caution unless contraceptive advice is available.

**RENAL IMPAIRMENT**

Manufacturer advises caution in moderate to severe impairment due to cirrhosis.

**PREGNANCY**

Manufacturer advises caution in moderate to severe impairment due to cirrhosis.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate to severe impairment due to cirrhosis.

**MONITORING REQUIREMENTS**

- Monitor for worsening of dyspnoea, cough and fever—discontinue if interstitial lung disease confirmed.

- Monitor liver function—consider discontinuing if severe changes in liver function occur.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Gefitinib** for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (July 2010) NICE TA192
  - Gefitinib is recommended as an option for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer if the patient tests positive for the epidermal growth receptor tyrosine kinase (EGFR-TK) mutation and the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.
  - www.nice.org.uk/TA192

- **Erlotinib** and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (December 2015) NICE TA374
  - Gefitinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in patients with tumours that are EGFR-TK mutation-positive.

- Patients who are already receiving gefitinib should continue treatment until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA374

**Scottish Medicines Consortium (SMC) Decisions**

The **Scottish Medicines Consortium** has advised (December 2015) that gefitinib (Iressa®) is accepted for restricted use within NHS Scotland for the treatment of adult patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of epidermal growth factor receptor tyrosine kinase (EGFR-TK).

**MEDICINAL FORMS**

- **Tablet**

  - **Iressa** (AstraZeneca UK Ltd)

  - Gefitinib 250 mg Iressa 250mg tablets | 30 tablet | £2,167.71

**Drug action**

**Indications and dose**

**Treatment of relapsed or refractory mantle cell lymphoma**

- **By mouth**
  - Adult: 560 mg once daily, for dose adjustments due to side effects consult product literature

**Treatment of chronic lymphocytic leukaemia, in patients who have received at least one prior therapy, or as first-line treatment in patients with 1p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy**

- **By mouth**
  - Adult: 420 mg once daily, for dose adjustments due to side effects consult product literature

**Treatment of relapsed or refractory mantle cell lymphoma (reduced dose for patients taking concomitant moderate or potent CYP3A4 inhibitors)**

- **By mouth**
  - Adult: 140 mg once daily, for dose adjustments due to side effects consult product literature
headache · musculoskeletal pain · peripheral oedema · petechiae · pyrexia · rash · respiratory tract infection · sepsis · sinusitis · skin infection · subdural haematoma · urinary tract infection

- **Uncommon** Leukostasis
- **Frequency not known** Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION** Highly effective contraception (must include a non-hormonal method) required during and for 3 months after stopping treatment.

**PREGNANCY** Manufacturer advises avoid—tobacco in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Manufacturer advises discontinue breastfeeding—no information available.

**HEPATIC IMPAIRMENT** Reduce dose to 280 mg daily in mild impairment and reduce dose to 140 mg daily in moderate impairment—monitor for toxicity and adjust dose if necessary (consult product literature). Avoid in severe impairment.

**RENAL IMPAIRMENT** Use in severe impairment only if benefit outweighs risk and with close monitoring for toxicity. Maintain hydration and monitor serum creatinine periodically in mild to moderate renal impairment.

**MONITORING REQUIREMENTS**

- Monitor full blood count once a month.
- Monitor for atrial fibrillation (increased risk in cardiac risk factors, acute infections and history of atrial fibrillation), monitor all patients periodically and complete ECG if arrhythmic symptoms or dyspnoea develop—consult product literature for treatment options.

**MEDICINAL FORMS**

There can be a variation in the licensing of different medicines containing the same drug.

**Capsule**

| CAUTIONARY AND ADVISORY LABELS 25 |
| Imbruvica (Janssen-Cilag Ltd) ✔ |
| Ibrutinib 140 mg | Imbruvica 140mg capsules | 90 capsule (Pom) £4,599.00 | 120 capsule (Pom) £6,132.00 |

**Idelalisib**

16-Nov-2016

**DRUG ACTION** Idelalisib is a protein kinase inhibitor.

**INDICATIONS AND DOSE**

Treatment of chronic lymphocytic leukaemia in patients who have received at least one previous therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies (in combination with rituximab).

Treatment of follicular lymphoma refractory to two lines of treatment (monotherapy)

- **BY MOUTH**
  - Adult: 150 mg twice daily, for dose adjustment due to side effects, consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**MHRA/CHM ADVICE: IDELALISIB (ZYDELIG®): UPDATED INDICATIONS AND ADVICE ON MINIMISING THE RISK OF INFECTION (SEPTEMBER 2016)**

In light of a recent safety review the indications for idelalisib have been updated. Manufacturer recommendations regarding monitoring for infection and prophylaxis of *Pneumocystis jiroveci* pneumonia have also been updated. Patients should be advised on the risk of serious or fatal infections during treatment, and idelalisib should not be initiated in patients with any evidence of infection.

**CAUTIONS**

- Active hepatitis · diarrhoea—symptomatic management recommended (consult product literature) · pneumonitis—withhold treatment (consult product literature)

**INTERACTIONS** → Appendix 1 (idelalisib).

**SIDE-EFFECTS**

- Alopecia · bone-marrow suppression · diarrhoea · hyperuricaemia · infections · nausea · neutropenia · oral mucositis · pneumonitis · pyrexia · rash · thromboembolism · tumour lysis syndrome · vomiting

**CONCEPTION AND CONTRACEPTION** Highly effective contraception (in addition to barrier method) required during and for one month after treatment.

**PREGNANCY**

- Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**

- Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in hepatic impairment.

**MONITORING REQUIREMENTS**

- Manufacturer advises monitor liver function—consult product literature.

- Manufacturer advises monitor for signs and symptoms of infection, including *cytomegalovirus* infection and respiratory infections; new symptoms should be reported promptly. Neutrophil count should be monitored in all patients every 2 weeks for the first 6 months of treatment; patients with neutrophil count <1000 per mm$^3$ should be monitored weekly.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Idelalisib for treating chronic lymphocytic leukaemia (October 2015) NICE TA359

Idelalisib, in combination with rituximab, is recommended as an option for treatment in adults:

- who have untreated chronic lymphocytic leukaemia or
- who have chronic lymphocytic leukaemia when the disease has been treated but has relapsed within 24 months and

- if the manufacturer provides idelalisib with the discount agreed in the simple discount agreement.

Patients who are already receiving idelalisib should continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA359

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (March 2015) that idelalisib (Zydelig®) is accepted for restricted use within NHS Scotland, in combination with rituximab, for the treatment of relapsed chronic lymphocytic leukaemia in patients who are unsuitable for chemotherapy and treatment naïve patients with 17p deletion or TP53 mutation who are unsuitable for chemomunotherapy, only whilst idelalisib is available at the price agreed in the patient access scheme.

**MEDICINAL FORMS**

There can be a variation in the licensing of different medicines containing the same drug.

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 25 |
| Idelalisib 100 mg | Zydelig 100mg tablets | 60 tablet (Pom) £1,114.75 (Hospital only) |
| Idelalisib 150 mg | Zydelig 150mg tablets | 60 tablet (Pom) £1,114.75 (Hospital only) |
**Imatinib**

**DRUG ACTION** Imatinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

Treatment of chronic myeloid leukaemia in chronic phase after failure with interferon alfa

- **BY MOUTH**
- Adult: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in accelerated phase, or in blast crisis

- **BY MOUTH**
- Adult: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

Treatment of newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy) | Monotherapy for relapsed or refractory acute lymphoblastic leukaemia

- **BY MOUTH**
- Adult: 600 mg once daily

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST) | Adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse | Treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement

- **BY MOUTH**
- Adult: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protubera nier or metastatic dermatofibrosarcoma protubera nier, in patients who cannot have surgery

- **BY MOUTH**
- Adult: 800 mg daily in 2 divided doses

Treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia

- **BY MOUTH**
- Adult: 100–400 mg once daily

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS**

An EU wide review has concluded that imatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

**CAUTIONS**

- Cardiac disease • hepatitis B infection • history of renal failure • risk factors for heart failure

**CAUTIONS, FURTHER INFORMATION**

- Hepatitis B infection • The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

**INTERACTIONS**

- Appendix 1 (imatinib).

**SIDE-EFFECTS**

- Common or very common • Abdominal pain • appetite changes • arthralgia • ascites • conjunctivitis • constipation • cough • cramps • diarrhea • dizziness • dry eyes • dry mouth • dry skin • dysphagia • epistaxis • fatigue • flatulence • flushing • gastro-oesophageal reflux • haemorrhage • headache • hypoesthesia • increased lacrimation • influenza-like symptoms • insomnia • oedema • paraesthesia • photosensitivity • pleural effusion • pruritus • pulmonary oedema • rash • sweating • taste disturbance • visual disturbances • weight changes

- Uncommon • Acute respiratory failure • anxiety • cold extremities • cough • depression • drowsiness • dysphagia • electrolyte disturbances • gastric ulceration • gout • gynaecomastia • haemoptysis • hearing loss • heart failure • hepatic dysfunction • hepatitis • hypertension • hypotension • impaired memory • irregular menstruation • menorrhagia • migraine • palpitation • pancreatitis • peripheral neuropathy • renal failure • sexual dysfunction • skin hyperpigmentation • syncope • tachycardia • tinnitus • tremor • urinary frequency • vertigo

- Rare • Angina • angioedema • arrhythmia • asptic necrosis of bone • atrial fibrillation • ataraxia • confusion • convulsions • exfoliative dermatitis • gastro-intestinal perforation • glaucoma • haemolytic anaemia • hepatic failure • hepatic failure (fatal cases reported) • hepatic necrosis • increased intracranial pressure • inflammatory bowel disease • intestinal obstruction • myocardial infarction • myopathy • pulmonary fibrosis • pulmonary hypertension • rhabdomyolysis • Stevens-Johnson syndrome

- Frequency not known • Alopecia • bone-marrow suppression • drug rash with eosinophilia and systemic symptoms (DRESS) • growth retardation in children • hepatitis B reactivation • hyperurcaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomit ing

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment.

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING**

Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

Max. 400 mg daily; reduce dose further if not tolerated.

**RENAL IMPAIRMENT**

Maximum starting dose 400 mg daily if creatinine clearance less than 60 mL/minute; reduce dose further if not tolerated.

**MONITORING REQUIREMENTS**

- Monitor for gastrointestinal haemorrhage.
- Monitor complete blood counts regularly.
- Monitor for fluid retention.
- Monitor liver function.

**DIRECTIONS FOR ADMINISTRATION**

Tablets may be dispersed in water or apple juice.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer imatinib tablets.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Imatinib for the adjuvant treatment of gastro-intestinal stromal tumours (November 2014) NICE TA326
  Imatinib is recommended as an option for adjuvant treatment of adult patients who are at high risk of relapse after surgery for kit (CD117)-positive gastro-intestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location, and mitotic rate), for up to 3 years.
  Patients currently receiving treatment initiated within the NHS with imatinib that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
  www.nice.org.uk/TA326

- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (April 2012) NICE TA251
  Standard-dose imatinib is recommended as an option for the first-line treatment of adults with chronic phase...
Philadelphia–chromosome-positive chronic myeloid leukaemia (CML).

www.nice.org.uk/TA251

- **Imatinib for chronic myeloid leukaemia (October 2003)**
  NICE TA70
  Imatinib is recommended as first-line treatment for Philadelphia–chromosome-positive chronic myeloid leukaemia in the chronic phase and as an option for patients presenting in the accelerated phase or with blast crisis, provided that imatinib has not been used previously.
  www.nice.org.uk/TA70

- **Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (January 2012)**
  NICE TA241
  High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib.
  www.nice.org.uk/TA241

- **Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (October 2004)**
  NICE TA86
  Imatinib 400 mg daily is recommended as first-line management of KIT (CD117)-positive unresectable or metastatic, or both, gastro-intestinal stromal tumours. Continued therapy is recommended only if a response to initial treatment (as defined by Southwest Oncology Group criteria available at www.nice.org.uk/TA86) is achieved within 12 weeks. Patients who have responded should be assessed at 12-week intervals. Discontinue if tumour ceases to respond.
  www.nice.org.uk/TA86

- **Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (November 2010)**
  NICE TA209
  Imatinib 600 mg daily or 800 mg daily is not recommended for unresectable or metastatic, or both, gastro-intestinal stromal tumours whose disease has progressed after treatment with imatinib 400 mg daily.
  www.nice.org.uk/TA209

**Scottish Medicines Consortium (SMC) Decisions**

The **Scottish Medicines Consortium** has advised (March 2002) that imatinib (Glivec®) should be used for chronic myeloid leukaemia only under specialist supervision in accordance with British Society of Haematology guidelines (November 2001).

The **Scottish Medicines Consortium** has also advised (February 2012) that imatinib (Glivec®) is accepted for restricted use within NHS Scotland for the treatment of adult patients who are at significant risk of relapse following resection of a KIT (CD117) positive gastrointestinal stromal tumour (GIST) and who are at high risk of recurrence following complete resection (according to the Armed Forces Institute of Pathology (AFIP) risk criteria).

**Lapatinib**

- **DRUG ACTION** Lapatinib is a tyrosine kinase inhibitor.

- **INDICATIONS AND DOSE**

  Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2) with hormone-receptor-negative disease who have had previous treatment with trastuzumab in combination with chemotherapy (in combination with trastuzumab)
  
  **BY MOUTH**
  
  - Adult: 1 g once daily

  Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for patients who have had previous treatment with an anthracycline, a taxane, and trastuzumab (in combination with capecitabine)
  
  **BY MOUTH**
  
  - Adult: 1.25 g once daily

  Treatment of advanced or metastatic breast cancer with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for postmenopausal women with hormone-receptor-positive disease (in combination with an aromatase inhibitor)
  
  **BY MOUTH**
  
  - Adult: 1.5 g once daily

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

- **CAUTIONS** Diarrhoea— withhold treatment if severe (consult product literature) - low gastric pH (reduced absorption) - susceptibility to QT-interval prolongation (including electrolyte disturbances)

- **INTERACTIONS** → Appendix 1 (lapatinib).
  
  Caution with concomitant use of drugs that prolong QT-interval.

- **SIDE-EFFECTS**
  
  - **Common or very common** Anorexia - cardiac failure (fatal cases reported) - decreased left ventricular ejection fraction - diarrhoea (treat promptly) - hepatotoxicity (discontinue permanently if severe) - hyperbilirubinaemia - malaise - nail disorders - rash

  - **Uncommon** Interstitial lung disease

  - **Frequency not known** Alopecia - bone-marrow suppression - hyperuricaemia - nausea - oral mucositis - respiratory failure (including fatal cases) - thromboembolism - tumour lysis syndrome - vomiting

- **CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **PREGNANCY** Avoid unless potential benefit outweighs risk— toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** Caution in moderate to severe impairment— metabolism reduced.

- **RENAL IMPAIRMENT** Caution in severe impairment— no information available.

- **MONITORING REQUIREMENTS**
  
  - **DIRECTIONS FOR ADMINISTRATION** Always take at the same time in relation to food: either one hour before or one hour after food.
Nilotinib

27-Jul-2016

Drug action
Nilotinib is a tyrosine kinase inhibitor.

indications and dose
Treatment of newly diagnosed chronic myeloid leukaemia in the chronic phase
- **By mouth**
  - Adult: 300 mg twice daily

Treatment of chronic and accelerated phase chronic myeloid leukaemia in patients who have resistance to or intolerance of previous therapy, including imatinib
- **By mouth**
  - Adult: 400 mg twice daily

Caution
- **History of pancreatitis**
- **Susceptibility to QT-interval prolongation (including electrolyte disturbances)**

Important safety information
Risks of incorrect dosing of oral anti-cancer medicines
See Cytotoxic drugs p. 797.

MHRA/CHM advice (May 2016): Risk of Hepatitis B Virus Reactivation with Tyrosine Kinase Inhibitors
An EU wide review has concluded that nilotinib can cause hepatitis B virus reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

Side-effects
- **Common or very common** Abdominal pain · anorexia · arthralgia · asthenia · blood glucose changes · bone pain · constipation · cough · diarrhoea · dizziness · dry skin · dyspepsia · dysphonia · dyspnoea · erythema · fatigue · flatulence · flushing · headache · hyperhidrosis · hyperkaemia · hypertension · hypomagnesaemia · insomnia · muscle spasm · oedema · palpitation · paraesthesia · pruritus · QT-interval prolongation · rash · urticaria · vertigo · weight changes

Uncommon
- Anxiety · arthralgia · bradycardia · breast pain · cardiac failure · cardiac murmur · cardiomyalgia · chest pain · conjunctivitis · coronary artery disease · decreased visual acuity · dehydration · depression · dry eyes · dry mouth · dysuria · ecchymosis · epistaxis · erectile dysfunction · gynaecomastia · haematoma · haemorrhage · hepatitis · hyperaesthesia · hypertensive crisis · hyperthyroidism · hypoaesthesia · hypocalcaemia · hypokalaemia · hyponatraemia · hypophosphataemia · influenza-like symptoms · interstitial lung disease · melaena · migrane · pancreatitis · peripheral effusion · pleural effusion · tremor · urinary frequency
- Frequency not known
  - Alopecia · bone-marrow suppression · hepatic failure (fatal cases reported) · hepatitis D reactivation · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

Conception and contraception
Effective contraception required during treatment.

Pregnancy
Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

Breast feeding
Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment
Manufacturer advises caution.

NATIONAL FUNDING / ACCESS DECISIONS

NICE technology appraisals (TAs)
- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (April 2012) NICE TA251
- Dasatinib, nilotinib and high-dose imatinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (January 2012) NICE TA241

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (February 2008) that nilotinib (Tasigna®) is accepted for restricted use within NHS Scotland for the treatment of chronic-phase chronic myeloid leukaemia in adults resistant to or intolerant of at least one previous therapy, including imatinib, and (July 2011) for the treatment of adults with newly diagnosed chronic myeloid leukaemia in the chronic phase.
Pazopanib

**DRUG ACTION** Pazopanib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

First-line treatment of advanced renal cell carcinoma

Treatment of advanced renal cell carcinoma in patients who have had previous treatment with cytokine therapy

**BY MOUTH**

Adult: 800 mg daily, adjust dose in steps of 200 mg according to tolerability; maximum 800 mg per day

Treatment of selective subtypes of advanced soft-tissue sarcoma

**BY MOUTH**

Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**CONTRA-INDICATIONS**

Cerebral haemorrhage - clinically significant gastro-intestinal haemorrhage - haemoptysis in the past 6 months

**CAUTIONS**

Cardiac disease - increased risk of gastro-intestinal fistulas - increased risk of gastro-intestinal perforation - increased risk of haemorrhage - increased risk of thrombotic microangiopathy - permanently discontinue if symptoms develop - ischaemic stroke - myocardial infarction - risk of thrombotic events - susceptibility to QT-interval prolongation (including electrolyte disturbances) - transient ischaemic attack

**CAUTIONS, FURTHER INFORMATION**

Elective surgery Discontinue treatment 7 days before elective surgery and restart only if adequate wound healing.

Blood pressure Blood pressure must be controlled before initiating treatment.

**INTERACTIONS** ▶ Appendix 1 (pazopanib).

Caution with concomitant use of drugs that prolong QT-interval.

**SIDE-EFFECTS**


**Rare** Thrombotic microangiopathy

**Frequency not known** Alopecia - bone-marrow suppression - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRAPLICATION** Effective contraception advised during treatment.

**PREGNANCY** Avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Reduce dose to 200 mg once daily in moderate impairment. Use with caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT** Use with caution if creatinine clearance less than 30 ml/minute—no information available.

**MONITORING REQUIREMENTS**

Monitor liver function before treatment and at weeks 3, 7, and 9, then at months 3 and 4, and periodically thereafter as clinically indicated—consult product literature if elevated liver enzymes observed.

Monitor blood pressure within 1 week of treatment initiation, then frequently throughout treatment (consider dose reduction or interruption if hypertension uncontrolled despite anti-hypertensive therapy; discontinue if blood pressure persistently elevated despite anti-hypertensive therapy and pazopanib dose reduction—consult product literature).

Monitor for signs or symptoms of congestive heart failure—monitor left ventricular ejection fraction in patients at risk of heart failure before and during treatment.

Monitor for proteinuria.

Monitor thyroid function.

Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including headache, hypertension, seizure, lethargy, confusion, visual and neurological disturbances)—permanently discontinue treatment if symptoms occur.

**PATIENT AND CARER ADVICE** Patients should be advised not to take antacids for at least 1 hour before or 2 hours after pazopanib.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

Pazopanib for the first-line treatment of advanced renal cell carcinoma (updated August 2013) NICE TA215

Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma:

who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1 and

if the manufacturer provides pazopanib at the discounted price agreed under the patient access scheme.

www.nice.org.uk/TA215

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (February 2011) that pazopanib (Votrient®) is accepted for restricted use within NHS Scotland for the first-line treatment of advanced renal cell carcinoma and (December 2012) is not recommended for use within NHS Scotland for the treatment of selective subtypes of advanced soft tissue sarcoma in patients who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after neoadjuvant therapy.
CAUTIONS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 23, 25
▶ Votrient (Novartis Pharmaceuticals UK Ltd)
Pazopanib (as Pazopanib hydrochloride) 200 mg Votrient 200mg tablets | 30 tablet | £660.50
Pazopanib (as Pazopanib hydrochloride) 400 mg Votrient 400mg tablets | 30 tablet | £1,121.00

Ponatinib

INDICATIONS AND DOSE
Treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib or nilotinib, and for whom subsequent treatment with imatinib is not clinically appropriate.

Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib, and for whom subsequent treatment with imatinib is not clinically appropriate.

BY MOUTH
Adult: 45 mg once daily, for dose adjustment due to side effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Consider reducing the initial dose to 30 mg once daily with concomitant use of potent inhibitors of cytochrome P450 enzyme CYP3A4 (e.g. clarithromycin, indinavir, itraconazole, ritonavir, saquinavir, telithromycin or voriconazole).

IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: PONATINIB: RISK OF VASCULAR OCCLUSIVE EVENTS (NOVEMBER 2014)
The benefits and risks of ponatinib have been reviewed by the European Medicines Agency’s Committee on Medicinal Products for Human Use, which has recommended that strengthened warnings should be added to the product information aimed at minimising the risk of blood clots and blockages in the arteries. The review concluded that available evidence shows that the risk of blood vessel blockage with ponatinib is likely to be dose-dependent. However, the data is insufficient to recommend reducing the dose of ponatinib, and there is a risk that a lower dose might not be as effective as the current dose in all patients and in long-term treatment. Therefore, no change has been made to the recommended starting dose.

Prescribers may wish to consider reducing the dose in patients with chronic phase chronic myeloid leukaemia who are responding well to treatment, and who might be at high risk of blood vessel blockage. Stop ponatinib if a complete response has not occurred within 3 months of treatment, and monitor patients for high blood pressure or signs of heart problems.

MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS An EU wide review has concluded that ponatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 797.

CAUTIONS
Alcohol abuse—increased risk of pancreatitis—current severe hypertriglyceridaemia—increased risk of pancreatitis—discontinue treatment if a complete haematologic response has not occurred within 3 months—hepatitis B infection—history of myocardial infarction—do not use unless potential benefit outweighs potential risk—history of pancreatitis—history of stroke—do not use unless potential benefit outweighs potential risk—hypertension—medically control during treatment and interrupt treatment if uncontrolled

CAUTIONS, FURTHER INFORMATION

Dose adjustments due to interactions


Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

INTERACTIONS
Appendix 1 (ponatinib).

SIDE-EFFECTS


Uncommon Atopic dermatitis—cerebral artery stenosis—cerebral infarction—gastro haemorrhage—hepatotoxicity—jaundice—retinal vein occlusion—retinal vein thrombosis—visual impairment

Frequency not known Alopecia—bone/marrow suppression—hepatic failure (fatal cases reported)—hepatitis—hepatitis B reactivation—hyperuricaemia—nausea—oral mucositis—thromboembolism—tumour lysis syndrome—vomiting

CONCEPTION AND CONTRACEPTION
Ensure effective contraception during treatment in men and women; effectiveness of hormonal contraception unknown—alternative or additional methods of contraception should be used.

PREGNANCY
Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

BREAST FEEDING
Manufacturer advises discontinue breastfeeding—no information available.

HEPATIC IMPAIRMENT
Manufacturer advises caution in severe impairment.

RENAL IMPAIRMENT
No information available—manufacturer advises caution if creatinine clearance less than 50 mL/minute.

MONITORING REQUIREMENTS

Manufacturer advises monitor serum lipase every 2 weeks for the first 2 months and periodically thereafter—withdraw treatment if lipase elevated and abdominal symptoms occur.

Manufacturer advises a full blood count every 2 weeks for the first 3 months and then monthly thereafter or as clinically indicated.

Manufacturer advises monitor liver function periodically.

Manufacturer advises monitor for vascular occlusion or thromboembolism—interrupt treatment immediately if this occurs.

Immune system and malignant disease

Targeted therapy responsive malignancy 873
Regorafenib

**DRUG ACTION** Regorafenib is an inhibitor of several protein kinases.

**INDICATIONS AND DOSE**

Treatment of metastatic colorectal cancer in patients who have previously been treated with, or who are unsuitable for standard treatment including fluoropyrimidine-based chemotherapy, a vascular endothelial growth factor inhibitor, and an epidermal growth factor receptor inhibitor. Treatment of unresectable or metastatic gastrointestinal stromal tumours in patients who progressed on or are intolerant to previous treatment with imatinib and sunitinib.

- **By mouth**
  - Adult: 160 mg once daily for 21 consecutive days of repeated 28-day cycles, for dose adjustment due to side effects—consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOsing OF ORAL ANti-CANCer MEDICINES**

See Cytotoxic drugs p. 797.

**CAUTIONS**

Ensure measures to prevent hand-foot skin reaction. Gilbert’s syndrome—risk of hyperbilirubinaemia. History of ischaemic heart disease—monitor for signs and symptoms of myocardial ischaemia and interrupt treatment if signs of ischaemia or infarction develop. Hypertension—control blood pressure before treatment initiation and monitor as clinically indicated during treatment (review dose and consider treatment interruption if severe or persistent hypertension develops; discontinue treatment if hypertensive crisis occurs). May impair wound healing— withhold treatment for major surgical procedures. Predisposition to bleeding.

**INTERACTIONS** → Appendix 1 (regorafenib).

Caution in concomitant treatment with drugs that may increase the risk of bleeding (increased risk of haemorrhagic events).

**SIDE-EFFECTS**


- **Uncommon** Gastro-intestinal perforation (including fatal cases) and fistula—discontinue treatment. Hypertensive crisis. Myocardial infarction. Myocardial ischaemia. Severe (including fatal) liver injury.


**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

3, 25

- **Iclusig** (Ariad Pharma (UK) Ltd)

Ponatinib (as Ponatinib hydrochloride) 15 mg Iclusig 15 mg tablets 60 tablet (POM) £5.050.00

Ponatinib (as Ponatinib hydrochloride) 45 mg Iclusig 45 mg tablets 30 tablet (POM) £5.050.00

**Ruxolitinib**

**DRUG ACTION** Ruxolitinib is a selective inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2.

**INDICATIONS AND DOSE**

Treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.

- **By mouth**

  - Adult: (consult product literature or local protocols)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOsing OF ORAL ANti-CANCer MEDICINES**

See Cytotoxic drugs p. 797.
Ruxolitinib for treating disease-related splenomegaly or symptoms (March 2016)
NICE TA386
Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only if the patient has intermediate-2 or high-risk disease, and if the manufacturer provides ruxolitinib with the discount agreed in the patient access scheme.

Patients currently receiving ruxolitinib whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA386

### Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Jakavi (Novartis Pharmaceuticals UK Ltd)

  - **Ruxolitinib (as Ruxolitinib phosphate) 5 mg** Jakavi 5mg tablets | 56 tablet blister pack | £1,428.00
  - **Ruxolitinib (as Ruxolitinib phosphate) 10 mg** Jakavi 10mg tablets | 56 tablet blister pack | £2,856.00
  - **Ruxolitinib (as Ruxolitinib phosphate) 15 mg** Jakavi 15mg tablets | 56 tablet blister pack | £2,856.00
  - **Ruxolitinib (as Ruxolitinib phosphate) 20 mg** Jakavi 20mg tablets | 56 tablet blister pack | £2,856.00

### Indications and dose
**Treatment of advanced renal cell carcinoma when treatment with interferon alfa or interleukin-2 has failed or is unsuitable**

- Treatment of progressive, locally advanced, or metastatic, differentiated thyroid carcinoma that is refractory to radioactive iodine
- Treatment of hepatocellular carcinoma

**Drug action**
Sorafenib is an inhibitor of multiple kinases.

**Common or very common**
- Dizziness
- Flatulence
- Headache
- Hypercholesterolaemia
- Weight gain

**Uncommon**
- Tuberculosis

**Frequency not known**
- Alopecia
- Bone-marrow suppression
- Hyperuricaemia
- Nausea
- Oral mucositis
- Progressive multifocal leucoencephalopathy
- Thromboembolism
- Tumour lysis syndrome
- Vomiting

**Conception and contraception**
Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**Pregnancy**
Avoid—activity in animal studies.

**Breast feeding**
Avoid—present in milk in animal studies.

**Hepatic impairment**
Reduce dose (consult product literature).

**Renal impairment**
Reduce dose in severe impairment (consult product literature).

**Monitoring requirements**
- Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
- Monitor for infection during treatment.
- Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

**National funding/access decisions**

### Sorafenib

**DRUG ACTION**
Sorafenib is an inhibitor of multiple kinases.

**Indications and dose**

**Treatment of advanced renal cell carcinoma when treatment with interferon alfa or interleukin-2 has failed or is unsuitable**

- Treatment of progressive, locally advanced, or metastatic, differentiated thyroid carcinoma that is refractory to radioactive iodine
- Treatment of hepatocellular carcinoma

**By mouth**
- Adult: 400 mg twice daily, for dose adjustments due to side effects, consult product literature

**Important safety information**

**Risks of incorrect dosing of oral anti-cancer medicines**
See Cytotoxic drugs p. 797.

**Caution**
- Cardiac ischaemia
- Major surgical procedures
- Potential risk of bleeding—treat tracheal, bronchial, or oesophageal infiltration with localised therapy before initiating sorafenib in patients with differentiated thyroid carcinoma (DTC) and consider permanent withdrawal of sorafenib in any patient that requires medical intervention for bleeding—susceptibility to QT-interval prolongation

**Interactions**
Appendix 1 (sorafenib).

**Side-effects**
- Common or very common
  - Acne
  - Anorexia
  - Arthralgia
  - Asthenia
  - Congestive heart failure
  - Constipation
  - Depression
  - Dermatitis
  - Desquamation
  - Diarrhoea
  - Dry skin
  - Dyspepsia
  - Dysphagia
  - Dysphonia
  - Electrolyte disturbances
  - Erectile dysfunction
  - Erythema
  - Fatigue
  - Fever
  - Flushing
  - Gastro-oesophageal reflux disease
  - Haemorrhage
  - Hand-foot skin reaction
  - Hoarseness
  - Hyperkeratosis
  - Hypertension
  - Hypophysioptalamic disease
  - Hypophysioptalamic disease
  - Keratoacanthoma
  - Malaise
  - Muscle spasm
  - Myalgia
  - Myocardial infarction
  - Myocardial ischaemia
  - Peripheral neuropathy
  - Proteinuria
  - Pruritus
  - Rash
  - Renal failure
  - Rhinorrhea
  - Thyroid dysfunction
  - Tinnitus
- Uncommon
  - Altered INR
  - Altered prothrombin time
  - Cholangitis
  - Cholecystitis
  - Dehydration
  - Eczema
  - Erythema multiforme
  - Gastritis
  - Gastro-intestinal perforations
  - Gynaecomastia
  - Hypertensive crisis
  - Intestinal lung disease
  - Pancreatitis
  - Posterior reversible encephalopathy syndrome
- Rare
  - Hepatitis
  - Leucocytoelastic vasculitis
  - Nephrotic syndrome
  - QT-interval prolongation
  - Rhabdomyolysis
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
- Frequency not known
  - Alopecia
  - Bone-marrow suppression
  - Hyperuricaemia
  - Nausea
  - Oral mucositis
  - Thromboembolism
  - Tumour lysis syndrome
- Cautions
  - Cardiac ischaemia
  - Major surgical procedures
  - Potential risk of bleeding—treat tracheal, bronchial, or oesophageal infiltration with localised therapy before initiating sorafenib in patients with differentiated thyroid carcinoma (DTC) and consider permanent withdrawal of sorafenib in any patient that requires medical intervention for bleeding—susceptibility to QT-interval prolongation

**Conception and contraception**
Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**Pregnancy**
Manufacturer advises avoid unless essential—activity in animal studies. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 797.

**Breast feeding**
Discontinue breast-feeding.

**Hepatic impairment**
Manufacturer advises caution in severe impairment—no information available.

**Monitoring requirements**
- Consider periodic monitoring of ECG and electrolytes in patients susceptible to QT-interval prolongation.
- Monitor blood pressure regularly and consider permanent discontinuation of sorafenib if resistant to antihypertensive therapy.
- Monitor plasma—calcium concentration (increased risk of hypocalcaemia if history of hypoparathyroidism).
Targeted therapy responsive malignancy

- Monitor thyroid stimulating hormone in patients with differentiated thyroid carcinoma.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Sorafenib for the treatment of advanced hepatocellular carcinoma (May 2010) NICE TA189
  - Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are unsuitable.
  - www.nice.org.uk/TA189

- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
  - Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma.
  - Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma.
  - www.nice.org.uk/TA178

**Scottish Medicines Consortium (SMC) Decisions**

- The Scottish Medicines Consortium (SMC) has advised (January 2016) that sorafenib (Nexavar®) is accepted for restricted use within NHS Scotland for the treatment of advanced hepatocellular carcinoma in patients where surgical or loco-regional therapies have failed or are unsuitable.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 23
- Nexavar (Bayer Plc)
- Sorafenib (as Sorafenib tosylate) 200 mg Nexavar 200mg tablets
- 112 tablet (Pack) £3,576.56

### Drug Action

- Sunitinib is a tyrosine kinase inhibitor.

#### Indications and Dose

- Treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours, after failure of imatinib.
- Treatment of advanced or metastatic renal cell carcinoma
  - BY MOUTH
  - Adult: 50 mg once daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle, adjusted in steps of 12.5 mg, doses adjusted according to tolerability; usual dose 25–75 mg daily

- Treatment of unresectable or metastatic pancreatic neuroendocrine tumours
  - BY MOUTH
  - Adult: 37.5 mg once daily without treatment-free period; adjusted in steps of 12.5 mg, doses adjusted according to tolerability; maximum 50 mg per day

#### Important Safety Information

**Risk of Osteonecrosis of the Jaw (January 2011)**

- Treatment with sunitinib may be a risk factor for the development of osteonecrosis of the jaw.
- Patients treated with sunitinib, who have previously received bisphosphonates, or are treated concurrently with bisphosphonates, may be particularly at risk.
- Dental examination and appropriate preventive dentistry should be considered before treatment with sunitinib.
- If possible, invasive dental procedures should be avoided in patients treated with sunitinib who have previously received, or who are currently receiving, intravenous bisphosphonates.

**Risks of Incorrect Dosing of Oral Anti-Cancer Medicines**

- See Cytotoxic drugs p. 797.

#### CAUTIONS

- Cardiovascular disease—discontinue if congestive heart failure develops.
- Hypertension—increased risk of bleeding.
- Susceptibility to QT-interval prolongation.

#### Interactions

- Appendix 1 (sunitinib).

#### Side-Effects

- Rare
  - Nephrotic syndrome
- Frequency not known
  - Abdominal pain, alopecia, anorexia, arthralgia, bone-marrow suppression, constipation, cough, dehydration, diarrhoea, dizziness, dry skin, dysphoria, epistaxis, fatigue, fistula formation (interrupt treatment if occurs), gastro-intestinal perforation, hair discoloration, hand-foot syndrome, headache, hepatic failure, hypertension, hyperuricaemia, hypothyroidism, increased lacrimation, insomnia, myalgia, nausea, oedema, oral mucositis, osteonecrosis of the jaw, pancreatitis, paraesthesia, peripheral neuropathy, proteinuria, rash, seizures, skin discoloration, taste disturbance, thromboembolism, tumour lysis syndrome, urine discoloration, vomiting

#### Conception and Contraception

- Effective contraception required during treatment.

#### Pregnancy

- Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

#### Breast Feeding

- Discontinue breast-feeding.

#### Monitoring Requirements

- Monitor for thyroid dysfunction.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Sunitinib for advanced or metastatic renal cell carcinoma (March 2009) NICE TA169
  - Sunitinib is recommended as first-line treatment for advanced or metastatic renal cell carcinoma in patients who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1.
  - www.nice.org.uk/TA169

- Sunitinib for the treatment of gastrointestinal stromal tumours (September 2009) NICE TA179
  - Sunitinib is recommended as an option for treatment in patients with unresectable or metastatic gastrointestinal tumours if imatinib treatment has failed because of resistance or intolerance, and the cost of sunitinib for the first treatment cycle is met by the manufacturer.
  - www.nice.org.uk/TA179

- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
  - Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma.
  - www.nice.org.uk/TA178

**Scottish Medicines Consortium (SMC) Decisions**

- The Scottish Medicines Consortium (SMC) has advised (October 2009 and April 2011) that sunitinib (Sutent®) is accepted for restricted use within NHS Scotland for the treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours after failure of imatinib and for unresectable or metastatic pancreatic neuroendocrine tumours.
Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 14**

- **Sutent (Pfizer Ltd)**
  - Sunitinib (as Sunitinib malate) 12.5 mg: Sutent 12.5 mg capsules | 28 capsule [POM] £784.70
  - Sunitinib (as Sunitinib malate) 25 mg: Sutent 25 mg capsules | 28 capsule [POM] £1,569.40
  - Sunitinib (as Sunitinib malate) 50 mg: Sutent 50 mg capsules | 28 capsule [POM] £3,130.80

Drug Action

**Temosirolimus**

- **INDICATIONS AND DOSE**
  - First-line treatment of advanced renal cell carcinoma | Treatment of relapsed or refractory mantle cell lymphoma
  - **BY INTRAVENOUS INFUSION**
  - **Adult:** (consult product literature or local protocols)

- **INTERACTIONS**
  - **Uncommon** Intracerebral bleeding
  - **Frequency not known** Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Hypersensitivity reactions
  - Hypersensitivity reactions, including some life-threatening and rare fatal reactions, are associated with temsirolimus therapy, usually during administration of the first dose. Symptoms include flushing, chest pain, dyspnoea, apnoea, hypotension, loss of consciousness, and anaphylaxis. Where possible, patients should receive an intravenous dose of antihistamine 30 minutes before starting the temsirolimus infusion. The infusion may have to be stopped temporarily for the treatment of infusion-related effects—consult product literature for appropriate management. If adverse reactions are not managed with dose delays, a dose reduction should be considered—consult product literature.

- **CONCEPTION AND CONTRA IndICATIONS**
  - Ensure effective contraception during treatment in men and women.

- **PREGNANCY**
  - Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- **BREAST FEEDING**
  - Manufacturer advises discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**

In mantle cell lymphoma, avoid in moderate or severe impairment.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution in severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor respiratory function.
  - Monitor blood lipids.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
  - Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma.
  - www.nice.org.uk/TA178

**Vandetanib**

- **DRUG ACTION**
  - Vandetanib is a tyrosine kinase inhibitor.

- **INDICATIONS AND DOSE**
  - Treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease
  - **BY MOUTH**
  - **Adult:** 300 mg once daily, for dose adjustment due to side effects—consult product literature

- **CONTRA-INDICATIONS**
  - Congenital long QT syndrome - QT interval greater than 480 milliseconds

- **CAUTIONS**
  - Brain metastases (intracranial haemorrhage reported) - electrolyte disturbances - history of torsades de pointes - hypertension - phototoxicity reactions reported (wear protective clothing and/or sunscreen) - susceptibility to QT-prolongation

- **INTERACTIONS**

- **SIDE-EFFECTS**
  - Caution with concomitant use of drugs that prolong QT interval.

**IMPORTANT SAFETY INFORMATION**

**RISks OF INCORRECT DOsiNG OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.
Vemurafenib

**DRUG ACTION** Vemurafenib is a BRAF kinase inhibitor.

**INDICATIONS AND DOSE**

Monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma

- **BY MOUTH**
  - Adult: 960 mg twice daily, for dose adjustment due to side effects—consult product literature

**IMPORTANT SAFETY INFORMATION**

**DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME)**

DRESS syndrome has been reported in patients taking vemurafenib. DRESS syndrome starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal.

Patients should be advised to stop taking vemurafenib and consult their doctor immediately if skin rash develops. Treatment with vemurafenib should not be restarted.

MHRA/CHM ADVICE (NOVEMBER 2015): RISK OF POTENTIATION OF RADIATION TOXICITY

Potentiation of radiation toxicity has been reported in patients treated with vemurafenib before, during, or after radiotherapy—use with caution.

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 797.

**CONTRA-INDICATIONS**

Wild-type BRAF malignant melanoma

**CAUTIONS**

Electrolyte disturbances - prior or concurrent cancer associated with RAS mutation—increased risk of tumour progression - susceptibility to QT-prolongation

**INTERACTIONS** → Appendix 1 (vemurafenib). Caution with concomitant use of drugs that prolong QT interval.

**SIDE-EFFECTS**


- **Uncommon** Non-cutaneous squamous cell carcinoma - peripheral neuropathy - retinal vein occlusion - Stevens-Johnson syndrome - toxic epidermal necrolysis - vasculitis

- **Rare** Progression of pre-existing NRAS mutated chronic myelomonocytic leukaemia

- **Frequency not known** Alopecia - bone-marrow suppression - hypersensitivity reactions - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION** Effective contraception required during for at least 6 months after treatment.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises more frequent monitoring in moderate to severe hepatic

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Caprelsa (AstraZeneca UK Ltd)
- Vandetanib 100 mg Caprelsa 100mg tablets | 30 tablet £2,500.00
- Vandetanib 300 mg Caprelsa 300mg tablets | 30 tablet £5,000.00
impairment (including monthly ECG monitoring during first 3 months of treatment).

- **RENAI L IMPAI RMENT** Manufacturer advises caution in severe impairment.

- **MONITORING REQUIREMENTS**
  - Monitor ECG and electrolytes before treatment, after one month and following dose adjustment (treatment not recommended if QT interval greater than 500 milliseconds at baseline).
  - Monitor liver function before treatment and periodically thereafter.
  - Monitor for uveitis, iritis and retinal vein occlusion.

- **DIRECTIONS FOR ADMINISTRATION** Food may affect absorption (take at the same time with respect to food).

- **PATIENT AND CARER ADVICE** Counselling advised (administration).

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)**
    - Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (December 2012) NICE TA269
      - Vemurafenib is recommended as an option for the treatment of BRAF V600 mutation-positive unresctable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme.
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium has advised (November 2013) that vemurafenib (Zelboraf®) is accepted for restricted use within NHS Scotland as monotherapy for the first-line treatment of BRAF V600 mutation-positive unresctable or metastatic melanoma.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 25
    - Zelboraf (Roche Products Ltd)
    - Vemurafenib 240 mg Zelboraf 240mg tablets | 56 tablet (PaM £1,750.00 (Hospital only))

- **ANTINEOPLASTIC DRUGS**

  - **PROTEIN KINASE INHIBITORS**
  - **ANTIFIBROTICS**

  - **Nin tedan ib** 23-Feb-2016

  - **DRUG ACTION**
    - Nin tedan ib is a tyrosine protein kinase inhibitor.

  - **INDICATIONS AND DOSE**
    - **OFEV®**
      - Treatment of idiopathic pulmonary fibrosis
        - **BY MOUTH**
        - Adult: 150 mg twice daily, reduced if not tolerated to 100 mg twice daily, for dose adjustments due to side-effects, consult product literature

- **VARGATEF®**
  - Treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy (in combination with docetaxel) (initiated under specialist supervision)
    - **BY MOUTH**
    - Adult: 200 mg twice daily on days 2–21 of a standard 21 day docetaxel cycle, for treatment following discontinuation of docetaxel and for dose adjustments due to side-effects, consult product literature

  - **IMPORTANT SAFETY INFORMATION FOR VARGATEF®—RISKS OF INCORRECT DOSING OF ORAL ANTICANCER MEDICINES**
    - See Cytotoxic drugs p. 797.

  - **CAUTIONS**
    - History of organ perforation - history or risk factors for QT prolongation - impaired wound healing - increased risk of bleeding - patients at high risk of cardiovascular disease - previous abdominal surgery - theoretical increased risk of gastrointestinal perforation - theoretical increased risk of venous thromboembolism

  - **INTERACTIONS**
    - **Common or very common** Abdominal pain - decreased appetite - diarrhoea - hyperbilirubinaemia - hypertension - nausea - raised hepatic enzymes - vomiting
    - **OFEV®**
      - Epistaxis - weight loss
    - **VARGATEF®**
      - Abductory - bleeding - dehydration - electrolyte imbalance - mucositis - neutropenia - peripheral neuropathy - venous thromboembolism
      - **Uncommon** Gastrointestinal perforation

  - **ALLERGY AND CROSS-SENSITIVITY**
    - Contra-indicated in patients with peanut or soya hypersensitivity.

  - **CONCEPTION AND CONTRACEPTION**
    - Manufacturer advises exclude pregnancy before treatment and ensure effective contraception (in addition to barrier method) during treatment and for at least 3 months after last dose.

  - **PREGNANCY**
    - Manufacturer advises avoid—toxicity in animal studies.

  - **VARGATEF®** See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

  - **BREAST FEEDING**
    - Manufacturer advises avoid—present in milk in animal studies.

  - **HEPATIC IMPAIRMENT**
    - Consult product literature for dose adjustment in worsening liver function. Manufacturer advises avoid in moderate to severe impairment—no information available.

  - **RENAI L IMPAI RMENT**
    - Manufacturer advises caution in severe impairment—no information available.

  - **MONITORING REQUIREMENTS**
    - For Vargatef®, monitor full blood count and hepatic function before each treatment cycle and regularly thereafter, monitor prothrombin time and INR if used concomitantly with anticoagulants and monitor for signs and symptoms of cerebral bleeding.

  - **PRESCRIBING AND DISPENSING INFORMATION**
    - VARGATEF® Not to be taken on the same day as docetaxel therapy.

  - **NATIONAL FUNDING/ACCESS DECISIONS**

    - **NICE technology appraisals (TAs)**
      - Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small cell lung cancer (July 2015) NICE TA347
      - Nintedanib (Vargatef®), in combination with docetaxel is recommended as an option for the treatment of patients...
with locally advanced, metastatic, or locally recurrent non-small cell lung cancer of adenocarcinoma histology, that has progressed after first-line chemotherapy, only if the manufacturer provides nintedanib with the discount agreed in the patient access scheme.

www.nice.org.uk/TA347
- Nintedanib for treating idiopathic pulmonary fibrosis (January 2016) NICE TA379
  - Nintedanib is recommended as an option for treating idiopathic pulmonary fibrosis, only if:
    - the patient has a forced vital capacity (FVC) between 50% and 80% of predicted,
    - the manufacturer provides nintedanib with the discount agreed in the patient access scheme, and,
    - treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period.

www.nice.org.uk/TA379
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (September 2015) that nintedanib (Ofev®) is accepted for restricted use within NHS Scotland for the treatment of idiopathic pulmonary fibrosis in patients with a predicted forced vital capacity less than or equal to 80%.

- MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
- CAUTIONARY AND ADVISORY LABELS 25 EXCIPIENTS: May contain Lecithin
- Ofev (Boehringer Ingelheim Ltd) ▼
  - Nintedanib (as Nintedanib esilate) 100 mg Ofev 100mg capsules |
    - 60 capsule (P) £2,151.10 (Hospital only)
  - Nintedanib (as Nintedanib esilate) 150 mg Ofev 150mg capsules |
    - 60 capsule (P) £2,151.10 (Hospital only)
- Vargatef (Boehringer Ingelheim Ltd) ▼
  - Nintedanib (as Nintedanib esilate) 100 mg Vargatef 100mg capsules |
    - 120 capsule (P) £2,151.10 (Hospital only)
  - Nintedanib (as Nintedanib esilate) 150 mg Vargatef 150mg capsules |
    - 60 capsule (P) £2,151.10 (Hospital only)

- ANTINEOPLASTIC DRUGS ► OTHER

Bortezomib

- INDIICATIONS AND DOSE
  Treatment of multiple myeloma that has progressed despite the use of at least one therapy, and where the patient has already had, or is unable to have, haematopoietic stem cell transplantation (either as monotherapy, or in combination with pegylated liposomal doxorubicin or dexamethasone) ▶ Treatment of previously untreated multiple myeloma in patients who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with melphalan and prednisolone) ▶ Induction treatment of previously untreated multiple myeloma in patients who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with dexamethasone, or with dexamethasone and thalidomide)
  - By INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
  - Adult: (consult local protocol)

- IMPORTANT SAFETY INFORMATION
  Bortezomib injection is for intravenous or subcutaneous administration only. Inadvertent intrathecal administration with fatal outcome has been reported.

- CONTRA-INDICATIONS
  Acute diffuse infiltrative pulmonary disease • pericardial disease

- CAUTIONS
  Amyloidosis • cardiovascular disease • consider antiviral prophylaxis for herpes zoster infection • dehydration • history of syncope • pulmonary disease (discontinue if interstitial lung disease develops) • risk factors for seizures • risk of neuropathy—consult product literature

- INTERACTIONS ▶ Appendix 1 (bortezomib).
  Caution with concurrent use of medication which may cause hypotension.

- SIDE-EFFECTS
  ◀ Common or very common Constipation (cases of ileus reported) • decreased appetite • diarrhoea • dyspnoea • fatigue • headache • herpes zoster • hypotension • myalgia • paraesthesia • peripheral neuropathy • pyrexia • rash • reactivation of herpes zoster • sensory neuropathy
  ◀ Uncommon Acute diffuse infiltrative pulmonary disorders • heart failure • posterior reversible encephalopathy syndrome (discontinue treatment) • pulmonary hypertension • seizures
  ◀ Rare Autonomic neuropathy
  ◀ Very rare Progressive multifocal leucoencephalopathy
  ◀ Frequency not known Alopecia • bone marrow suppression • extravasation • hyperuriaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting

SIDE-EFFECTS, FURTHER INFORMATION
For further information on side-effects, consult product literature.

- CONCEPTION AND CONTRACEPTION
  Manufacturer advises effective contraception during and for 3 months after treatment in men or women.

- PREGNANCY
  Toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 797.

- BREAST FEEDING
  Discontinue breast-feeding.

- HEPATIC IMPAIRMENT
  Reduce dose in moderate to severe impairment—consult product literature.

- RENAL IMPAIRMENT
  No information available for creatinine clearance less than 20 mL/minute/1.73 m².

- MONITORING REQUIREMENTS
  Monitor blood-glucose concentration in patients on oral antidiabetics.

  Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological signs or symptoms)—discontinue treatment if diagnosed.

  Chest x-ray recommended before treatment to monitor for pulmonary disease—discontinue if interstitial lung disease develops.

- NATIONAL FUNDING/ACCESS DECISIONS
  NICE technology appraisals (TAs)
  ◀ Bortezomib for previously untreated mantle cell lymphoma (December 2015) NICE TA370
  Bortezomib is recommended as an option for the treatment of previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable.
  www.nice.org.uk/TA370
  ◀ Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (April 2014) NICE TA311
  Bortezomib is recommended as an option within its marketing authorisation, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
  www.nice.org.uk/TA311

14-Apr-2016

BNF 73

Immune system and malignant disease
Bortezomib and thalidomide for the first-line treatment of multiple myeloma (July 2011) NICE TA228
Bortezomib in combination with an alkylating drug and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
- high-dose chemotherapy with stem cell transplantation is considered inappropriate and
- the person is unable to tolerate or has contra-indications to thalidomide.
www.nice.org.uk/TA228

Bortezomib monotherapy for relapsed multiple myeloma (October 2007) NICE TA129
Bortezomib monotherapy is an option for the treatment of progressive multiple myeloma in patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone-marrow transplantation, under the following circumstances:
- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in patients who have a reduction in serum M protein of 50% or more (where serum M protein is not measurable, an appropriate alternative biochemical measure of response should be used) and
- the manufacturer rebates the full cost of bortezomib if there is an inadequate response (as defined above) after four cycles of treatment.
www.nice.org.uk/TA129

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium, has advised (December 2013) that bortezomib (Velcade®) is accepted for restricted use within NHS Scotland in combination with dexamethasone and thalidomide for the induction treatment of adults with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
- Velcade® (Janssen-Cigli Ltd)
  Bortezomib 3.5 mg Velcade 3.5mg powder for solution for injection vials | 1 vial (60) £76.23 (Hospital only)

Olaparib
14-Dec-2016

DRUG ACTION
Olaparib is a PARP inhibitor. PARP are enzymes that repair damaged DNA in cancer cells and, in the absence of functional BRCA, inhibition of PARP results in an inability of cancer cells to repair. Therefore inhibition of PARP results in an antineoplastic effect.

INDICATIONS AND DOSE
Monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy (initiated under specialist supervision)
- BY MOUTH
  - Adults: 400 mg twice daily; reduced if not tolerated to 200 mg twice daily, then reduced if not tolerated to 100 mg twice daily, take at least 1 hour after food and avoid food for 2 hours after taking, patients should start treatment within 8 weeks of receiving the final dose of their platinum-containing chemotherapy regimen

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Avoid concomitant use, or reduce dose to 150 mg twice daily with concomitant use of potent or moderate CYP3A4 inhibitors (e.g. boceprevir, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, HIV-protease inhibitors boosted with cobicistat or ritonavir, itraconazole, telaprevir, or verapamil).

PHARMACOKINETICS
Peak plasma concentrations are typically achieved 1 to 3 hours after dosing; steady-state is achieved within 3 to 4 days.

INTERACTIONS
- Appendix 1 (olaparib).

SIDE-EFFECTS
- Common or very common: Anaemia, decreased appetite, diarrhoea, dizziness, dysgeusia, dyspepsia, fatigue, headache, lymphopenia, nausea, neutropenia, stomatitis, thrombocytopenia, upper abdominal pain, vomiting
- Frequency not known: Pneumonitis (occasionally fatal)

SIDE-EFFECTS, FURTHER INFORMATION
Haematological toxicity Withhold treatment if severe haematological toxicity develops; further analysis recommended if toxicity still present 4 weeks after treatment withdrawal.
- Pneumonitis: If dyspnoea, cough and fever, or radiological abnormalities develop, withhold treatment and investigate; if pneumonitis confirmed, discontinue.

CONCEPTION AND CONTRACEPTION
Manufacturer advises effective contraception during treatment and for 1 month after receiving the last dose. Consider an additional non-hormonal method of contraception.

PREGNANCY
Manufacturer advises avoid—xicity in animal studies.

BREAST FEEDING
Manufacturer advises avoid during treatment and for 1 month after last dose—no information available.

HEPATIC IMPAIRMENT
Manufacturer advises avoid—no information available.

RENAL IMPAIRMENT
Manufacturer advises avoid if creatinine clearance less than 50 mL/minute/1.73m² unless benefit outweighs potential risk—limited information available.

MONITORING REQUIREMENTS
Manufacturer advises monitor full blood count every month for the first 12 months of treatment and periodically thereafter.

PATIENT AND CARER ADVICE
Missed doses
If a dose is missed, the missed dose should not be taken and the next dose should be taken at the usual time.

Driving and skilled tasks
Malaise and dizziness may affect performance of skilled tasks e.g. driving or operating machinery.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (January 2016) NICE TA381
Olaparib is recommended as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy only if:
- they have had 3 or more courses of platinum-based chemotherapy and;
- the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.
www.nice.org.uk/guidance/ta381

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2015) that olaparib (Lynparza®) is not recommended for use within NHS Scotland as monotherapy for the maintenance...
treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  
  **Capsule**
  - Lynparza (AstraZeneca UK Ltd) ▼
  Olaparib 50 mg Lynparza 50mg capsules | 448 capsule £3,550.00

- **Vismodegib**
  - **DRUG ACTION**
    Vismodegib is a hedgehog pathway inhibitor.
  
  - **INDICATIONS AND DOSE**
    Symptomatic metastatic basal cell carcinoma | Locally advanced basal cell carcinoma not appropriate for surgery or radiotherapy
    - **BY MOUTH**
    - Adult: 150 mg once daily

- **SIDE-EFFECTS**
  - Common or very common
    Abdominal pain • abnormal hair growth • alopecia • amenorrhoea • arthralgia • constipation • decreased appetite • dehydration • diarrhoea • dyspepsia • hyponatraemia • malaise • muscle spasms • musculoskeletal pain • nausea • pruritus • rash • taste disturbances • vomiting • weight loss
  
  - Uncommon
    Abdominal pain • aphthous stomatitis • arthralgia • constipation • decreased appetite • diarrhoea • dyspepsia • fatigue • fever • headache • hypertension • increased intracranial pressure • increased intraocular pressure • alopecia • pruritus • rash • taste disturbances • vomiting • weight loss
  
  - Rare
    Abdominal pain • alopecia • constipation • decreased appetite • diarrhoea • dyspepsia • fatigue • fever • headache • hypertension • increased intracranial pressure • increased intraocular pressure • skin rash • taste disturbances • vomiting • weight loss

- **CONCEPTION AND CONTRACEPTION**
  For women of child-bearing potential, pregnancy must be excluded before initiation of treatment, and monthly during treatment. Women must use two contraceptive methods (including one highly effective method and one barrier method) during treatment and for 24 months after the final dose of vismodegib. Men must use a condom during treatment and for 2 months after the final dose.

- **PREGNANCY**
  Important: teratogenic risk — may cause severe birth defects and embryo–foetal death.

- **BREAST FEEDING**
  Avoid during treatment and for 24 months after final dose.

- **HEPATIC IMPAIRMENT**
  No information available — manufacturer advises caution in moderate to severe impairment.

- **RENAL IMPAIRMENT**
  No information available — manufacturer advises caution in severe impairment.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Prescribers and pharmacists must comply with prescribing and dispensing restrictions as specified in the manufacturer’s Pregnancy Prevention Programme, and ensure that the patient fully acknowledges the programme’s pregnancy prevention measures—consult product literature for further information.

- **PATIENT AND CARER ADVICE**
  Patient advice required around conception and contraception. Counselling on pregnancy and contraception advised. Patients must comply with the manufacturer’s pregnancy prevention programme.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  
  **Capsule**
  - CAUTIONARY AND ADVISORY LABELS
    - Erivedge (Roche Products Ltd) ▼
    - Vismodegib 150 mg Erivedge 150mg capsules | 28 capsule £6,285.00 (Hospital only)

- **ANTINEO VASCULARISATION DRUGS**
  VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

- **Aflibercept**
  - **DRUG ACTION**
    Aflibercept is a recombinant fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factors A and B (VEGF-A, VEGF-B) and placental growth factor (PIGF). Aflibercept inhibits the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

  - **INDICATIONS AND DOSE**
    In combination with irinotecan, fluorouracil and folinic acid (FOLFIRI) chemotherapy, in metastatic colorectal cancer that is resistant to, or has progressed after, an oxaliplatin-containing regimen
    - **BY INTRAVENOUS INFUSION**
    - Adult: (consult local protocol)

  - **CONTRA-INDICATIONS**
    Moderate or severe congestive heart failure • uncontrolled hypertension

  - **CAUTIONS**
    Febrile neutropenia • history of cardiovascular disease (may be exacerbated by hypertension) • increased risk of haemorrhage (including fatal events) • increased risk of hypertension • increased risk of thromboembolic events (consult product literature if event occurs) • may impair wound healing— withhold treatment for at least 4 weeks before elective surgery and for at least 4 weeks after major surgery, or until wound fully healed • neutropenic infection • risk of fistula formation (discontinue if fistula develops) • risk of neutropenia • risk of thrombocytopenia

  - **SIDE-EFFECTS**
    - Common or very common
      Abdominal pain • aphthous stomatitis • decreased appetite • dehydration • diarrhoea • dyspnoea • increased risk of thromboembolic events (consult product literature if event occurs) • may impair wound healing— withhold treatment for at least 4 weeks before elective surgery and for at least 4 weeks after major surgery, or until wound fully healed • neutropenic infection • risk of fistula formation (discontinue if fistula develops) • risk of neutropenia • risk of thrombocytopenia

- **CONCEPTION AND CONTRACEPTION**
  Exclude pregnancy before treatment. Effective contraception required during and for at least 6 months after treatment in men and women. Contraceptive advice should be given to men and women before therapy begins (and should cover the duration of contraception required after therapy has ended).

- **PREGNANCY**
  Manufacturer advises avoid—toxicity in animal studies. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.
● BREAST FEEDING  Manufacturer advises avoid—no information available.

● HEPATIC IMPAIRMENT  Caution in severe impairment—no information available.

● RENAL IMPAIRMENT  Caution in severe impairment—no information available.

● MONITORING REQUIREMENTS
  ▶ Monitor blood pressure at initiation and at least fortnightly during treatment (do not initiate treatment if pre-existing hypertension is uncontrolled)—consult product literature if hypertension develops during treatment.
  ▶ Monitor for signs of gastro-intestinal perforation (discontinue if perforation develops).
  ▶ Monitor full blood count, including differential count and platelets at baseline and before each treatment cycle.
  ▶ Monitor for proteinuria before each treatment administration (consult product literature if symptoms develop).
  ▶ Monitor for signs and symptoms of diarrhoea and dehydration, particularly in elderly—consult product literature if severe diarrhoea occurs.
  ▶ Monitor for posterior reversible encephalopathy syndrome (presenting as seizures, altered mental status, nausea, vomiting, headache, or visual disturbance).

● NATIONAL FUNDING/ACCESS DECISIONS
  ∨ Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (March 2014) NICE TA307
  Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.
  www.nice.org.uk/TA307

● MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Solution for infusion
  ∨ Zaltrap (Sanofi) ▼
    Aflibercept 25 mg per 1 ml Zaltrap 200mg/8ml concentrate for solution for infusion vials | 1 vial (£59.30) (Hospital only)
    Zaltrap 100mg/4ml concentrate for solution for infusion vials | 1 vial (£29.65) (Hospital only)
Chapter 9
Blood and nutrition

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Blood and blood-forming organs

1 Anaemias

Anaemias

Initiation of treatment
Before initiating treatment for anaemia it is essential to determine which type is present. Iron salts may be harmful and result in iron overload if given alone to patients with anaemias other than those due to iron deficiency.

Sickle-cell anaemia
Sickle-cell disease is caused by a structural abnormality of haemoglobin resulting in deformed, less flexible red blood cells. Acute complications in the more severe forms include sickle-cell crisis, where infarction of the microvasculature and blood supply to organs results in severe pain. Sickle-cell crisis requires hospitalisation, intravenous fluids, analgesia and treatment of any concurrent infection. Chronic complications include skin ulceration, renal failure, and increased susceptibility to infection. Pneumococcal vaccine, haemophilus influenzae type b vaccine, an annual influenza vaccine and prophylactic penicillin reduce the risk of infection. Hepatitis B vaccine should be considered if the patient is not immune.

In most forms of sickle-cell disease, varying degrees of haemolytic anaemia are present accompanied by increased erythropoiesis; this may increase folate requirements and folate supplementation may be necessary.

Hydroxycarbamide p. 833 can reduce the frequency of crises and the need for blood transfusions in sickle-cell disease. The beneficial effects of hydroxycarbamide may not become evident for several months.

G6PD deficiency
Glucose 6-phosphate dehydrogenase (G6PD) deficiency is highly prevalent in individuals originating from most parts of Africa, from most parts of Asia, from Oceania, and from Southern Europe; it can also occur, rarely, in any other individuals. G6PD deficiency is more common in males than in females.

Individuals with G6PD deficiency are susceptible to developing acute haemolytic anaemia when they take a number of common drugs. They are also susceptible to developing acute haemolytic anaemia when they eat fava beans (broad beans, Vicia faba); this is termed favism and can be more severe in children or when the fresh fava beans are eaten raw.

When prescribing drugs for patients with G6PD deficiency, the following three points should be kept in mind:

- G6PD deficiency is genetically heterogeneous;
- susceptibility to the haemolytic risk from drugs varies;
thus, a drug found to be safe in some G6PD-deficient individuals may not be equally safe in others;
• manufacturers do not routinely test drugs for their effects in G6PD-deficient individuals;
• the risk and severity of haemolysis is almost always dose-related.

The lists below should be read with these points in mind. Ideally, information about G6PD deficiency should be available before prescribing a drug listed below. However, in the absence of this information, the possibility of haemolysis should be considered, especially if the patient belongs to a group in which G6PD deficiency is common.

A very few G6PD-deficient individuals with chronic non-spherocytic haemolytic anaemia have haemolysis even in the absence of an exogenous trigger. These patients must be regarded as being at high risk of severe exacerbation of haemolysis following administration of any of the drugs listed below.

**Drugs with definite risk of haemolysis in most G6PD-deficient individuals**

- Dapsone and other sulfones (higher doses for dermatitis herpetiformis more likely to cause problems)
- Methylthioninium chloride
- Niridazole [not on UK market]
- Nitrofurantoin
- Pamaquin [not on UK market]
- Primaquine (30 mg weekly for 8 weeks has been found to be without undue harmful effects in African and Asian people)
- Quinolones (including ciprofloxacin, moxifloxacin, nalidixic acid, norfloxacin, and ofloxacin)
- Rashburicase
- Sulfonamides (including co-trimoxazole; some sulfonamides, e.g. sulfadiazine, have been tested and found not to be haemolytic in many G6PD-deficient individuals)

**Drugs with possible risk of haemolysis in some G6PD-deficient individuals**

- Aspirin (acceptable up to a dose of at least 1 g daily in most G6PD-deficient individuals)
- Chloroquine (acceptable in acute malaria and malaria chemoprophylaxis)
- Menadione, water-soluble derivatives (e.g. menadiol sodium phosphate)
- Quinidine (acceptable in acute malaria) [not on UK market]
- Quinine (acceptable in acute malaria)
- Sulfonylureas

Naphthalene in mothballs also causes haemolysis in individuals with G6PD deficiency.

**Drugs used in hypoplastic, haemolytic, and renal anaemias**

Anabolic steroids, pyridoxine hydrochloride p. 950, antilymphocyte immunoglobulin, and various corticosteroids are used in hypoplastic and haemolytic anaemias.

**Antilymphocyte immunoglobulin** given intravenously through a central line over 12–18 hours each day for 5 days produces a response in about 50% of cases of acquired aplastic anaemia; the response rate may be increased when ciclosporin p. 766 is given as well. Severe reactions are common in the first 2 days and profound immunosuppression can occur; antilymphocyte immunoglobulin should be given under specialist supervision with appropriate resuscitation facilities. Alternatively, oxymetholone tablets (available from ‘special order’ manufacturers or specialist importing companies) can be used in aplastic anaemia for 3 to 6 months.

It is unlikely that dietary deprivation of pyridoxine hydrochloride produces clinically relevant haematological effects. However, certain forms of sideroblastic anaemia respond to pharmacological doses, possibly reflecting its role as a co-enzyme during haemoglobin synthesis. Pyridoxine hydrochloride is indicated in both idiopathic acquired and hereditary sideroblastic anaemias. Although complete cures have not been reported, some increase in haemoglobin can occur; the dose required is usually high. Reversible sideroblastic anaemias respond to treatment of the underlying cause but in pregnancy, haemolytic anaemias, and alcohol dependence, or during isoniazid p. 541 treatment, pyridoxine hydrochloride is also indicated.

**Corticosteroids** have an important place in the management of haematological disorders. They include conditions with an autoimmune haemolytic anaemia, immune thrombocytopenias and neutropenias, and major transfusion reactions. They are also used in chemotherapy schedules for many types of lymphoma, lymphoid leukemias, and paraproteinaemias, including multiple myeloma.

**Erythropoietins**

Epoetins (recombinant human erythropoietins) are used to treat the anaemia associated with erythropoietin deficiency in chronic renal failure, to increase the yield of autologous blood in normal individuals and to shorten the period of symptomatic anaemia in patients receiving cytotoxic chemotherapy.

Epoetin beta p. 889 is also used for the prevention of anaemia in preterm neonates of low birth-weight: only unpreserved formulations should be used in neonates because other preparations may contain benzyl alcohol. Darbepoetin alfa p. 886 is a hyperglycosylated derivative of epoetin; it has a longer half life and can be administered less frequently than epoetin.

Methoxy polyethylene glycol-epoetin beta p. 891 is a continuous erythropoietin receptor activator that is licensed for the treatment of symptomatic anaemia associated with chronic kidney disease. It has a longer duration of action than epoetin.

### 1.1 Hypoplastic, haemolytic, and renal anaemias

**ANABOLIC STEROIDS › ANDROSTAN DERIVATIVES**

**Oxymetholone**

- **INDICATIONS AND DOSE**
  - Aplastic anaemia
    - BY MOUTH
    - Adult: 1–5 mg/kg daily for 3 to 6 months
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
    - Capsule
      - Oxymetholone (Non-proprietary)
        - Oxymetholone 50 mg (Oxymetholone 50mg capsules) 50 capsule
          - PoM: £75.00 [CD4-2]

**EPOETINS**

Epoetins

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (DECEMBER 2007) ERYTHROPOIETINS—HAEMOGLOBIN CONCENTRATION

Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of death and serious cardiovascular events, and in
patients with cancer may increase the risk of thrombosis and related complications:

- patients should not be treated with erythropoietins for the licensed indications in chronic kidney disease or cancer in patients receiving chemotherapy unless symptoms of anaemia are present
- the haemoglobin concentration should be maintained within the range 10–12 g/100 mL
- haemoglobin concentrations higher than 12 g/100 mL should be avoided
- the aim of treatment is to relieve symptoms of anaemia, and in patients with chronic kidney disease to avoid the need for blood transfusion; the haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia (in some patients, this may be achieved at concentrations lower than the recommended range)

MHRA/CHM ADVICE (DECEMBER 2007 AND JULY 2008) ERYTHROPOIETINS—TUMOUR PROGRESSION AND SURVIVAL IN PATIENTS WITH CANCER

Clinical trial data show an unexplained excess mortality and increased risk of tumour progression in patients with anaemia associated with cancer who have been treated with erythropoietins. Many of these trials used erythropoietins outside of the licensed indications (i.e. overcorrected haemoglobin concentration or given to patients who have not received chemotherapy):

- erythropoietins licensed for the treatment of symptomatic anaemia associated with cancer, are licensed only for patients who are receiving chemotherapy
- the decision to use erythropoietins should be based on an assessment of the benefits and risks for individual patients; blood transfusion may be the preferred treatment for anaemia associated with cancer chemotherapy, particularly in those with a good cancer prognosis

CONTRA-INDICATIONS

- Patients unable to receive thromboprophylaxis - pure red cell aplasia following erythropoietin therapy - uncontrolled hypertension

CAUTIONS

- Aluminium toxicity (can impair the response to erythropoietin) - concurrent infection (can impair the response to erythropoietin) - correct factors that contribute to the anaemia of chronic renal failure, such as iron or folate deficiency, before treatment - during dialysis (increase in unfractionated or low molecular weight heparin dose may be needed) - epilepsy - inadequately treated or poorly controlled blood pressure—interrupt treatment if blood pressure uncontrolled - ischaemic vascular disease - malignant disease - other inflammatory disease (can impair the response to erythropoietin) - risk of thrombosis may be increased when used for anaemia before orthopaedic surgery—avoid in cardiovascular disease including recent myocardial infarction or cerebrovascular accident - risk of thrombosis may be increased when used for anaemia in adults receiving cancer chemotherapy - sickle-cell disease (lower target haemoglobin concentration may be appropriate) - sudden stabbing migraine-like pain (warning of a hypertensive crisis) - thrombocytosis (monitor platelet count for first 8 weeks)

SIDE-EFFECTS

- Common or very common Aggravation of hypertension (dose-dependent) - cardiovascular events - diarrhoea - dose-dependent increase in platelet count regressing during treatment (but thrombocytosis rare) - headache - hypertensive crisis (in isolated patients with normal or low blood pressure) - increase in blood pressure (dose-dependent) - influenza-like symptoms (may be reduced if intravenous injection given over 5 minutes) - nausea - shunt thrombosis especially if tendency to hypotension or arteriovenous shunt complications - vomiting

- Very rare Sudden loss of efficacy because of pure red cell aplasia, particularly following subcutaneous administration in patients with chronic renal failure

- Frequency not known Anaphylaxis - angioedema - hyperkalaemia - hypersensitivity reactions - injection-site reactions - peripheral oedema - skin reactions

SIDING EFFECTS, FURTHER INFORMATION

- Hypertensive crisis - In isolated patients with normal or low blood pressure, hypertensive crisis with encephalopathy-like symptoms and generalised tonic-clonic seizures requiring immediate medical attention has occurred with epoetin.

- Pure red cell aplasia - There have been very rare reports of pure red cell aplasia in patients treated with erythropoietins. In patients who develop a lack of efficacy with erythropoietin therapy and with a diagnosis of pure red cell aplasia, treatment with erythropoietins must be discontinued and testing for erythropoietin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another form of erythropoietin.

MONITORING REQUIREMENTS

- Monitor closely blood pressure, reticulocyte counts, haemoglobin, and electrolytes—interrupt treatment if blood pressure uncontrolled.

- Other factors, such as iron or folate deficiency, that contribute to the anaemia of chronic renal failure should be corrected before treatment and monitored during therapy. Supplemental iron may improve the response in resistant patients.

Darbepoetin alfa

INDICATIONS AND DOSE

Symptomatic anaemia associated with chronic renal failure in patients on dialysis

- BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INJECTION

- Adult: Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 2 weeks, maintenance dose to be given once weekly or once every 2 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL, reduce dose to be adjusted according to response by approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

Symptomatic anaemia associated with chronic renal failure in patients not on dialysis

- BY SUBCUTANEOUS INJECTION

- Adult: Initially 450 nanograms/kg once weekly, alternatively initially 750 nanograms/kg every 2 weeks, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose can be given once weekly, every 2 weeks, or once a month, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL, reduce dose, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment
changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

Symptomatic anaemia associated with chronic renal failure in patients not on dialysis

- **BY INTRAVENOUS INJECTION**
- **Adult:** Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose given once weekly, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** Initially 6.75 micrograms/kg every 3 weeks, alternatively initially 2.25 micrograms/kg once weekly, if response inadequate after 9 weeks further treatment may not be effective; if adequate response obtained then reduce dose by 25–50%, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

- **SIDE-EFFECTS** Injection-site pain • oedema
- **PREGNANCY** No evidence of harm in animal studies—manufacturer advises caution.
- **BREAST FEEDING** No information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid—no information available.
- **NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used. www.nice.org.uk/TA323

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- **Aranesp**
  - **Darbepoetin alfa 25 microgram per 1 ml** Aranesp
    - 10micrograms/0.4ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £99.65
  - **Darbepoetin alfa 100 microgram per 1 ml** Aranesp
    - 50micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £125.40
  - **Aranesp SureClick**
    - 25 micrograms/kg once weekly, dose adjusted in steps of 25 units/kg 3 times a week, dose adjusted according to response at intervals of at least 4 weeks; maintenance 25–100 units/kg 3 times a week, intravenous injection to be given over 1–5 minutes, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia associated with chronic renal failure in patients on peritoneal dialysis

- **BY INTRAVENOUS INJECTION**
- **Adult:** Initially 50 units/kg twice weekly; maintenance 25–50 units/kg weekly, intravenous injection to be given over 1–5 minutes, reduce dose by continued →

Epoeitin alfa

- **INDICATIONS AND DOSE**

**BINOCRIT® PRE-FILLED SYRINGES**

Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

- **BY INTRAVENOUS INJECTION**
- **Adult:** Initially 50 units/kg 3 times a week, dose adjusted according to response at intervals of at least 4 weeks; maintenance 25–100 units/kg 3 times a week, intravenous injection to be given over 1–5 minutes, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

- **BY INTRAVENOUS INJECTION**
- **Adult:** Initially 50 units/kg twice weekly; maintenance 25–50 units/kg weekly, intravenous injection to be given over 1–5 minutes, reduce dose by continued →
Blood and nutrition

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888 ANAEMIAS

Moderate anaemia (haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

- BY INTRAVENOUS INJECTION
  - Adult: Initially 50 units/kg 3 times a week, increased in steps of 25 units/kg 3 times a week, adjusted according to response, dose to be increased at intervals of at least 4 weeks; maintenance 75–300 units/kg once weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 mL per injection site, maintenance dose can be given as a single dose or in divided doses, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia in adults receiving cancer chemotherapy

- BY SUBCUTANEOUS INJECTION
  - Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, subcutaneous injection maximum 1 mL per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

To increase yield of autologous blood (to avoid homologous blood in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery

- BY INTRAVENOUS INJECTION
  - Adult: 600 units/kg twice weekly for 3 weeks before surgery, consult product literature for details and advice on ensuring high iron stores, intravenous injection to be given over 1–5 minutes

Moderate anaemia (haemoglobin concentration 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

- BY SUBCUTANEOUS INJECTION
  - Adult: 600 units/kg once weekly for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, consult product literature for details, subcutaneous injection maximum 1 mL per injection site

Eprex® pre-filled syringes

Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
  - Adult: Initially 50 units/kg 3 times a week, adjusted in steps of 25 units/kg 3 times a week, dose adjusted according to response at intervals of at least 4 weeks; maintenance 75–300 units/kg once weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 mL per injection site, maintenance dose can be given as a single dose or in divided doses, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
  - Adult: Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 mL per injection site, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
  - Adult: Initially 50 units/kg 3 times a week, increased in steps of 25 units/kg 3 times a week, adjusted according to response, dose to be increased at intervals of at least 4 weeks; maintenance 17–33 units/kg 3 times a week (max. per dose 200 units/kg 3 times a week), intravenous injection to be given over 1–5 minutes, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia in adults receiving cancer chemotherapy

- BY SUBCUTANEOUS INJECTION
  - Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, subcutaneous injection maximum 1 mL per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Discontinue approximately 4 weeks after ending chemotherapy

Subcutaneous injection maximum 1 mL before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

- BY SUBCUTANEOUS INJECTION
  - Adult: 600 units/kg once weekly for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, consult product literature for details, subcutaneous injection maximum 1 mL per injection site

Initial injection to be given over 5 minutes, subcutaneous injection maximum 1 mL before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

- BY SUBCUTANEOUS INJECTION
  - Adult: 600 units/kg once weekly for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, consult product literature for details, subcutaneous injection maximum 1 mL per injection site

BNF 73
To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery

▷ BY INTRAVENOUS INJECTION
▷ Adult: 600 units/kg twice weekly for 3 weeks before surgery, consult product literature for details and advice on ensuring high iron stores, intravenous injection to be given over 1–5 minutes

Moderate anaemia (haemoglobin concentration 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

▷ BY SUBCUTANEOUS INJECTION
▷ Adult: 600 units/kg once weekly for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, consult product literature for details, subcutaneous injection maximum 1 mL per injection site

- BREAST FEEDING Unlikely to be present in milk. Minimal effect on infant.
- HEPATIC IMPAIRMENT Manufacturers advise caution in chronic hepatic failure.
- PRESCRIBING AND DISPENSING INFORMATION Epoetin alfa is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

NICE funding/access decisions

▷ Erythropoiesis-stimulating agents (epoetin and darbepoetin for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

www.nice.org.uk/TA323

- MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

▷ Eprex (Janssen-Cilag Ltd)
Epoetin alfa 2000 unit per 1 ml Eprex 1.0000units/0.5ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £33.18
Epoetin alfa 4000 unit per 1 ml Eprex 2.0000units/0.5ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £66.37
Epoetin alfa 10000 unit per 1 ml Eprex 6.0000units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £199.11
Eprex 4.0000units/0.4ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £132.74
Eprex 5.0000units/0.5ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £185.92
Eprex 3.0000units/0.2ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £99.55
Eprex 10.0000units/1ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £331.85
Eprex 8.0000units/0.8ml solution for injection pre-filled syringes | 6 pre-filled disposable injection £265.48

Epoetin beta

- INDICATIONS AND DOSE
Symptomatic anaemia associated with chronic renal failure

▷ BY SUBCUTANEOUS INJECTION
▷ Adult: Initially 20 units/kg 3 times a week for 4 weeks, increased in steps of 20 units/kg 3 times a week, according to response at intervals of 4 weeks, total weekly dose may be divided into daily doses; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks, total weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses. Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose; maximum 720 units/kg per week

▷ BY INTRAVENOUS INJECTION
▷ Adult: Initially 40 units/kg 3 times a week for 4 weeks, then increased to 80 units/kg 3 times a week, then increased in steps of 20 units/kg 3 times a week if required, at intervals of 4 weeks; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks. Intravenous injection to be administered over 2 minutes. Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose; maximum 720 units/kg per week

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy

▷ BY SUBCUTANEOUS INJECTION
▷ Adult: Initially 450 units/kg once weekly for 4 weeks, dose to be given weekly as a single dose or in 3–7 divided doses, increase dose after 4 weeks (if a rise in haemoglobin of at least 1 g/100 mL not achieved), increased to 900 units/kg once weekly, dose to be given weekly as a single dose or in 3–7 divided doses, if adequate response obtained reduce dose by 25–50%, discontinue treatment if haemoglobin concentration does not increase by at least 1 g/100 mL after 8 weeks of therapy (response unlikely). Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy; maximum 60 000 units per week continued
To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia when blood-conserving procedures are insufficient or unavailable

- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
- Adult: (consult product literature)

- BREAST FEEDING Unlikely to be present in milk. Minimal effect on infant.
- HEPATIC IMPAIRMENT Manufacturers advise caution in chronic hepatic failure.

- NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323
Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

www.nice.org.uk/TA323

- MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
EXCIPIENTS: May contain Phenylalanine

- NEOrecombinant heterogenous blood (to avoid homologous blood) in predonation programme in moderate anaemia when blood-conserving procedures are insufficient or unavailable

1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis
- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
- Adult: Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis
- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
- Adult: Initially 50 units/kg 3 times a week, adjusted according to response, adjusted in steps of 25 units/kg 4 times a week, dose to be increased at intervals of at least 4 weeks; maintenance 17–33 units/kg 3 times a week (max. per dose 200 units/kg 3 times a week), intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Symptomatic anaemia in adults receiving cancer chemotherapy
- BY SUBCUTANEOUS INJECTION
- Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, only increase dose if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, maximum 1 mL per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery
- BY INTRAVENOUS INJECTION
- Adult: 600 units/kg twice weekly for 3 weeks before surgery, intravenous injection to be given over 1–5 minutes, consult product literature for details

Moderate anaemia (haemoglobin concentration 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable
- BY SUBCUTANEOUS INJECTION
- Adult: 600 units/kg every week for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, maximum 1 mL per injection site, consult product literature for details


Epoetin zeta

- INDICATIONS AND DOSE
Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis
- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
- Adult: Initially 50 units/kg 3 times a week, adjusted according to response, adjusted in steps of 25 units/kg 3 times a week, dose to be adjusted at intervals of at least 4 weeks; maintenance 25–100 units/kg 3 times a week, intravenous injection to be given over

- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION
- Adult: (consult product literature)
Haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

**Symptomatic anaemia associated with chronic kidney disease in patients not on dialysis and not currently treated with erythropoietins**

- **Initially by subcutaneous injection**
- **Adult:** Initially 1.2 micrograms/kg every 4 weeks, alternatively (by subcutaneous injection or by intravenous injection) initially 600 nanograms/kg every 2 weeks, dose to be adjusted according to response at intervals of at least 4 weeks; patients treated once every 2 weeks may be given a maintenance dose of double the previous fortnightly dose every 4 weeks, subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks; or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

**Symptomatic anaemia associated with chronic kidney disease in patients currently treated with erythropoietins**

- **By subcutaneous injection, or by intravenous injection**
- **Adult:** (consult product literature)

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**Excipients:** May contain Phenylalanine

- **Retacrit (Pfizer Ltd)**
  - Epoetin zeta 3333 unit per 1 ml Retacrit 2,000 units/0.6 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 57.70 (Hospital only)
  - Retacrit 3,000 units/0.9 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 68.55 (Hospital only)
  - Retacrit 1,000 units/0.3 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 28.85 (Hospital only)

- **Epoetin zeta 10,000 unit per 1 ml** Retacrit 6,000 units/0.6 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 173.09 (Hospital only)
  - Retacrit 10,000 units/1 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 288.48 (Hospital only)
  - Retacrit 8,000 units/0.8 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 230.79 (Hospital only)
  - Retacrit 4,000 units/0.4 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (£) 115.40 (Hospital only)

- **Epoetin zeta 40,000 unit per 1 ml** Retacrit 20,000 units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 96.16 (Hospital only)
  - Retacrit 40,000 units/1 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 193.32 (Hospital only)
  - Retacrit 30,000 units/0.75 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 144.25 (Hospital only)

**Methoxy polyethylene glycol-epoetin beta**

**Indications and Dose**

Symptomatic anaemia associated with chronic kidney disease in patients on dialysis and not currently treated with erythropoietins

- **By subcutaneous injection, or by intravenous injection**
- **Adult:** Initially 600 nanograms/kg every 2 weeks, dose to be adjusted according to response at intervals of at least 4 weeks, maintenance dose of double the previous fortnightly dose may be given every 4 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks; or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

**Side-effects**

- **Hotflushes**
- **Pregnancy** No evidence of harm in animal studies—manufacturer advises caution.
- **Breast feeding** Manufacturer advises use only if potential benefit outweights risk—present in milk in animal studies.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Mircera (Roche Products Ltd)**
  - Methoxy polyethylene glycol-epoetin beta 100 microgram per 1 ml Mircera 30 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 144.05
  - Methoxy polyethylene glycol-epoetin beta 166.67 microgram per 1 ml Mircera 50 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 173.41
  - Methoxy polyethylene glycol-epoetin beta 250 microgram per 1 ml Mircera 75 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 110.11
  - Methoxy polyethylene glycol-epoetin beta 333.33 microgram per 1 ml Mircera 100 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 146.81
  - Methoxy polyethylene glycol-epoetin beta 400 microgram per 1 ml Mircera 120 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 176.18
  - Methoxy polyethylene glycol-epoetin beta 500 microgram per 1 ml Mircera 150 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 220.22
  - Methoxy polyethylene glycol-epoetin beta 600 microgram per 1 ml Mircera 360 micrograms/0.6 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 528.56
  - Methoxy polyethylene glycol-epoetin beta 666.67 microgram per 1 ml Mircera 200 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 293.62
  - Methoxy polyethylene glycol-epoetin beta 833.33 microgram per 1 ml Mircera 250 micrograms/0.3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£) 367.03
1.1a Atypical haemolytic uraemic syndrome and paroxysmal nocturnal haemoglobinuria

**IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES**

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- **BREAST FEEDING** No information available—manufacturer advises avoid breast-feeding during and for 5 months after treatment.
- **MONITORING REQUIREMENTS** Monitor for 1 hour after infusion.
  - For paroxysmal nocturnal haemoglobinuria, monitor for intravascular haemolysis (including serum-lactate dehydrogenase concentration) during treatment and for at least 8 weeks after discontinuation.
  - For atypical haemolytic uraemic syndrome, monitor for thrombotic microangiopathy (measure platelet count, serum–lactate dehydrogenase concentration, and serum creatinine) during treatment and for at least 12 weeks after discontinuation.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Soliris®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Dilute requisite dose to a concentration of 5 mg/mL and mix gently; give over 25–45 minutes (infusion time may be increased to 2 hours if infusion-related reactions occur). Consult product literature for details of supplemental doses with concomitant plasmapheresis, plasma exchange, or plasma infusion.
- **PATIENT AND CARER ADVICE** A patient information card should be provided. Patient or carers should be advised to report promptly any signs of meningococcal infection.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium

- **Soliris** (Alexion Pharma UK Ltd)
  - Eculizumab 10 mg per 1 ml
  - Soliris 300mg/30ml concentrate for solution for infusion vials | 1 vial | £3,150.00 (Hospital only)

### 1.2 Iron deficiency anaemia

**Anaemia, iron deficiency**

**Treatment and prophylaxis**

_Treatment_ with an iron preparation is justified only in the presence of a demonstrable iron-deficiency state. Before starting treatment, it is important to exclude any serious underlying cause of the anaemia (e.g. gastric erosion, gastrointestinal cancer).

_Prophylaxis_ with an iron preparation may be appropriate in malabsorption, menorrhagia, pregnancy, after subtotal or total gastrectomy, in haemodialysis patients, and in the management of low birth-weight infants such as preterm neonates.

**Oral iron**

Iron salts should be given by mouth unless there are good reasons for using another route.

Ferrous salts show only marginal differences between one another in efficiency of absorption of iron. Haemoglobin regeneration rate is little affected by the type of salt used provided sufficient iron is given, and in most patients the speed of response is not critical. Choice of preparation is thus usually decided by the incidence of side-effects and cost.

The oral dose of elemental iron for iron-deficiency anaemia should be 100 to 200 mg daily. It is customary to give this as dried ferrous sulfate; for prophylaxis of iron-deficiency anaemia, ferrous sulfate may be effective.
Iron content of different iron salts

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<th>Iron salt/amount</th>
<th>Content of ferrous iron</th>
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<tr>
<td>ferrous fumarate</td>
<td>200 mg</td>
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<td></td>
<td>65 mg</td>
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<td>ferrous gluconate</td>
<td>300 mg</td>
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<td></td>
<td>35 mg</td>
</tr>
<tr>
<td>ferrous sulfate</td>
<td>300 mg</td>
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<tr>
<td></td>
<td>60 mg</td>
</tr>
<tr>
<td>ferrous sulfate, dried</td>
<td>200 mg</td>
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<td>65 mg</td>
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**Compound preparations**

Preparations containing iron and folic acid p. 898 are used during pregnancy in women who are at high risk of developing iron and folic acid deficiency; they should be distinguished from those used for the prevention of neural tube defects in women planning a pregnancy.

It is important to note that the small doses of folic acid contained in these preparations are inadequate for the treatment of megaloblastic anemia.

Some oral preparations contain ascorbic acid p. 952 to aid absorption of the iron but the therapeutic advantage of such preparations is minimal and cost may be increased.

There is no justification for the inclusion of other ingredients, such as the B group of vitamins (except folic acid for pregnant women).

**Modified-release preparations**

Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is released past the first part of the duodenum into an area of the gut where absorption may be poor.

Parenteral iron

Iron can be administered parenterally as iron dextran p. 894, ferric carboxymaltose, below, or iron isomaltoside 1000 p. 894. Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss, or in malabsorption. Parenteral iron may also have a role in the management of chemotherapy-induced anaemia, when given with erythropoietins, in specific patient groups (see NICE guidance).

Many patients with chronic renal failure who are receiving haemodialysis (and some who are receiving peritoneal dialysis) also require iron by the intravenous route on a regular basis.

With the exception of patients with severe renal failure receiving haemodialysis, parenteral iron does not produce a faster haemoglobin response than oral iron provided that the oral iron preparation is taken reliably and is absorbed adequately. If parenteral iron is necessary, the dose should be calculated according to the patient’s body-weight and total iron deficit. Depending on the preparation used, parenteral iron is given as a total dose or in divided doses. Further treatment should be guided by monitoring haemoglobin and serum iron concentrations.

**MINERALS AND TRACE ELEMENTS**

**Iron (injectable)**

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: SERIOUS HYPERSENSITIVITY REACTIONS WITH INTRAVENOUS IRON (AUGUST 2013)

Serious hypersensitivity reactions, including life-threatening and fatal anaphylactic reactions, have been reported in patients receiving intravenous iron. These reactions can occur even when a previous administration has been tolerated (including a negative test dose). Test doses are no longer recommended and caution is needed with every dose of intravenous iron.

Intravenous iron products should only be administered when appropriately trained staff and resuscitation facilities are immediately available; patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated.

The risk of hypersensitivity is increased in patients with known allergies, immune or inflammatory conditions, or those with a history of severe asthma, eczema, or other atopic allergy; in these patients intravenous iron should only be used if the benefits outweigh the risks.

Intravenous iron should be avoided in the first trimester of pregnancy and used in the second or third trimesters only if the benefit outweighs the potential risks for both mother and fetus.

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<tr>
<td>Anaphylactic reactions Anaphylactic reactions can occur with parenteral administration of iron complexes and facilities for cardiopulmonary resuscitation must be available.</td>
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<tr>
<td>Overdose</td>
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<tr>
<td>For details on the management of poisoning, see iron salts, under Emergency treatment of poisoning p. 1204.</td>
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**Ferric carboxymaltose**

**INDICATIONS AND DOSE**

**Iron-deficiency anaemia**

- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- Adult: Dose calculated according to body-weight and iron deficit (consult product literature)

**CAUTIONS**

- Allergic disorders - asthma, eczema, hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available; infection (discontinue if ongoing bacteraemia); oral iron should not be given until 5 days after last injection

**SIDE-EFFECTS**

- **Common or very common** Dizziness - gastro-intestinal disturbances - headache - injection-site reactions - rash
- **Uncommon** Anaphylaxis - arthralgia - back pain - chest pain - fatigue - flushing - hypertension - hypotension - malaise - myalgia - paraesthesia - peripheral oedema - pruritus - pyrexia - rigors - urticaria
- **Rare** Dyspnoea

**PREGNANCY** Avoid in first trimester; crosses the placenta in animal studies. May influence skeletal development.

**HEPATIC IMPAIRMENT** Use with caution. Avoid in conditions where iron overload increases risk of impairment.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Ferinject®), give intermittently in Sodium chloride 0.9%, dilute 200–500 mg in up to 100 mL infusion fluid and give over at least 6 minutes; dilute 0.5–1 g in up to 250 mL infusion fluid and give over at least 15 minutes.

**PRESCRIBING AND DISPENSING INFORMATION** A ferric carboxymaltose complex containing 5% (50 mg/mL) of iron.
Iron dextran

**INDICATIONS AND DOSE**

**Iron-deficiency anaemia**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: Intramuscular injection to be administered into the gluteal muscle, doses calculated according to body-weight and iron deficit (consult product literature)
- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Doses calculated according to body-weight and iron deficit (consult product literature)

**CONTRA-INDICATIONS** Active rheumatoid arthritis - asthma - eczema - history of allergic disorders - infection

**CAUTIONS** Hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available - oral iron should not be given until 5 days after last injection

**SIDE-EFFECTS**
- **Uncommon** Abdominal pain - anaphylaxis - blurred vision - cramps - dyspnoea - flushing - nausea - numbness - pruritus - rash - vomiting
- **Rare** Angioedema - arrhythmias - arthralgia - chest pain - diarrhea - dizziness - fatigue - hypotension - impaired consciousness - injection-site reactions - myalgia - restlessness - seizures - sweating - tachycardia - tremor
- **Very rare** Haemolysis - headache - hypertension - palpitation - paraesthesia - transient deafness

**PREGNANCY** Avoid in first trimester.

**HEPATIC IMPAIRMENT** Avoid in compensated liver disease and hepatitis.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Monofer®), give intermittently in Sodium chloride 0.9%. For details consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION** A complex of ferric iron and isomaltosides containing 10% (100 mg/mL) of iron.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **CosmoFer** (Pharmacosmos UK Ltd) ▼
  - **Iron (as Iron dextran) 50 mg per 1 ml** CosmoFer 500mg/10ml solution for injection ampoules | 2 ampoule | £33.70
  - CosmoFer 100mg/2ml solution for injection ampoules | 5 ampoule | £59.85
Iron deficiency anaemia 895

**SIDE-EFFECTS**
- **Common or very common** Taste disturbances
- **Uncommon** Abdominal pain; bronchospasm; chest pain; diarrhoea; dizziness; dyspnoea; fever; flushing; headache; hypotension; injection-site reactions; myalgia; nausea; palpitation; pruritus; rash; tachycardia; vomiting
- **Rare** Anaphylaxis; asthma; fatigue; hypertension; paraesthesia; peripheral oedema
- **Frequency not known** Arthralgia; bradycardia; confusion; increased sweating
- **PREGNANCY** Avoid in first trimester.
- **HEPATIC IMPAIRMENT** Use with caution. Avoid in conditions where iron overload increases risk of impairment.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Venofer®), give intermittently in Sodium chloride 0.9%, dilute 100 mg in up to 100 mL infusion fluid; give 25 mg over 15 minutes initially, then give at a rate not exceeding 3.33 mg/minute.

**PRESCRIBING AND DISPENSING INFORMATION** A complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron.

**MINERALS AND TRACE ELEMENTS**  
**IRON, ORAL**

**SIDE-EFFECTS**
- Constipation
- Diarrhoea
- Epigastric pain
- Gastritis
- Headache
- Rash
- Vomiting

**Ferrous fumarate**

**INDICATIONS AND DOSE**
- **Iron-deficiency anaemia (prophylactic)**
  - **BY MOUTH USING TABLETS**
    - Child 1–12 years: 210 mg 1–2 times a day
    - Adult: 210 mg 1–2 times a day
  - **BY MOUTH USING SYRUP**
    - Child 12–17 years: 140 mg twice daily
    - Adult: 140 mg twice daily
- **Iron-deficiency anaemia (therapeutic)**
  - **BY MOUTH USING TABLETS**
    - Child 12–17 years: 210 mg 2–3 times a day
    - Adult: 210 mg 2–3 times a day
  - **BY MOUTH USING SYRUP**
    - Child 12–17 years: 280 mg twice daily
    - Adult: 280 mg twice daily
- **GALFER® CAPSULES**
  - **Iron-deficiency anaemia (prophylactic)**
    - **BY MOUTH**
      - Child 12–17 years: 305 mg daily
      - Adult: 305 mg daily
  - **Iron-deficiency anaemia (therapeutic)**
    - **BY MOUTH**
      - Child 12–17 years: 305 mg twice daily
      - Adult: 305 mg twice daily
- **GALFER® SYRUP**
  - **Iron-deficiency anaemia (prophylaxis)**
    - **BY MOUTH**
      - Child 1 month–11 years: 0.25 mL/kilogram twice daily, the total daily dose may alternatively be given in 3 divided doses, prophylactic iron supplementation may be required in babies of low birth-weight who are solely breast-fed; supplementation is started 4–6 weeks after birth and continued until mixed feeding is established; maximum 20 mL per day
      - Child 12–17 years: 10 mL once daily
      - Adult: 10 mL once daily
  - **Iron-deficiency anaemia (therapeutic)**
    - **BY MOUTH**
      - Child 1 month–11 years: 0.25 mL/kilogram twice daily, the total daily dose may alternatively be given in 3 divided doses; maximum 20 mL per day
      - Child 12–17 years: 10 mL 1–2 times a day
      - Adult: 10 mL 1–2 times a day

**INTERACTIONS**
- Appendix I (iron salts).

**PRESCRIBING AND DISPENSING INFORMATION**
- Non-proprietary ferrous fumarate tablets may
contain 210 mg (68 mg iron), syrup may contain approx.
140 mg (45 mg iron)/5 mL; Galfer® capsules contain
ferrous fumarate 305 mg (100 mg iron); Fersaday® tablets
contain ferrous fumarate 322 mg (100 mg iron).

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Ferrous fumarate for iron-deficiency anaemia www.medicinesforchildren.org.uk/
ferrous-fumarate-for-iron-deficiency-anaemia

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines
containing the same drug.
- **Tablet**
  - Ferrous fumarate (Non-proprietary)
    - Ferrous fumarate 210 mg. Ferrous fumarate 210 mg tablets | 84 tablet | £3.50 DT price = £3.50 | 84 tablet no price available DT price = £3.50
    - Ferrous fumarate 322 mg. Ferrous fumarate 322 mg tablets | 28 tablet | £1.00 DT price = £0.95
- **Capsule**
  - Galfer (Thornton & Ross Ltd)
    - Ferrous fumarate 305 mg. Galfer 305 mg capsules | 100 capsule | £2.33 DT price = £2.33 | 250 capsule | £5.00
- **Oral solution**
  - Ferrous fumarate (Non-proprietary)
    - Ferrous fumarate 28 mg per 1 ml. Ferrous fumarate 140 mg/5 ml oral solution | 200 ml | £3.73 DT price = £3.73
  - Galfer (Thornton & Ross Ltd)
    - Ferrous fumarate 28 mg per 1 ml. Galfer 140 mg/5 ml syrup sugar-free | 300 ml | £5.33 DT price = £5.33

**Ferrous fumarate with folic acid**
The properties listed below are those particular to the
combination only. For the properties of the components
please consider, ferrous fumarate p. 895, folic acid p. 898.

**INDICATIONS AND DOSE**
Iron-deficiency anaemia
- **BY MOUTH USING CAPSULES**
  - Adult: 1 capsule daily, to be taken before food
  - **BY MOUTH USING TABLETS**
  - Adult: 1 tablet daily

**PRESCRIBING AND DISPENSING INFORMATION**
Pregaday® contains ferrous fumarate 322 mg (100 mg iron), folic acid 350 micrograms; Galfer FA® contains ferrous fumarate 305 mg (100 mg iron), folic acid 350 micrograms.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines
containing the same drug.
- **Tablet**
  - Pregaday (Focus Pharmaceuticals Ltd)
    - Ferrous fumarate 322 mg, Folic acid 350 microgram. Pregaday 322mg/350microgram tablets | 28 tablet | £1.25 DT price = £1.25
  - Galfer FA (Thornton & Ross Ltd)
    - Ferrous fumarate 305 mg, Folic acid 350 microgram. Galfer FA capsules | 100 capsule | £3.25 DT price = £3.25

**Ferrous gluconate**

**INDICATIONS AND DOSE**
Prophylaxis of iron-deficiency anaemia
- **BY MOUTH USING TABLETS**
  - Child 6–11 years: 300–900 mg daily
  - Child 12–17 years: 600 mg daily
  - Adult: 600 mg daily

Treatment of iron-deficiency anaemia
- **BY MOUTH USING TABLETS**
  - Child 6–11 years: 300–900 mg daily
  - Child 12–17 years: 1.2–1.8 g daily in divided doses
  - Adult: 1.2–1.8 g daily in divided doses

**INTERACTIONS** → Appendix 1 (iron salts).

**PRESCRIBING AND DISPENSING INFORMATION**
Ferrous gluconate 300 mg contains 35 mg iron.

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Ferrous gluconate for iron-deficiency anaemia www.medicinesforchildren.org.uk/ferrous-gluconate-for-iron-deficiency-anaemia

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines
containing the same drug.
- **Tablet**
  - Ferrous gluconate (Non-proprietary)
    - Ferrous gluconate 300 mg. Ferrous gluconate 300 mg tablets | 28 tablet | £3.35 DT price = £1.95 | 1000 tablet | £119.64

**Ferrous sulfate**

**INDICATIONS AND DOSE**
Iron-deficiency anaemia (prophylactic)
- **BY MOUTH USING TABLETS**
  - Child 6–17 years: 200 mg daily
  - Adult: 200 mg daily

Iron-deficiency anaemia (therapeutic)
- **BY MOUTH USING TABLETS**
  - Child 6–17 years: 200 mg 2–3 times a day
  - Adult: 200 mg 2–3 times a day

**FEOSPAN®**
Iron-deficiency anaemia
- **BY MOUTH**
  - Child 1–7 years: 1 capsule daily, capsule can be opened and sprinkled on food
  - Adult: 1–2 capsules daily, capsule can be opened and sprinkled on food

**FERROGRAD®**
Iron-deficiency anaemia (prophylactic and therapeutic)
- **BY MOUTH**
  - Child 12–17 years: 1 tablet daily
  - Adult: 1 tablet daily

**IRONORM® DROPS**
Iron-deficiency anaemia (prophylactic)
- **BY MOUTH**
  - Adult: 2.4–4.8 mL daily

Iron-deficiency anaemia (therapeutic)
- **BY MOUTH**
  - Adult: 4 mL 1–2 times a day

**INTERACTIONS** → Appendix 1 (iron salts).

**PRESCRIBING AND DISPENSING INFORMATION**
Iron content Ferrous sulfate 200 mg is equivalent to 65 mg iron; Ironorm® drops contain ferrous sulfate 125 mg (equivalent to 25 mg iron)/mL; Feospan® suspensions contains ferrous sulfate 150 mg (47 mg iron) (spansule (= capsules m/r)); Ferrogard® tablets contain ferrous sulfate 325 mg (105 mg iron).

With oral use in adults Modified-release preparations of iron
are licensed for once-daily dosage, but have no therapeutic
advantage and should not be used. These preparations are
formulated to release iron gradually; the low incidence of
side-effects may reflect the small amounts of iron available
for absorption as the iron is carried past the first part of the
duodenum into an area of the gut where absorption may
be poor.

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Ferrous sulfate for iron-deficiency anaemia www.medicinesforchildren.org.uk/ferrous-sulfate-iron-deficiency-anaemia
Iron (as Polysaccharide-iron complex) 100 mg
(Tillomed Laboratories Ltd)
Iron-deficiency anaemia (prophylactic)
BY MOUTH
Child 1 month–1 year: 1 drop (approximately 500 micrograms iron) per 450 g body-weight to be given 3 times a day, dose to be administered from dropper bottle, prophylactic iron supplementation may be required in babies of low birth-weight who are solely breast-fed; supplementation is started 4–6 weeks after birth and continued until mixed feeding is established
Child 1–12 years: 2.5 mL daily
Adult: 2.5 mL daily
Iron-deficiency anaemia (therapeutic)
BY MOUTH
Child 2–5 years: 2.5 mL daily
Child 6–11 years: 5 mL daily
Child 12–17 years: 5 mL 1–2 times a day
Adult: 5 mL 1–2 times a day
Iron-deficiency anaemia (therapeutic) if required during second and third trimester of pregnancy
BY MOUTH
Child 12–17 years: 5 mL once daily
Adult: 5 mL once daily
INTERACTIONS Appendix 1 (iron salts).
PATIENT AND CARER ADVICE Counselling on the use of the dropper advised.
NATIONAL FUNDING/ACCESS DECISIONS
NHS restrictions Niferex® is not available on prescription under NHS, except 30-mL paediatric dropper bottle for prophylaxis and treatment of iron deficiency in infants born prematurely; endorse prescription 'SLS'.
MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Oral solution
Niferex (Tillomed Laboratories Ltd)
Iron (as Polysaccharide-iron complex) 100 mg Niferex 100 mg/5 mL elixir sugar-free | 30 mL £2.16 sugar-free | 240 mL £6.06
Sodium feredolate (Sodium ironedetate)
INDICATIONS AND DOSE
Iron-deficiency anaemia (therapeutic)
BY MOUTH USING ORAL SOLUTION
Child 1–11 months: Up to 2.5 mL twice daily, smaller doses to be used initially
continued
Blood and nutrition

898 Anaemias

1.3 Megaloblastic anaemia

Anaemia, megaloblastic

Overview

Most megaloblastic anaemias result from a lack of either vitamin B\textsubscript{12} or folate, and it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, when delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test while plasma assay results are awaited. Normally, however, appropriate treatment should not be instituted until the results of tests are available.

One cause of megaloblastic anaemia in the UK is pernicious anaemia in which lack of gastric intrinsic factor resulting from an autoimmune gastritis causes malabsorption of vitamin B\textsubscript{12}.

Vitamin B\textsubscript{12} is also needed in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia, which inactivates the vitamin, and in the rare syndrome of congenital transcobalamin II deficiency.

Vitamin B\textsubscript{12} should be given prophylactically after total gastrectomy or total ileal resection (or after partial gastrectomy if a vitamin B\textsubscript{12} absorption test shows vitamin B\textsubscript{12} malabsorption).

Apart from dietary deficiency, all other causes of vitamin B\textsubscript{12} deficiency are attributable to malabsorption. There is little place for the use of low-dose vitamin B\textsubscript{12} orally and none for vitamin B\textsubscript{12} intrinsic factor complexes given by mouth. Vitamin B\textsubscript{12} in larger oral doses [unlicensed] may be effective.

Hydroxocobalamin p. 899 has completely replaced cyanocobalamin p. 899 as the form of vitamin B\textsubscript{12} of choice for therapy; it is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted. There is no evidence that doses larger than those recommended provide any additional benefit in vitamin B\textsubscript{12} neuropathy.

Folic acid below has few indications for long-term therapy since most causes of folate deficiency are self-limiting or will yield to a short course of treatment. It should not be used in undiagnosed megaloblastic anaemia unless vitamin B\textsubscript{12} is administered concurrently otherwise neuropathy may be precipitated.

In folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy, or antiepileptic drugs), daily folic acid supplementation for 4 months brings about haematological remission and replenishes body stores.

For prophylaxis in chronic haemolytic states, malabsorption, or in renal dialysis, folic acid is given daily or sometimes weekly, depending on the diet and the rate of haemolysis.

Folic acid is also used for the prevention of methotrexate-induced side-effects in severe Crohn’s disease, rheumatic disease, and severe psoriasis.

Folinic acid p. 838 is also effective in the treatment of folate deficient megaloblastic anaemia but it is generally used in association with cytotoxic drugs; it is given as calcium folinate.

There is no justification for prescribing multiple ingredient vitamin preparations containing vitamin B\textsubscript{12} or folic acid.

For the use of folic acid before and during pregnancy, see Neural tube defects (prevention in pregnancy) p. 958.

VITAMINS AND TRACE ELEMENTS ▶ FOLATES

Folic acid

09-Jun-2016
Prevention of methotrexate side-effects in severe Crohn’s disease | Prevention of methotrexate side-effects in severe psoriasis

- BY MOUTH
  - Adult: 5 mg once weekly, dose to be taken on a different day to methotrexate dose

Prophylaxis in chronic haemolytic states

- BY MOUTH
  - Adult: 5 mg every 1–7 days, frequency dependent on underlying disease

Prophylaxis of folate deficiency in dialysis

- BY MOUTH
  - Child 1 month–11 years: 250 micrograms/kg once daily (max. per dose 10 mg)
  - Child 12–17 years: 5–10 mg once daily
  - Adult: 5 mg every 1–7 days

Prophylaxis of folate deficiency in patients receiving parenteral nutrition

- BY INTRAVENOUS INFUSION
  - Adult: 15 mg 1–2 times a week, usually given by intravenous infusion in the parenteral nutrition solution

- UNLICENSED USE
  - In adults Not licensed for prevention of methotrexate-induced side-effects in severe Crohn’s disease, rheumatic disease, or severe psoriasis.

- CAUTIONS
  - Should never be given alone for pernicious anaemia (may precipitate subacute combined degeneration of the spinal cord)

- INTERACTIONS
  - Rare Gastro-intestinal disturbances

- PATIENT AND CARER ADVICE
  - Medicines for Children leaflet: Folic acid for megaloblastic anaemia caused by folate deficiency and haemolytic anaemia

- EXCEPTIONS TO LEGAL CATEGORY
  - With oral use Can be sold to the public provided daily doses do not exceed 500 micrograms.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution, solution for injection

**Tablet**

- **Folic acid (Non-proprietary)**
  - Folic acid 400 microgram | 90 tablet [P] no price available DT price = £2.71 | 90 tablet £2.71 DT price = £2.71
  - Folic acid 5 mg | 28 tablet [P] £1.17 DT price = £0.92 | 1000 tablet [P] £33.21

**Oral solution**

- **Folic acid (Non-proprietary)**
  - Folic acid 2.5mg/5ml oral solution sugar free | 150 ml [P] £9.16 DT price = £9.16
  - Lepec (Rosemont Pharmaceuticals Ltd)
  - Folic acid 500 microgram per ml | 150 ml [P] £9.16 DT price = £9.16

**VITAMINS AND TRACE ELEMENTS > VITAMIN B GROUP**

### Cyanocobalamin

- **INDICATIONS AND DOSE**
  - Vitamin B12 deficiency of dietary origin
    - BY MOUTH
    - Adult: 50–150 micrograms daily, dose to be taken between meals
    - BY INTRAMUSCULAR INJECTION
    - Adult: Initially 1 mg every 2–3 days for 11 doses; maintenance 1 mg every month

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The BP directs that when vitamin B12 injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied.
  - Currently available brands of the tablet may not be suitable for vegans.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NHS restrictions Cyanocobalamin liquid, Cytac® tablets, and Cytamen® injection are not available on prescription under the NHS.

- **LESS SUITABLE FOR PRESCRIBING**
  - Cyanocobalamin is less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

  **Tablet**

  - Cyanocobalamin (Non-proprietary)
    - Cyanocobalamin 50 microgram | 50 tablet [P] £6.24 DT price = £8.99 | 50 tablet £8.99 DT price = £8.99 | 100 tablet no price available
    - Cytac® (AMCo)
    - Cyanocobalamin 50 microgram | 50 tablet [P] £8.99 DT price = £8.99

  **Oral solution**

  - Cyanocobalamin (Non-proprietary)
    - Cyanocobalamin 7 microgram per 1 ml | 75 micrograms/5ml oral solution | 200 ml [P] £8.75

  **Solution for injection**

  - Cytac® (Focus Pharmaceuticals Ltd)
    - Cyanocobalamin 1 mg per 1 ml | Cytamen 1000 micrograms/1ml solution for injection ampoules | 5 ampoule [P] £14.50 DT price = £14.50

### Hydroxocobalamin

- **INDICATIONS AND DOSE**
  - **Prophylaxis of macrocytic anaemias associated with vitamin B12 deficiency**
    - BY INTRAMUSCULAR INJECTION
    - Adult: 1 mg every 2–3 months
  - **Pernicious anaemia and other macrocytic anaemias without neurological involvement**
    - BY INTRAMUSCULAR INJECTION
    - Adult: Initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months
  - **Pernicious anaemia and other macrocytic anaemias with neurological involvement**
    - BY INTRAMUSCULAR INJECTION
    - Adult: Initially 1 mg once daily on alternate days until no further improvement, then 1 mg every 2 months
  - **Tobacco amblyopia**
    - BY INTRAMUSCULAR INJECTION
    - Adult: Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months
Leber’s optic atrophy
▶ By intramuscular injection
▶ Adult: Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months

**CYANOKIT®**
 Poisoning with cyanides
▶ By intravenous infusion
▶ Child (body-weight 5 kg and above): Initially 70 mg/kg (max. per dose 5 g), to be given over 15 minutes, then 70 mg/kg (max. per dose 5 g) if required, this second dose can be given over 15 minutes – 2 hours depending on severity of poisoning and patient stability
▶ Adult: Initially 5 g, to be given over 15 minutes, then 5 g if required, this second dose can be given over 15 minutes – 2 hours depending on severity of poisoning and patient stability

**CAUTIONS**
▶ With intramuscular use should not be given before diagnosis fully established
▶ INTERACTIONS ➔ Appendix 1 (hydroxocobalamin).

**SIDE-EFFECTS**
**GENERAL SIDE-EFFECTS**
Dizziness • headache • pruritus

**SPECIFIC SIDE-EFFECTS**
▶ With intramuscular use Hypokalaemia (during initial treatment) • injection-site reactions • rash • thrombocytosis (during initial treatment) • Chromatia • fever • hypersensitivity reactions • nausea
▶ With intravenous use Dyspnoea • eye disorders • gastrointestinal disturbances • hot flush • lymphocytopenia • memory impairment • peripheral oedema • pustular rashes • red coloration of urine • restlessness • reversible red coloration of skin and mucous membranes • throat disorders • transient hypertension
▶ BREAST FEEDING Present in milk but not known to be harmful.

**EFFECT ON LABORATORY TESTS**
▶ With intravenous use Deep red colour of hydroxocobalamin may interfere with laboratory tests.

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion (Cyanokit®), given intermittently in Sodium chloride 0.9%, reconstitute 5 g vial with 200 mL Sodium Chloride 0.9%; gently invert vial for at least 1 minute to mix (do not shake).

**PRESCRIBING AND DISPENSING INFORMATION**
▶ With intramuscular use The BP directs that when vitamin B₁₂ injection is prescribed or demanded, hydroxocobalamin injection shall be dispensed or supplied. Poisoning by cyanides
▶ With intravenous use Cyanokit® is the only preparation of hydroxocobalamin that is suitable for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

**NATIONAL FUNDING/ACCESS DECISIONS**
**NHS restrictions** Cobalin-H® is not prescribable under National Health Service (NHS).
Neo-Cytamen® is not prescribable under National Health Service (NHS).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug

**Solution for injection**
▶ Hydroxocobalamin (Non-proprietary)

Hydroxocobalamin 1 mg per 1 ml Hydroxocobalamin 1mg/1ml solution for injection ampoules | 5 ampoule [POT] £12.49 DT price = £7.11

▶ Cobalin (AMCo)
Hydroxocobalamin 1 mg per 1 ml Cobalin-H 1mg/1ml solution for injection ampoules | 5 ampoule [POT] £9.50 DT price = £7.11

▶ Neo-Cytamen (Focus Pharmaceuticals Ltd)
Hydroxocobalamin 1 mg per 1 ml Neo-Cytamen 1000micrograms/1ml solution for injection ampoules | 5 ampoule [POT] £12.49 DT price = £7.11

**Powder for solution for infusion**
▶ Cyanokit (Swedish Orphan Biovitrum Ltd)
Hydroxocobalamin 5 gram Cyanokit 5g powder for solution for infusion vials | 1 vial [POT] no price available

### 2 Iron overload

**Iron overload**

**Overview**
Severe tissue iron overload can occur in aplastic and other refractory anaemias, mainly as the result of repeated blood transfusions. It is a particular problem in refractory anaemias with hyperplastic bone marrow, especially thalassaemia major, where excessive iron absorption from the gut and inappropriate iron therapy can add to the tissue siderosis.

Iron overload associated with haemochromatosis can be treated with repeated venesection. Venesection may also be used for patients who have received multiple transfusions and whose bone marrow has recovered. Where venesection is contra-indicated, the long-term administration of the iron chelating compound desferrioxamine mesilate p. 902 is useful. Desferrioxamine mesilate (up to 2 g per unit of blood) may also be given at the time of blood transfusion, provided that the desferrioxamine mesilate is not added to the blood and is not given through the same line as the blood (but the two may be given through the same cannula).

Iron excretion induced by desferrioxamine mesilate is enhanced by administration of ascorbic acid p. 952 (vitamin C) daily by mouth; it should be given separately from food since it also enhances iron absorption. Ascorbic acid should not be given to patients with cardiac dysfunction; in patients with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine mesilate. Desferrioxamine mesilate infusion can be used to treat aluminium overload in dialysis patients; theoretically 100 mg of desferrioxamine binds with 4.1 mg of aluminium.

**ANTIDOTES AND CHELATORS ➔ IRON CHELATORS**

**Deferasirox**

**DRUG ACTION**
Deferasirox is an oral iron chelator.

**INDICATIONS AND DOSE**
Transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells) | Transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with other anaemias | Treatment of chronic iron overload in patients with thalassaemia major who receive frequent blood transfusions (more than 7 mL/kg/month of packed red blood cells)
▶ BY MOUTH
▶ Adult: Initially 10–30 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature; adjusted in steps of 5–10 mg/kg every 3–6 months, maintenance dose adjusted according to
serum-ferritin concentration; maximum 40 mg/kg per day; Usual maximum 30 mg/kg

**Treatment of chronic iron overload when desferrioxamine is contra-indicated or inadequate (with non-transfusion-dependent thalassaemia syndromes)**

- **BY MOUTH**
  - Adult: Initially 10 mg/kg once daily; adjusted in steps of 5–10 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration and liver-iron concentration (consult product literature); maximum 20 mg/kg per day

- **CAUTIONS** Elderly (increased risk of side-effects) - history of liver cirrhosis - not recommended in conditions which may reduce life expectancy (e.g. high-risk myelodysplastic syndromes) - platelet count less than 50x10^9/litre - risk of gastro-intestinal ulceration and haemorrhage - unexplained cytopenia—consider treatment interruption

- **INTERACTIONS** → Appendix 1 (deferasirox).

- **SIDE-EFFECTS**
  - **Common or very common** Fatal gastro-intestinal haemorrhage - gastro-intestinal disturbances - gastro-intestinal ulceration - headache - proteinuria - pruritus - rash
  - **Uncommon** Anxiety - cholelithiasis - disturbances of hearing and vision - dizziness - fatigue - glucosuria - hepatitis - lens opacity - maculopathy - oedema - pharyngitis - pyrexia - renal tubulopathy - skin pigmentation - sleep disorder
  - **Frequency not known** Acute renal failure - agranulocytosis - alopecia - anaemia - anaphylaxis - angioedema - blood disorders - hepatic failure - hypersensitivity reactions - neutropenia - pancytopenia - thrombocytopenia - tubulointerstitial nephritis

- **PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Use with caution in moderate impairment, reduce dose considerably then gradually increase to max. 50% of normal dose. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Reduce dose by 10 mg/kg if eGFR 60–90 mL/minute/1.73 m² and if serum creatinine increased by more than 33% of baseline measurement on 2 consecutive occasions—interrupt treatment if deterioration in renal function persists after dose reduction. Avoid if eGFR less than 60 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Eye and ear examinations required before treatment and annually during treatment.
  - Monitor serum-ferritin concentration monthly.
  - Test liver function before treatment, then every 2 weeks during the first month, and then monthly.
  - Measure baseline serum creatinine and monitor renal function weekly during the first month of treatment and monthly thereafter.
  - Test for proteinuria monthly.

- **DIRECTIONS FOR ADMINISTRATION** Tablets should be dispensed in water, orange juice, or apple juice; if necessary resuspend residue.

- **PATIENT AND CARER ADVICE** Patient or carers should be given advice on how to administer deferasirox dispersible tablets.

- **NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (January 2007) that deferasirox is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Deferasirox (non-proprietary) ▼
      - Deferasirox 90 mg □ Exjade 90 mg tablets | 30 tablet | £126.00
      - Deferasirox 180 mg □ Exjade 180 mg tablets | 30 tablet | £252.00
      - Deferasirox 360 mg □ Exjade 360 mg tablets | 30 tablet | £504.00
  - **Dispersible tablet**
    - CAUTIONARY AND ADVISORY LABELS ▼ 13, 22
      - Exjade (Novartis Pharmaceuticals UK Ltd) ▼
      - Deferasirox 125 mg □ Exjade 125 mg dispersible tablets sugar-free □ 28 tablet | £117.60
      - Deferasirox 250 mg □ Exjade 250 mg dispersible tablets sugar-free □ 28 tablet | £235.20
      - Deferasirox 500 mg □ Exjade 500 mg dispersible tablets sugar-free □ 28 tablet | £470.40

**Deferiprone**

- **DRUG ACTION** Deferiprone is an oral iron chelator.

- **INDICATIONS AND DOSE**
  - Treatment of iron overload in patients with thalassaemia major in whom desferrioxamine is contra-indicated or is inadequate
  - **BY MOUTH**
    - Adult: 25 mg/kg 3 times a day; maximum 100 mg/kg per day

- **CONTRA-INDICATIONS** History of agranulocytosis or recurrent neutropenia

- **INTERACTIONS** → Appendix 1 (deferiprone).

- **SIDE-EFFECTS** Agranulocytosis - arthropathy - blood dyscrasias - gastro-intestinal disturbances (reducing dose and increasing gradually may improve tolerance) - headache - increased appetite - neutropenia - red-brown urine discoloration - zinc deficiency

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises avoid before intended conception—teratogenic and embryotoxic in animal studies. Contraception advised in females of child-bearing potential.

- **PREGNANCY** Manufacturer advises avoid during pregnancy—teratogenic and embryotoxic in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises monitor liver function—interrupt treatment if persistent elevation in serum alanine aminotransferase.

- **RENAL IMPAIRMENT** Manufacturer advises caution—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor neutrophil count weekly and discontinue if recurrent neutropenia develops.
  - Monitor plasma-zinc concentration.

- **PATIENT AND CARER ADVICE** Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever or sore throat develop.
Desferrioxamine mesilate (Deferoxamine Mesilate)

**INDICATIONS AND DOSE**

**Iron poisoning**
- BY CONTINUOUS INTRAVENOUS INFUSION
  - Adult: Initially up to 15 mg/kg/hour, max. 80 mg/kg in 24 hours, dose to be reduced after 4–6 hours, in severe cases, higher doses may be given on advice from the National Poisons Information Service

**Aluminium overload in dialysis patients**
- BY INTRAVENOUS INFUSION
  - Adult: (consult product literature or local protocols)

**Chronic iron overload (low iron overload)**
- BY SUBCUTANEOUS INFUSION
  - Adult: The dose should reflect the degree of iron overload

**Chronic iron overload (established overload)**
- BY SUBCUTANEOUS INFUSION
  - Adult: 20–50 mg/kg daily

**CAUTIONS**
- Aluminium-related encephalopathy (may exacerbate neurological dysfunction)

**SIDE-EFFECTS**
- Common or very common
  - Abdominal pain
  - arthralgia
  - bone disorders
  - growth retardation
  - headache
  - hearing disturbances
  - injection-site reactions
  - myalgia
  - nausea
  - pyrexia
  - vomiting

- Rare
  - Anaphylaxis
  - blood dyscrasias
  - bone pain
  - diarrhoea
  - hepatic impairment
  - hypotension (especially when given too rapidly by intravenous injection)
  - leg cramps
  - lens opacity
  - leucopenia
  - rash
  - retinopathy
  - thrombocytopenia
  - visual disturbances
  - Yersinia and mucormycosis infections

- Very rare
  - Acute respiratory distress
  - convulsions
  - dizziness
  - neurological disturbances
  - neuropathy
  - paraesthesia
  - renal impairment

- Frequency not known
  - Muscle spasms

**PREGNANCY**
Teratogenic in animal studies. Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**
Manufacturer advises use only if potential benefit outweighs risk—no information available.

**RENAI IMPAIRMENT**
Use with caution.

**MONITORING REQUIREMENTS**
- Eye and ear examinations before treatment and at 3-month intervals during treatment.

**DIRECTIONS FOR ADMINISTRATION**
For full details and warnings relating to administration, consult product literature.

For intravenous infusion (Desferal®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%.

Reconstitute with water for injections to a concentration of 100 mg/mL; dilute with infusion fluid.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Desferrioxamine mesilate (Non-proprietary)
  - Desferrioxamine mesilate 500 mg
    - Desferrioxamine 500mg powder for solution for injection vials | 10 vial
    - £39.90–£50.00
  - Desferrioxamine mesilate 2 gram
    - Desferrioxamine 2g powder for solution for injection vials | 1 vial
    - £17.95–£20.00

- Desferal (Novartis Pharmaceuticals UK Ltd)
  - Desferal mesilate 2 gram
    - Desferal 2g powder for solution for injection vials | 1 vial
    - £18.66
  - Desferal mesilate 500 mg
    - Desferal 500mg powder for solution for injection vials | 10 vial
    - £46.63

**IMMUNOSTIMULANTS**
- GRANULOCYTE-COLONY STIMULATING FACTORS

**Granulocyte-colony stimulating factors**

**DRUG ACTION**
Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils.

**CAUTIONS**
Malignant myeloid conditions—pre-malignant myeloid conditions—risk of splenomegaly and rupture—spleen size should be monitored—sickle-cell disease

**CAUTIONS, FURTHER INFORMATION**
- Acute respiratory distress syndrome
  - There have been reports of pulmonary infiltrates leading to acute respiratory distress syndrome—patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

**SIDE-EFFECTS**
- Common or very common
  - Alopecia
  - anorexia
  - asthenia
  - bone pain
  - chest pain
  - fever
  - gastro-intestinal disturbances
  - headache
  - injection-site reactions
  - leucocytosis
  - musculoskeletal pain
  - rash
  - thrombocytopenia

**Neutropenia and stem cell mobilisation**

**3.1 Neutropenia**

**Neutropenia**

**Management**
Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils and may reduce the duration of chemotherapy-induced neutropenia and thereby reduce the incidence of associated sepsis; there is as yet no evidence that it improves overall survival. Filgrastim, p. 903 (unglycosylated rhG-CSF) and lenograstim p. 904 (glycosylated rhG-CSF) have similar effects; both have been used in a variety of clinical settings, but they do not have any clear-cut routine indications. In congenital neutropenia filgrastim usually increases the neutrophil count with an appropriate clinical response. Pegfilgrastim p. 904 is a polyethylene glycol-conjugated (‘pegylated’) derivative of filgrastim; pegylation increases the duration of filgrastim activity. Lipegfilgrastim p. 904 is a polyethylene glycol-conjugated via a glycine linker derivative of filgrastim.

Granulocyte-colony stimulating factors should only be prescribed by those experienced in their use.

**IMMUNOSTIMULANTS**
- GRANULOCYTE-COLONY STIMULATING FACTORS

**Granulocyte-colony stimulating factors**

**DRUG ACTION**
Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils.

**CAUTIONS**
Malignant myeloid conditions—pre-malignant myeloid conditions—risk of splenomegaly and rupture—spleen size should be monitored—sickle-cell disease

**CAUTIONS, FURTHER INFORMATION**
- Acute respiratory distress syndrome
  - There have been reports of pulmonary infiltrates leading to acute respiratory distress syndrome—patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

**SIDE-EFFECTS**
- Common or very common
  - Alopecia
  - anorexia
  - asthenia
  - bone pain
  - chest pain
  - fever
  - gastro-intestinal disturbances
  - headache
  - injection-site reactions
  - leucocytosis
  - musculoskeletal pain
  - rash
  - thrombocytopenia
Spleen size should be monitored during treatment.

**MONITORING REQUIREMENTS**

**BREAST FEEDING**

**PREGNANCY**

Pulmonary infiltration

Rare potential benefits outweigh the risk.

**PERSISTENT NEUTROPENIA IN HIV INFECTION (SPECIALIST USE ONLY)**

Adult: Initially 1 microgram/kg daily, subsequent doses increased as necessary until neutrophil count in normal range, then adjusted to maintain neutrophil count in normal range—consult product literature; maximum 4 micrograms/kg per day

### Filgrastim

*(Recombinant human granulocyte-colony stimulating factor; G-CSF)*

**INDICATIONS AND DOSE**

Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) (specialist use only)

**BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INFUSION**

**Adult:** 5 micrograms/kg daily until neutrophil count in normal range, usually for up to 14 days (up to 38 days in acute myeloid leukaemia), to be started at least 24 hours after cytotoxic chemotherapy. Preferably given by subcutaneous injection; if given by intravenous infusion, administer over 30 minutes

Reduction in duration of neutropenia (and associated sequelae) in myeloablative therapy followed by bone-marrow transplantation (specialist use only)

**BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INFUSION**

**Adult:** 10 micrograms/kg daily, to be started at least 24 hours following cytotoxic chemotherapy and within 24 hours of bone-marrow infusion, then adjusted according to neutrophil count—consult product literature, doses administered over 30 minutes or 24 hours via intravenous route and over 24 hours via subcutaneous route

Mobilisation of peripheral blood progenitor cells for autologous infusion, used alone (specialist use only)

**BY SUBCUTANEOUS INJECTION**

**Adult:** 10 micrograms/kg daily for 5–7 days, to be administered over 24 hours if given by subcutaneous infusion

Mobilisation of peripheral blood progenitor cells for autologous infusion, used following adjunctive myelosuppressive chemotherapy—to improve yield (specialist use only)

**BY SUBCUTANEOUS INJECTION**

**Adult:** 5 micrograms/kg daily until neutrophil count in normal range, to be started the day after completing chemotherapy, for timing of leucopheresis, consult product literature

Mobilisation of peripheral blood progenitor cells in normal donors for allogenic infusion (specialist use only)

**BY SUBCUTANEOUS INJECTION**

**Adult 18–59 years:** 10 micrograms/kg daily for 4–5 days, for timing of leucopheresis, consult product literature

**CONTRA-INDICATIONS**

Severe congenital neutropenia (Kostmann’s syndrome) with abnormal cytogenetics

**CAUTIONS**

Osteoporotic bone disease (monitor bone density if given for more than 6 months) · secondary acute myeloid leukaemia

**INTERACTIONS**

Appendix 1 (filgrastim).

**SIDE-EFFECTS**

- Common or very common: Anaemia · dysuria · epistaxis · exacerbation of rheumatoid arthritis · haematuria · hepatomegaly · mucositis · osteoporosis · proteinuria · pseudogout · raised uric acid · splenic enlargement · transient decrease in blood glucose · transient hypotension · urinary abnormalities
- Uncommon: Capillary leak syndrome (including fatal cases)
- Rare: Splenic rupture

**MONITORING REQUIREMENTS**

Regular morphological and cytogenetic bone-marrow examinations recommended in severe congenital neutropenia (possible risk of myelodysplastic syndromes or leukaemia).

**DIRECTIVE FOR ADMINISTRATION**

For intravenous infusion (Neupogen®); (Nivestim®); (Ratiogran®); (Zarzio®) give continuously or intermittently in glucose 5%; for a filgrastim concentration of less than 1 500 000 units/mL (15 micrograms/mL) albumin solution (human albumin solution) is added to produce a final albumin concentration of 2 mg/mL; should not be diluted to a filgrastim concentration of less than 200 000 units/mL (2 micrograms/mL) and should not be diluted with sodium chloride solution.

**PRESCRIBING AND DISPENSING INFORMATION**

Filgrastim is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

1 million units of filgrastim solution for injection contains 10 micrograms filgrastim.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Accofil (Accord Healthcare Ltd)**
  - Filgrastim 60 mega u per 1 ml Accofil 30 million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection £284.20
  - Filgrastim 96 mega u per 1 ml Accofil 48 million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection £455.70
**Neupogen** (Amgen Ltd)
Filgrastim 30 mega u per 1 ml Neupogen 30 million units/1 ml solution for injection vials | 5 vial PoM £263.52

**Neupogen Singleject** (Amgen Ltd)
Filgrastim 60 mega u per 1 ml Neupogen Singleject 30 million units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection PoM £52.70

Filgrastim 96 mega u per 1 ml Neupogen Singleject 48 million units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection PoM £94.06

**Nivestim** (Pfizer Ltd)
Filgrastim 60 mega u per 1 ml Nivestim 30 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection PoM £246.50 (Hospital only)
Nivestim 12 million units/0.2 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection PoM £153.00 (Hospital only)
Filgrastim 96 mega u per 1 ml Nivestim 48 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection PoM £395.25 (Hospital only)

**Zarzio** (Sanloz Ltd)
Filgrastim 60 mega u per 1 ml Zarzio 30 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection PoM £250.75
Filgrastim 96 mega u per 1 ml Zarzio 48 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection PoM £399.50

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**Lenograstim**

(Recombinant human granulocyte-colony stimulating factor; rHuG-CSF)

- **INDICATIONS AND DOSE**
  Reduction in the duration of neutropenia and associated complications following bone-marrow transplantation for non-myeloid malignancy (specialist use only)
  Reduction in the duration of neutropenia and associated complications following peripheral stem cell transplantation for non-myeloid malignancy (specialist use only)
  - **BY INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range (max. 28 days), to be started the day after transplantation. Intravenous infusion to be given over 30 minutes
  
  Reduction in the duration of neutropenia and associated complications following treatment with cytotoxic chemotherapy associated with a significant incidence of febrile neutropenia (specialist use only)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range (max. 28 days), to be started on the day after completion of chemotherapy
  
  Mobilisation of peripheral blood progenitor cells for harvesting and subsequent infusion, used alone (specialist use only)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 10 micrograms/kg daily for 4–6 days (5–6 days in healthy donors)
  
  Mobilisation of peripheral blood progenitor cells, used following adjunctive myelosuppressive chemotherapy (to improve yield) (specialist use only)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range, to be started 1–5 days after completion of chemotherapy, for timing of leucopheresis, consult product literature

- **SIDE-EFFECTS**
  Mucositis · splenic rupture · toxic epidermal necrolysis

- **DIRECTIONS FOR ADMINISTRATION**
  For intravenous infusion (Granocyte®), give intermittently in Sodium chloride 0.9%; initially reconstitute with 1 ml water for injection provided (do not shake vigorously) then dilute with up to 50 ml infusion fluid for each vial of Granocyte-13 or up to 100 ml infusion fluid for Granocyte-34; give over 30 minutes.

- **PRESCRIBING AND DISPENDING INFORMATION**
  Granocyte® solution for injection contains 105 micrograms of lenograstim per 13.4 mega unit vial and 263 micrograms lenograstim per 33.6 mega unit vial.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

EXCIPIENTS: May contain Phenylalanine

- **Granocyte** (Chugai Pharma UK Ltd)
  Lenograstim 13.4 mega u Granocyte-13 powder and solvent for solution for injection vials | 1 vial PoM £40.11 | 5 vial PoM £200.55
  Lenograstim 33.6 mega u Granocyte-34 powder and solvent for solution for injection vials | 1 vial PoM £62.54 | 5 vial PoM £312.69

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**Lipegfilgrastim**

(Glycopegylated recombinant methionyl human granulocyte-colony stimulating factor)

- **INDICATIONS AND DOSE**
  Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult (specialist use only): 6 mg, for each chemotherapy cycle, given approximately 24 hours after chemotherapy, dose expressed as filgrastim

- **CAUTIONS**
  Myelosuppressive chemotherapy

- **INTERACTIONS** → Appendix 1 (lepifilgrastim).

- **SIDE-EFFECTS**
  Hypokalaemia

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - Lonquex (Teva UK Ltd) Lipegfilgrastim 10 mg per 1 ml Lonquex 6 mg/0.6 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £652.06

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**Pegfilgrastim**

(Pegylated recombinant methionyl human granulocyte-colony stimulating factor)

- **INDICATIONS AND DOSE**
  Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) (specialist use only)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 6 mg for each chemotherapy cycle, to be given at least 24 hours after chemotherapy, dose expressed as filgrastim

- **CAUTIONS**
  Acute leukaemia · myelosuppressive chemotherapy

- **INTERACTIONS** → Appendix 1 (pegfilgrastim).

- **SIDE-EFFECTS**
  Rare · Capillary leak syndrome (including fatal cases)
  Very rare · Splenic rupture
3.2 Stem cell mobilisation

IMMUNOSTIMULANTS > CHEMOKINE RECEPTOR ANTAGONISTS

Plerixafor

- **DRUG ACTION** Plerixafor is a chemokine receptor antagonist.

- **INDICATIONS AND DOSE**
  
  Mobilise haematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma or multiple myeloma (specialist use only)
  
  ▶ **BY SUBCUTANEOUS INJECTION**
  
  ▶ Adult: 240 micrograms/kg daily usually for 2–4 days (max 7 days), to be administered 6–11 hours before initiation of apheresis, dose to be given following 4 days treatment with a granulocyte-colony stimulating factor

- **SIDE-EFFECTS**
  
  ▶ Common or very common Arthralgia · dizziness · dry mouth · erythema · fatigue · gastrointestinal disturbances · headache · injection-site reactions · insomnia · musculoskeletal pain · oral hypoaesthesia · sweating
  
  ▶ Uncommon Dyspnoea · hypersensitivity reactions · periorbital swelling

- **CONCEPTION AND CONTRACEPTION** Use effective contraception during treatment—teratogenic in animal studies.

- **PREGNANCY**
  
  Manufacturer advises avoid unless essential—teratogenic in animal studies.

- **BREAST FEEDING**
  
  Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT**
  
  Reduce dose to 160 micrograms/kg daily if creatinine clearance 20–50 ml/minute. No information available if creatinine clearance less than 20 ml/minute.

- **MONITORING REQUIREMENTS**
  
  Monitor platelets and white blood cell count.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  
  ▶ Mozobil (Sanofi)
  
  Plerixafor 20 mg per 1 ml Mozobil 24mg/1.2ml solution for injection vials | 1 vial £4.88,277

4 Platelet disorders

Platelet disorders

Idiopathic thrombocytopenic purpura

Acute idiopathic thrombocytopenic purpura is usually self-limiting in children. In adults, idiopathic thrombocytopenic purpura can be treated with a corticosteroid, e.g. prednisolone p. 622, gradually reducing the dose over several weeks. Splenectomy is considered if a satisfactory platelet count is not achieved or if there is a relapse on reducing the dose of corticosteroid or withdrawing it.

Immunoglobulin preparations, are also used in idiopathic thrombocytopenic purpura or where a temporary rapid rise in platelets is needed, as in pregnancy or pre-operatively; they are also used for children often in preference to a corticosteroid. Anti-D (Rh) immunoglobulin p. 1140 is effective in raising the platelet count in about 80% of unspenectomised rhesus-positive individuals; its effects may last longer than normal immunoglobulin p. 1141 for intravenous use, but further doses are usually required.

Other therapy that has been tried in refractory idiopathic thrombocytopenic purpura includes azathioprine p. 765, cyclophosphamide p. 802, vincristine sulfate p. 830, ciclosporin p. 766, and danazol p. 678. Rituximab p. 792 may also be effective and in some cases induces prolonged remission. For patients with chronic severe thrombocytopenia refractory to other therapy, tranexamic acid p. 104 may be given to reduce the severity of haemorrhage.

Eltrombopag p. 906 and romiplostim p. 907 are thrombopoietin receptor agonists licensed for the treatment of chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments, such as corticosteroids or immunoglobulins, or as a second-line treatment in non-splenectomised patients when surgery is contra-indicated (see also NICE guidance). Eltrombopag is an oral preparation and romiplostim is an injection which is made biosynthetically by recombinant DNA technology; they should both be used under the supervision of a specialist.

Essential thrombocytopenia

Anagrelide below inhibits platelet formation. It is licensed for essential thrombocytopenia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs. An at risk patient is defined by one or more of the following features: over 60 years of age, or a platelet count greater than 1000 x 10⁹/L, or history of thrombo-haemorrhagic events. Anagrelide should be initiated under specialist supervision.

4.1 Essential thrombocytopenia

ANTITHROMBOTIC DRUGS > CYCLIC AMP PHOSPHODIESTERASE III INHIBITORS

Anagrelide

- **INDICATIONS AND DOSE**
  
  Essential thrombocytopenia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs (initiated under specialist supervision)
  
  ▶ **BY MOUTH**
  
  ▶ Adult: Initially 500 micrograms twice daily, dose to be adjusted at weekly intervals according to response, increased in steps of 500 micrograms daily; usual dose 1–3 mg daily in divided doses (max. per dose 2.5 mg); maximum 10 mg per day

- **CAUTIONS**
  
  Cardiovascular disease—assess cardiac function before and regularly during treatment · concomitant use of drugs that prolong QT-interval—assess cardiac function before and regularly during treatment · risk factors for QT-interval prolongation—assess cardiac function before and regularly during treatment
Blood and nutrition

906 Platelet disorders

INTERACTIONS
Caution with concomitant aspirin in patients at risk of haemorrhage. Appendix 1 (anagrelide).

SIDE-EFFECTS
- Common or very common Anaemia, dizziness, fatigue, fluid retention, gastro-intestinal disturbances, headache, palpitation, rash, tachycardia
- Uncommon Alopecia, anemia, anorexia, arrhythmias, arthralgia, back pain, blood disorders, chest pain, confusion, congestive heart failure, depression, dry mouth, dysphonia, ecchymosis, epistaxis, fever, gastro-intestinal haemorrhage, haemorrhage, hypertension, hypoaesthesia, impotence, malaise, myalgia, nervousness, oedema, pancreatitis, paraesthesia, pneumonia pleural effusion, pruritus, skin discoloration, sleep disturbances, syncope, weight changes
- Rare Angina, asthenia, cardiomegaly, cardiomyopathy, colitis, dry skin, dysarthria, gastritis, gingival bleeding, impaired coordination, migraine, myocardial infarction, nocturia, pericardial effusion, postural hypotension, pulmonary hypertension, pulmonary infiltrates, renal failure, somnolence, tinnitus, vasodilatation, visual disturbances
- Frequency not known Hepatitis, interstitial lung disease, Torsades de pointes, tubulointerstitial nephritis

CONCEPTION AND CONTRACEPTION
Effective contraception required during treatment.

PREGNANCY
Manufacturer advises avoid (toxicity in animal studies).

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Manufacturer advises caution in mild impairment. Avoid in moderate to severe impairment.

RENAL IMPAIRMENT
Manufacturer advises avoid if eGFR less than 50 mL/minute/1.73 m².

MONITORING REQUIREMENTS
- Monitor full blood count (monitor platelet count every 2 days for 1 week, then weekly until maintenance dose established).
- Monitor liver function.
- Monitor serum creatinine.
- Monitor urea.
- Monitor electrolytes (including potassium, magnesium and calcium) before and during treatment.

PATIENT AND CARER ADVICE
- Driving and skilled tasks
  Dizziness may affect performance of skilled tasks (e.g. cycling, driving).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
- Xagrid (Shire Pharmaceuticals Ltd) ▼
- Anagrelide (as Anagrelide hydrochloride) 500 microgram Xagrid 500microgram capsules | 100 capsule POM £40.57

4.2 Idiopathic thrombocytopenic purpura

ANTIHAEMORRHAGICS ▶ THROMBOPOIETIN RECEPTOR AGONISTS

Eltrombopag

INDICATIONS AND DOSE
Treatment of chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments (such as corticosteroids or immunoglobulins) (under expert supervision) ▶ Second-line treatment of chronic idiopathic thrombocytopenic purpura in non-splenectomised patients when surgery is contra-indicated (under expert supervision)

▶ BY MOUTH
- Adult: Initially 50 mg once daily, dose to be adjusted to achieve a platelet count of 50x10⁹/litre or more—consult product literature for dose adjustments, discontinue if inadequate response after 4 weeks treatment at maximum dose; maximum 75 mg per day
- Adult (patients of East Asian origin): Initially 25 mg once daily, dose to be adjusted to achieve a platelet count of 50x10⁹/litre or more—consult product literature for dose adjustments, discontinue if inadequate response after 4 weeks treatment at maximum dose; maximum 75 mg per day.

Treatment of thrombocytopenia associated with chronic hepatitis C infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (under expert supervision)

▶ BY MOUTH
- Adult: Initially 25 mg once daily, dose to be adjusted to achieve a platelet count sufficient to initiate antiviral therapy then a platelet count of 50–75x10⁹/litre during antiviral therapy—consult product literature for dose adjustments, discontinue if inadequate response after 2 weeks treatment at maximum dose; maximum 100 mg per day.

CAUTIONS
Patients of East Asian origin—risk factors for thromboembolism

INTERACTIONS ▶ Appendix 1 (eltrombopag).

SIDE-EFFECTS
- Common or very common Abdominal pain, alopecia, arthralgia, bone pain, cataract, constipation, diarrhoea, dry eye, fatigue, gastro-intestinal disturbances, headache, insomnia, myalgia, nausea, paraesthesia, peripheral oedema, pruritus, rash
- Uncommon Acute myocardial infarction, anaemia, anorexia, anxiety, blood disorders, changes in appetite, cholesterol, cough, deep vein thrombosis, depression, dizziness, dry mouth, ecchymosis, eosinophilia, epistaxis, eye disorders, flushing, gingival bleeding, gout, haemolysis, haemorrhoids, hemiparesis, hepatitis, hypertension, migraine, mood changes, myelocytosis, nocturia, palpitation, peripheral neuropathy, pulmonary embolism, QT-interval prolongation, rectosigmoid cancer, renal failure, respiratory infections, skin reactions, sleep disorders, sweating, tachycardia, taste disturbances, thromboembolic events, tremor, urinary tract infections, vertigo, weight gain

CONCEPTION AND CONTRACEPTION
Ensure effective contraception during treatment.

PREGNANCY
Avoid—toxicity in animal studies.

BREAST FEEDING
Manufacturer advises avoid.
Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura

PATIENT AND CARER ADVICE
- Regular ophthalmological examinations for cataract
- Monitor liver function before treatment, every two weeks

RENAL IMPAIRMENT
- Use with caution.

HEPATIC IMPAIRMENT
- Monitor full blood count and peripheral blood smears for ecchymosis before and during treatment.
- Initially, dose adjustment, then monthly thereafter.

DIRECTIONS FOR ADMINISTRATION
- Each dose should be taken at least 4 hours before or after any dairy products (or foods containing calcium), indigestion remedies, or medicines containing aluminium, calcium, iron, magnesium, zinc, or selenium to reduce possible interference with absorption.

PATIENT AND CARER ADVICE
- Patient counselling is advised on how to administer eltrombopag tablets.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (July 2013) NICE TA293
  - Eltrombopag is recommended for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in splenectomised adults refractory to other treatments, or as a second-line treatment in non-splenectomised adults when surgery is contra-indicated, only if:
    - the manufacturer provides eltrombopag at the agreed discount as part of the patient access scheme and
    - their condition is refractory to standard active treatments and rescue therapies or
    - they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.
  - Patients currently receiving eltrombopag whose disease does not meet these criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA293

Scottish Medicines Consortium (SMC) Decisions
- The Scottish Medicines Consortium has advised (July 2010) that eltrombopag (Revolade®) is accepted for restricted use within NHS Scotland for the treatment of both splenectomised and non-splenectomised patients with severe symptomatic immune (idiopathic) thrombocytopenic purpura or a high risk of bleeding.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - Revolade (Novartis Pharmaceuticals UK Ltd)
      - Eltrombopag (as Eltrombopag olamine) 25 mg Revolade 25mg tablets | 28 tablet (POM) £770.00
      - Eltrombopag (as Eltrombopag olamine) 50 mg Revolade 50mg tablets | 28 tablet (POM) £1,540.00

INDICATIONS AND DOSE
- Treatment of chronic immune thrombocytopenic purpura in splenectomised patients refractory to other treatments (such as corticosteroids or immunoglobulins) (under expert supervision)
- Second-line treatment of chronic idiopathic thrombocytopenic purpura in non-splenectomised patients when surgery is contra-indicated (under expert supervision)
  - By subcutaneous injection
    - Adult: Initially 1 microgram/kg once weekly, adjusted in steps of 1 microgram/kg once weekly (max. per dose 10 micrograms/kg once weekly) until a stable platelet count of 50x10^9/litre or more is reached, discontinue treatment if inadequate response after 4 weeks at maximum dose, consult product literature for dose adjustments

SIDE-EFFECTS
- Arthralgia, asthenia, bone pain, dizziness, ecchymosis, fatigue, flushing, gastro-intestinal disturbances, increased bone marrow reticulin, influenza-like symptoms, injection site reactions, insomnia, migraine, muscle spasm, myalgia, oedema, paraesthesia, rash

PREGNANCY
- Manufacturer advises use only if essential—tocolic in animal studies.

BREAST FEEDING
- Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT
- Avoid in moderate or severe impairment unless potential benefit outweighs risk (e.g. of portal vein thrombosis).

RENAL IMPAIRMENT
- Manufacturer advises caution—no information available.

DIRECTIONS FOR ADMINISTRATION
- Monitor full blood count and peripheral blood smears for ecchymosis and platelet count before and after treatment.
- Initially, dose adjustment, then monthly thereafter.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (April 2011) NICE TA221
  - Romiplostim is recommended for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adults:
    - If the manufacturer provides romiplostim at the agreed discount as part of the patient access scheme and
    - whose condition is refractory to standard active treatments and rescue therapies or
    - who have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.
  - www.nice.org.uk/TA221

Scottish Medicines Consortium (SMC) Decisions
- The Scottish Medicines Consortium has advised (September 2009) that romiplostim (Nplate®) is accepted for restricted use within NHS Scotland for patients with severe symptomatic idiopathic thrombocytopenic purpura or those at high risk of bleeding.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
- Nplate (Amgen Ltd)
  - Romiplostim 250 microgram Nplate 250microgram powder and solvent for solution for injection pre-filled disposable devices | 1 pre-filled disposable injection (POM) £482.00
Nutrition and metabolic disorders

1 Fluid and electrolyte imbalances

Fluids and electrolytes

Electrolyte replacement therapy

The electrolyte concentrations (intravenous fluid) table and the electrolyte content (gastro-intestinal secretions) table may be helpful in planning replacement electrolyte therapy; faeces, vomit, or aspiration should be saved and analysed where possible if abnormal losses are suspected.

Oral preparations for fluid and electrolyte imbalance

Sodium and potassium salts, may be given by mouth to compensate for potassium loss is especially necessary: mild or moderate degree.

Oral potassium

Compensation for potassium loss is especially necessary:

- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmias;
- in patients in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, cirrhosis of the liver, the nephrotic syndrome, and severe heart failure;
- in patients with excessive losses of potassium in the faeces, e.g. chronic diarrhoea associated with intestinal malabsorption or laxative abuse.

Measures to compensate for potassium loss may also be required in the elderly since they frequently take inadequate amounts of potassium in the diet (but see warning on renal insufficiency). Measures may also be required during long-term administration of drugs known to induce potassium loss (e.g. corticosteroids). Potassium supplements are seldom required with the small doses of diuretics given to treat hypertension; potassium-sparing diuretics (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as furosemide p. 216 or the thiazides when these are given to eliminate oedema.

If potassium salts are used for the prevention of hypokalaemia, then doses of potassium chloride daily (in divided doses) by mouth are suitable in patients taking a normal diet. Smaller doses must be used if there is renal insufficiency (common in the elderly) to reduce the risk of hyperkalaemia.

Potassium salts cause nausea and vomiting and poor compliance is a major limitation to their effectiveness; when appropriate, potassium-sparing diuretics are preferable.

When there is established potassium depletion larger doses may be necessary, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma-potassium concentration and specialist advice would be required). Potassium depletion is frequently associated with chloride depletion and with metabolic alkalosis, and these disorders require correction.

Management of hyperkalaemia

Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/litre or in the presence of ECG changes) calls for urgent treatment with calcium gluconate 10% p. 920 by slow intravenous injection, titrated and adjusted to ECG improvement, to temporarily protect against myocardial excitability. An intravenous injection of soluble insulin (5–10 units) with 50 mL glucose 50% p. 915 given over 5–15 minutes, reduces serum-potassium concentration; this is repeated if necessary or a continuous infusion instituted. Salbutamol p. 239 [unlicensed indication], by nebulisation or slow intravenous injection may also reduce plasma-potassium concentration; it should be used with caution in patients with cardiovascular disease. The correction of causal or complicating acidosis with sodium bicarbonate infusion p. 910 should be considered (important: preparations of sodium bicarbonate and calcium salts should not be administered in the same line—risk of precipitation). Drugs exacerbating hyperkalaemia should be reviewed and stopped as appropriate; occasionally haemodialysis is needed.

Ion-exchange resins may be used to remove excess potassium in mild hyperkalaemia or in moderate hyperkalaemia when there are no ECG changes.

Oral sodium and water

Sodium chloride p. 914 is indicated in states of sodium depletion and usually needs to be given intravenously. In chronic conditions associated with mild or moderate degrees of sodium depletion, e.g. in salt-losing bowel or renal disease, oral supplements of sodium chloride or sodium bicarbonate, according to the acid-base status of the patient, may be sufficient.

Oral rehydration therapy (ORT)

As a worldwide problem diarrhoea is by far the most important indication for fluid and electrolyte replacement. Intestinal absorption of sodium and water is enhanced by glucose (and other carbohydrates). Replacement of fluid and electrolytes lost through diarrhoea can therefore be achieved by giving solutions containing sodium, potassium, and glucose or another carbohydrate such as rice starch.

Oral rehydration solutions should:

- enhance the absorption of water and electrolytes;
- replace the electrolyte deficit adequately and safely;
- contain an alkalinising agent to counter acidosis;
- be slightly hypo-osmolar (about 250 mmol/litre) to prevent the possible induction of osmotic diarrhoea;
- be simple to use in hospital and at home;
- be palatable and acceptable, especially to children;
- be readily available.

It is the policy of the World Health Organization (WHO) to promote a single oral rehydration solution but to use it flexibly (e.g. by giving extra water between drinks of oral rehydration solution to moderately dehydrated infants).

The WHO oral rehydration salts formulation contains sodium chloride 2.6 g, potassium chloride 1.5 g, sodium citrate 2.9 g, anhydrous glucose 13.5 g. It is dissolved in sufficient water to produce 1 litre (providing Na+ 75 mmol, K+ 20 mmol, Cl− 65 mmol, citrate 10 mmol, glucose 75 mmol/litre). This formulation is recommended by the WHO and the United Nations Children’s fund, but it is not commonly used in the UK.

Oral rehydration solutions used in the UK are lower in sodium (50–60 mmol/litre) than the WHO formulation since, in general, patients suffer less severe sodium loss.

Rehydration should be rapid over 3 to 4 hours (except in hypernatraemic dehydration in which case rehydration should occur more slowly over 12 hours). The patient should be reassessed after initial rehydration and if still dehydrated rapid fluid replacement should continue.

Once rehydration is complete, beta-blockade for prevention of myocardial deactivation is prevented by encouraging the patient to drink normal volumes of an appropriate fluid and by replacing continuing losses with an oral rehydration solution; in infants, breastfeeding or formula feeds should be offered between oral rehydration drinks.
Oral bicarbonate
Sodium bicarbonate is given by mouth for chronic acidotic states such as uraemic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For severe metabolic acidosis, sodium bicarbonate can be given intravenously.

Sodium bicarbonate may also be used to increase the pH of the urine; it is also used in dyspepsia.

Sodium bicarbonate supplements may increase blood pressure or cause fluid retention and pulmonary oedema in those at risk; hypokalaemia may be exacerbated. Where hyperchloremic acidosis is associated with potassium deficiency, as in some renal tubular and gastrointestinal disorders it may be appropriate to give oral potassium bicarbonate, although acute or severe deficiency should be managed by intravenous therapy.

Parenteral preparations for fluid and electrolyte imbalance
Electrolytes and water
Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated or vomiting and is unable to take adequate amounts by mouth. When intravenous administration is not possible, fluid (as sodium chloride 0.9% p. 914 or glucose 5% p. 915) can also be given by subcutaneous infusion (hypodermoclysis).

The nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical investigations. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance.

Isotonic solutions may be infused safely into a peripheral vein. Solutions more concentrated than plasma, e.g. 20% glucose, are best given through an indwelling catheter positioned in a large vein.

Intravenous sodium
Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentrations and is indicated in sodium depletion, which can arise from conditions associated with metabolic acidosis, diabetic ketoacidosis, ileus, and ascites. In a severe deficit of 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 hours; thereafter the infusion can usually be at a slower rate.

Chronic hyponatraemia arising from inappropriate secretion of antidiuretic hormone should ideally be corrected by fluid restriction. However, if sodium chloride is required for acute or chronic hyponatraemia, regardless of the cause, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome and the rise in plasma-sodium concentration should not exceed 10 mmol/litre in 24 hours. In severe hyponatraemia, sodium chloride 1.8% may be used cautiously.

Compound sodium lactate (Hartmann’s solution) can be used instead of isotonic sodium chloride solution during or after surgery, or in the initial management of the injured or wounded; it may reduce the risk of hyperchloremic acidosis.

Sodium chloride with glucose solutions p. 915 are indicated when there is combined water and sodium depletion. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na⁺ remains extracellular.

Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

Intravenous glucose
Glucose solutions (5%) are used mainly to replace water deficit. Average water requirements in a healthy adult are 1.5 to 2.5 litres daily and this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake, as may occur in coma or dysphagia or in the elderly or apathetic who may not drink enough water on their own initiative.

Excessive loss of water without loss of electrolytes is uncommon, occurring in fevers, hyperthyroidism, and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia. The volume of glucose solution needed to replace deficits varies with the severity of the disorder, but usually lies within the range of 2 to 6 litres.

Glucose solutions are also used to correct and prevent hypoglycaemia and to provide a source of energy in those too ill to be fed adequately by mouth; glucose solutions are a key component of parenteral nutrition.

Glucose solutions are given in regimens with calcium and insulin for the emergency management of hyperkalaemia. They are also given, after correction of hypoglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuing insulin infusion.

Intravenous potassium
Potassium chloride with sodium chloride intravenous infusion p. 913 is the initial treatment for the correction of severe hypokalaemia and when sufficient potassium cannot be taken by mouth.

Repeated measurement of plasma-potassium concentration is necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia, which is especially likely in renal impairment.

Initial potassium replacement therapy should not involve glucose infusions, because glucose may cause a further decrease in the plasma-potassium concentration.

Bicarbonate and lactate
Sodium bicarbonate p. 910 is used to control severe metabolic acidosis (pH<7.1) particularly that caused by loss of bicarbonate (as in renal tubular acidosis or from excessive gastro-intestinal losses). Severe metabolic acidosis associated with volume depletion should first be managed by appropriate fluid replacement because acidosis usually resolves as tissue and renal perfusion are restored. In more severe metabolic acidosis or when the acidosis remains unresponsive to correction of anoxia or hypovolaemia, sodium bicarbonate (1.26%) can be infused over 3–4 hours with plasma-pH and electrolyte monitoring. In severe shock, for example in cardiac arrest, metabolic acidosis can develop without sodium or volume depletion; in these circumstances sodium bicarbonate is best given as a small volume of hypertonic solution, such as 50 mL of 8.4% solution intravenously.

Sodium lactate intravenous infusion is no longer used in metabolic acidosis because of the risk of producing lactic acidosis, particularly in seriously ill patients with poor tissue perfusion or impaired hepatic function.

For chronic acidotic states, sodium bicarbonate can be given by mouth.

Plasma and plasma substitutes
Plasma and plasma substitutes (‘colloids’) contain large molecules that do not readily leave the intravascular space where they exert osmotic pressure to maintain circulatory volume. Compared to fluids containing electrolytes such as sodium chloride and glucose (‘crystalloids’), a smaller volume of colloid is required to produce the same expansion of blood volume, thereby shifting salt and water from the extravascular space. If resuscitation requires a volume of fluid that exceeds the maximum dose of the colloid then
Blood and nutrition

**Dextran**

Plasma substitutes required. Crystalloids can be given; packed red cells may also be given. Overload than isotonic solutions. Concentrated albumin because of interstitial patients with an intravascular correct plasma-volume de...

**Albumin solution**

They may be given without regard to the recipient factors, blood group antibodies, or plasma cholinesterases; they contain soluble proteins and electrolytes but no clotting...

**Albumin**

Recent evidence does not support the previous view that albumin increases mortality. Hypoalbuminaemic patients (e.g. in hepatic cirrhosis).

**Albumin solution** (m/)

Maintenance of alkaline urine

**Sodium bicarbonate**

Hydroxyethyl starches should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient; they should be used at the lowest effective dose for the first 24 hours of fluid resuscitation.

Flows and electrolyte imbalances

**Electrolyte concentrations**—intravenous fluids

<table>
<thead>
<tr>
<th>Millimoles per litre</th>
<th>H⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>HCO₃⁻</th>
<th>Cl⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal plasma values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Chloride 0.9%</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>Compound Sodium Lactate (Hartmann’s)</td>
<td>131</td>
<td>5</td>
<td>29</td>
<td>111</td>
<td>2</td>
</tr>
<tr>
<td>Sodium Chloride 0.18% and Glucose 4% (Adults only)</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Sodium Chloride 0.45% and Glucose 5% (Children only)</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.15% and Glucose 5% (Children only)</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.15% and Sodium Chloride 0.9% (Children only)</td>
<td>150</td>
<td>20</td>
<td>-</td>
<td>170</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Glucose 5%</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Sodium Chloride 0.9%</td>
<td>150</td>
<td>40</td>
<td>-</td>
<td>190</td>
<td>-</td>
</tr>
<tr>
<td><strong>To correct metabolic acidosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Bicarbonate 1.26%</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>Sodium Bicarbonate 8.4% for cardiac arrest</td>
<td>1000</td>
<td>-</td>
<td>-</td>
<td>1000</td>
<td>-</td>
</tr>
<tr>
<td>Sodium Lactate (m/6)</td>
<td>167</td>
<td>-</td>
<td>-</td>
<td>167</td>
<td>-</td>
</tr>
</tbody>
</table>

**Electrolyte content**—gastro-intestinal secretions

<table>
<thead>
<tr>
<th>Millimoles per litre</th>
<th>H⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>HCO₃⁻</th>
<th>Cl⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>40-60</td>
<td>20-80</td>
<td>5-20</td>
<td>-</td>
<td>100-150</td>
</tr>
<tr>
<td>Biliary</td>
<td>-</td>
<td>120-140</td>
<td>5-15</td>
<td>30-50</td>
<td>80-120</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>-</td>
<td>120-140</td>
<td>5-15</td>
<td>70-110</td>
<td>40-80</td>
</tr>
<tr>
<td>Small bowel</td>
<td>-</td>
<td>120-140</td>
<td>5-15</td>
<td>20-40</td>
<td>90-130</td>
</tr>
</tbody>
</table>

crystalloids can be given; packed red cells may also be required.

Albumin solution p. 920, prepared from whole blood, contain soluble proteins and electrolytes but no clotting factors, blood group antibodies, or plasma cholinesterases; they may be given without regard to the recipient’s blood group.

Albumin is usually used after the acute phase of illness, to correct a plasma-volume deficit; hypoalbuminaemia itself is not an appropriate indication. The use of albumin solution in acute plasma or blood loss may be wasteful; plasma substitutes are more appropriate. Concentrated albumin solution (20%) can be used under specialist supervision in patients with an intravascular fluid deficit and oedema because of interstitial fluid overload, to restore intravascular plasma volume with less exacerbation of the salt and water overload than isotonic solutions. Concentrated albumin solution p. 920 may also be used to obtain a diuresis in hypoalbuminaemic patients (e.g. in hepatic cirrhosis).

Recent evidence does not support the previous view that the use of albumin increases mortality.

**Plasma substitutes**

Dextran, gelatin p. 921, and the hydroxyethyl starch, tetrastarch, are macromolecular substances which are metabolised slowly. Dextran and gelatin may be used at the outset to expand and maintain blood volume in shock arising from conditions such as burns or sepsicaemia; they may also be used as an immediate short-term measure to treat haemorrhage until blood is available. Dextran and gelatin are rarely needed when shock is due to sodium and water depletion because, in these circumstances, the shock responds to water and electrolyte repletion.

**Dextran**

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Fluid and electrolyte imbalances

Chronic acidotic states such as uraemic acidosis or renal tubular acidosis

• BY MOUTH
  • Adult: 4.8 g daily, (57 mmol each of Na⁺ and HCO₃⁻), higher doses may be required and should be adjusted according to response

Severe metabolic acidosis

• BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
  • Adult: Administer an amount appropriate to the body base deficit, to be given by slow intravenous injection of a strong solution (up to 8.4%), or by continuous intravenous infusion of a weaker solution (usually 1.26%)

• CONTRA-INDICATIONS
  • With oral use Salt restricted diet

• CAUTIONS
  • Avoid prolonged use in urinary conditions - cardiac disease - elderly - patients on sodium-restricted diet - respiratory acidosis

• INTERACTIONS
  • Appendix 1 (antacids).

• SIDE-EFFECTS
  • When used for alkalisation of urine Alkalosis on prolonged use - eructation
  • When used for chronic acidotic states such as uraemic acidosis or renal tubular acidosis Fluid retention (in those at risk) - hypokalaemia may be exacerbated - increase blood pressure - pulmonary oedema (in those at risk)
  • When used for maintenance of alkaline urine Fluid retention (in those at risk) - hypokalaemia may be exacerbated - increase blood pressure - pulmonary oedema (in those at risk)
  • When used for relief of discomfort in mild urinary-tract infections Alkalosis on prolonged use - eructation

• PREGNANCY
  • With oral use Use with caution in urinary conditions.

• HEPATIC IMPAIRMENT
  • In patients with fluid retention, avoid large amounts of sodium.

• RENAL IMPAIRMENT
  • With oral use Avoid (except for specialised role in some forms of renal disease).

• MONITORING REQUIREMENTS
  • With intravenous use Plasma-pH and electrolytes should be monitored.

• DIRECTIONS FOR ADMINISTRATION
  • For slow intravenous injection use a small volume of hypertonic solution (such as 50 ml of 8.4%). For continuous intravenous infusion a weaker solution of 1.26% solution can be infused over 3–4 hours.
  • With oral use Sodium bicarbonate may affect the stability or absorption of other drugs if administered at the same time. If possible, allow 1–2 hours before administering other drugs orally.

• PRESCRIBING AND DISPENSING INFORMATION
  • With oral use Sodium bicarbonate 500 mg capsules contain approximately 6 mmol each of Na⁺ and HCO₃⁻; Sodium bicarbonate 600 mg capsules contain approximately 7 mmol each of Na⁺ and HCO₃⁻. Oral solutions of sodium bicarbonate are required occasionally; these are available from ‘special-order’ manufacturers or specialist importing companies; the strength of sodium bicarbonate should be stated on the prescription.
  • With intravenous use Usual strength Sodium bicarbonate 1.26% (12.6 g, 150 mmol each of Na⁺ and HCO₃⁻/litre), various other strengths available.

• PATIENT AND CARER ADVICE
  • Patients or carers should be given advice on the administration of sodium bicarbonate oral medicines.

• MEDICINAL FORMS
  • There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution, solution for injection, liquid

Tablet

• Sodium bicarbonate (Non-proprietary)
  • Sodium bicarbonate 600 mg Sodium bicarbonate 600mg tablets | 100 tablet GSK £25.75 | 100 tablet GSK £125.50

Capsule

• Sodium bicarbonate (Non-proprietary)
  • Sodium bicarbonate 500 mg Sodium bicarbonate 500mg capsules | 56 capsule P £17.56 DT price = £2.22 | 100 capsule P no price available

Oral solution

• Sodium bicarbonate (Non-proprietary)
  • Sodium bicarbonate 84 mg per 1 ml S-Bicarb SF 420mg/5ml (1mmol/ml) oral solution sugar-free | 100 ml £26.25 DT price = £39.80
  • S-Bicarb 420mg/5ml (1mmol/ml) oral solution | 100 ml no price available
  • SodiBic 420mg/5ml (1mmol/ml) oral solution sugar-free | 100 ml £17.71 DT price = £39.80
  • Thamicarb (Thame Laboratories Ltd)
    • Sodium bicarbonate 84 mg per 1 ml Thamicarb 84mg/1ml oral solution sugar-free | 100 ml P £39.80 DT price = £39.80 sugar-free | 500 ml P £199.20 DT price = £199.20

Solution for injection

• Sodium bicarbonate (Non-proprietary)
  • Sodium bicarbonate 84 mg per 1 ml Sodium bicarbonate 8.4% (1mmol/ml) solution for injection 10ml ampoules | 10 ampoule P £77.40
  • Sodium bicarbonate 8.4% (1mmol/ml) solution for injection 250ml bottles | 10 bottle P £65.34
  • Sodium bicarbonate 8.4% (1mmol/ml) solution for injection 100ml bottles | 10 bottle P £62.04

Infusion

• Sodium bicarbonate (Non-proprietary)
  • Sodium bicarbonate 12.6 mg per 1 ml Polyfusor BC sodium bicarbonate 1.26% infusion 500ml bottles | 1 bottle P £9.86 | 12 bottle P no price available
  • Sodium bicarbonate 14 mg per 1 ml Polyfusor B0 sodium bicarbonate 1.4% infusion 500ml bottles | 1 bottle P £9.86 | 12 bottle P no price available
  • Sodium bicarbonate 27.4 mg per 1 ml Polyfusor V sodium bicarbonate 2.74% infusion 500ml bottles | 1 bottle P £9.86 | 12 bottle P no price available
  • Sodium bicarbonate 42 mg per 1 ml Polyfusor BE sodium bicarbonate 4.2% infusion 500ml bottles | 1 bottle P £9.86 | 12 bottle P no price available
  • Sodium bicarbonate 84 mg per 1 ml Polyfusor B sodium bicarbonate 8.4% infusion 200ml bottles | 1 bottle P £9.86 | 12 bottle P no price available

Electrolytes and Minerals

Potassium chloride with calcium chloride and sodium chloride and sodium lactate

(Sodium Lactate Intravenous Infusion, Compound; Compound, Hartmann’s Solution for Injection; Ringer-Lactate Solution for Injection)

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, sodium chloride p. 914, calcium chloride p. 919.

• INDICATIONS AND DOSE
  • For prophylaxis, and replacement therapy, requiring the use of sodium chloride and lactate, with minimal amounts of calcium and potassium
  • BY INTRAVENOUS INFUSION
  • Adult: (consult product literature)
Potassium chloride with calcium chloride dihydrate and sodium chloride

(Ringer’s solution)
The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, sodium chloride p. 914.

**INDICATIONS AND DOSE**

**Electrolyte imbalance**

- Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION**

Ringer’s solution for injection provides the following ions (in mmol/litre), Ca\(^{2+}\) 2.2, K\(^+\) 4, Na\(^+\) 147, Cl\(^-\) 156.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

- **Potassium chloride with calcium chloride dihydrate and sodium chloride (Non-proprietary)**
  
  Potassium chloride 300 microgram per 1 ml, Calcium chloride 320 microgram per 1 ml, Sodium chloride 8.6 mg per 1 ml. Polyfloror C rinsers infusion 500ml bottles | 1 bottle POM £2.95 | 12 bottle POM no price available
  
  Steriflex No.9 rinsers infusion 1litre bags | 1 bag POM £2.22 | 10 bag POM no price available
  
  Steriflex No.9 rinsers infusion 500ml bags | 1 bag POM £1.96 | 15 bag POM no price available

- **Potassium chloride with sodium chloride (Non-proprietary)**
  
  Potassium chloride 3 mg per 1 ml, Glucose anhydrous 50 mg per 1 ml. Polyfloror C rinsers infusion 500ml bottles | 1 bottle POM £2.95 | 12 bottle POM no price available
  
  Steriflex No.9 rinsers infusion 1litre bags | 1 bag POM £2.22 | 10 bag POM no price available
  
  Steriflex No.9 rinsers infusion 500ml bags | 1 bag POM £1.96 | 15 bag POM no price available

- **Potassium chloride with calcium chloride dihydrate and sodium chloride (Proprietary)**
  
  Potassium chloride 3 mg per 1 ml, Glucose anhydrous 50 mg per 1 ml. Polyfloror C rinsers infusion 500ml bottles | 1 bottle POM £2.95 | 12 bottle POM no price available
  
  Steriflex No.10 rinsers infusion 1litre bags | 1 bag POM £2.22 | 10 bag POM no price available
  
  Steriflex No.10 rinsers infusion 500ml bags | 1 bag POM £1.96 | 15 bag POM no price available

- **Potassium chloride with glucose and sodium chloride (Non-proprietary)**
  
  Potassium chloride 3 mg per 1 ml, Glucose anhydrous 50 mg per 1 ml. Polyfloror C rinsers infusion 500ml bottles | 1 bottle POM £2.95 | 12 bottle POM no price available
  
  Steriflex No.10 rinsers infusion 1litre bags | 1 bag POM £2.22 | 10 bag POM no price available
  
  Steriflex No.10 rinsers infusion 500ml bags | 1 bag POM £1.96 | 15 bag POM no price available

**Potassium chloride with glucose**

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, glucose p. 915, sodium chloride p. 914.

**INDICATIONS AND DOSE**

**Electrolyte imbalance**

- Adult: Dosed according to the deficit or daily maintenance requirements

**PRESCRIBING AND DISPENSING INFORMATION**

Potassium chloride 0.3% contains 40 mmol each of K\(^+\) and Cl\(^-\) /litre or 0.15% contains 20 mmol each of K\(^+\) and Cl\(^-\) /litre with 5% of anhydrous glucose.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Infusion**

- **Potassium chloride with glucose (Non-proprietary)**
  
  Potassium chloride 3 mg per 1 ml, Glucose anhydrous 50 mg per 1 ml. Polyfloror C rinsers infusion 500ml bottles | 1 bottle POM £2.95 | 12 bottle POM no price available
  
  Steriflex No.10 rinsers infusion 1litre bags | 1 bag POM £2.22 | 10 bag POM no price available
  
  Steriflex No.10 rinsers infusion 500ml bags | 1 bag POM £1.96 | 15 bag POM no price available

- **Potassium chloride with calcium chloride dihydrate and sodium chloride**

  The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, glucose p. 915, sodium chloride p. 914.
**Potassium chloride with sodium bicarbonate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, sodium chloride p. 914.

**INDICATIONS AND DOSE**

*Electrolyte imbalance*

- **BY INTRAVENOUS INFUSION**
- **Adult:** Depending on the deficit or the daily maintenance requirements (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION**

Potassium chloride 0.15% with sodium chloride 0.9% contains K⁺ 20 mmol, Na⁺ 150 mmol, and Cl⁻ 170 mmol/litre or potassium chloride 0.3% with sodium chloride 0.9% contains K⁺ 40 mmol, Na⁺ 150 mmol, and Cl⁻ 150 mmol/litre.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Infusion**

- **Potassium chloride with glucose and sodium chloride (Non-proprietary)**
  - Sodium chloride 1.8 mg per 1 ml, Potassium chloride 3 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml
  - Infusion 1 litre Viaflo bags | 1 bag (POM) £2.20 | 10 bag (POM) no price available
  - Infusion 0.14 litre Viaflo bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Infusion 0.15 litre Viaflo bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Infusion 0.17 litre Viaflo bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Infusion 0.18 litre Viaflo bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Infusion 0.2 litre Viaflo bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Infusion 0.3 litre Viaflo bags | 1 bag (POM) no price available | 10 bag (POM) no price available

- **Potassium chloride 1.5 mg per 1 ml, Sodium chloride 1.8 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml**
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 1 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 0.14 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 0.15 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 0.17 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 0.18 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 0.2 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Potassium chloride 0.15% (potassium 20mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 0.3 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available

- **Sodium chloride 1.8 mg per 1 ml, Potassium chloride 2 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml**
  - Sodium chloride 0.18% infusion 1 litre bags | 1 bag (POM) £1.67 | 15 bag (POM) no price available
  - Sodium chloride 0.18% infusion 0.14 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Sodium chloride 0.18% infusion 0.15 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Sodium chloride 0.18% infusion 0.17 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Sodium chloride 0.18% infusion 0.18 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Sodium chloride 0.18% infusion 0.2 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available
  - Sodium chloride 0.18% infusion 0.3 litre bags | 1 bag (POM) no price available | 10 bag (POM) no price available

**Potassium chloride with sodium bicarbonate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, sodium chloride p. 914.

**INDICATIONS AND DOSE**

*Potassium depletion*

- **By Mouth**
- **Adult:** Dosed according to the deficit or daily maintenance requirements (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION**

Each Sando-K® tablet contains potassium 470 mg (12 mmol of K⁺) and chloride 285mg (8 mmol of Cl⁻).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Infusion**

- **Potassium bicarbonate 400 mg, Potassium chloride 600 mg**
  - Sando-K effervescent tablets | 100 tablet (P) £7.65 at price + £7.65

**Potassium chloride with sodium chloride**

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 929, sodium chloride p. 914.
Potassium chloride 0.15% (potassium 20mmol/1 litre) / Sodium chloride 0.9% infusion 1 litre Viaflo bags | 1 bag (Pom) no price available | 10 bag (Pom) no price available
Potassium chloride 0.15% (potassium 20mmol/1 litre) / Sodium chloride 0.9% infusion 1 litre Macoflex bags | 1 bag (Pom) no price available | 12 bag (Pom) no price available
Potassium chloride 2 mg per 1 ml, Sodium chloride 9 mg per 1 ml Steriflex No.28 potassium chloride 0.2% (potassium 13.3mmol/500ml) / sodium chloride 0.9% infusion 500ml bags | 1 bag (Pom) £1.67 | 15 bag (Pom) no price available
Steriflex No.28 potassium chloride 0.2% (potassium 27mmol/1 litre) / sodium chloride 0.9% infusion 1 litre bags | 1 bag (Pom) £2.20 | 10 bag (Pom) no price available

**ELECTROLYTES AND MINERALS > SODIUM CHLORIDE**

**Sodium chloride**

- **INDICATIONS AND DOSE**
  - **Prophylaxis of sodium chloride deficiency**
    - **BY MOUTH**
      - Adult: 4–8 tablets daily, to be taken with water, up to maximum 20 tablets daily in severe depletion

- **Chronic renal salt wasting**
  - **BY MOUTH**
    - Adult: Up to 20 tablets daily, to be taken with appropriate fluid intake

- **Management of diabetic ketoacidosis (to restore circulating volume if systolic blood pressure is below 90 mmHg and adjusted for age, sex, and medication as appropriate)**
  - **BY INTRAVENOUS INFUSION**
    - Adult: 500 ml, sodium chloride 0.9% to be given over 10–15 minutes, repeat if blood pressure remains below 90 mmHg and seek senior medical advice, when blood pressure is over 90 mmHg, sodium chloride 0.9% should be given by intravenous infusion at a rate that replaces deficit and provides maintenance, management regimen also includes administration of potassium chloride, soluble insulin, long acting insulin analogues and glucose 10% solution

- **Diluent for instillation of drugs to the bladder**
  - **BY INTRAVESICAL INSTILLATION**
    - Adult: (consult product literature)

- **CAUTIONS**
  - With intravenous use Avoid excessive administration - cardiac failure - dilutional hyponaatraemia especially in the elderly - hypertension - peripheral oedema - pulmonary oedema - restrict intake in impaired renal function - toxaemia of pregnancy

- **SIDE-EFFECTS**
  - With intravenous use Administration of large doses may give rise to sodium accumulation - hyperchloraemic acidosis - oedema

- **MONITORING REQUIREMENTS**
  - With intravenous use The jugular venous pressure should be assessed, the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - With intravenous use Sodium chloride 0.9% intravenous infusion contains Na+ and Cl− each 150 mmol/litre. The term ‘normal saline’ should not be used to describe sodium chloride intravenous infusion 0.9%; the term ‘physiological saline’ is acceptable but it is preferable to give the composition (i.e. sodium chloride intravenous infusion 0.9%).

- With oral use Each Slow Sodium® tablet contains approximately 10 mmol each of Na+ and Cl−; tablets can be crushed before administration.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, solution for injection, infusion, solution for infusion, irrigation

- **Modified-release tablet**

- **Slow Sodium (HK Pharma Ltd)**

- **Sodium chloride 600 mg Slow Sodium 600mg tablets | 100 tablet GSP £6.05 DT price = £6.05**

- **Solution for injection**

- **Sodium chloride (Non-proprietary)**

- **Sodium chloride 9 mg per 1 ml Sodium chloride 0.9% solution for injection 5ml Sure-Amp ampoules | 20 ampoule (Pom) £7.15**

- **Sodium chloride 0.9% solution for injection 50ml vials | 1 vial (Pom) £3.41 DT price = £3.41 | 25 vial (Pom) £85.00**

- **Sodium chloride 0.9% solution for injection 10ml ampoules | 10 ampoule (Pom) £2.96–£3.26 DT price = £2.96 | 50 ampoule (Pom) £14.75**

- **Sodium chloride 0.9% solution for injection 20ml Mini-Plasco ampoules | 20 ampoule (Pom) £18.93**

- **Sodium chloride 0.9% solution for injection 5ml Mini-Plasco ampoules | 20 ampoule (Pom) £8.96**

- **Sodium chloride 0.9% solution for injection 2ml Sure-Amp ampoules | 20 ampoule (Pom) £1.75**

- **Sodium chloride 0.9% solution for injection 20ml ampoules | 20 ampoule (Pom) £15.75**

- **Sodium chloride 0.9% solution for injection 5ml ampoules | 10 ampoule (Pom) £2.11–£2.32 DT price = £2.11 | 50 ampoule (Pom) £10.50**

- **Sodium chloride 0.9% solution for injection 10ml Sure-Amp ampoules | 20 ampoule (Pom) £8.15**

- **Sodium chloride 0.9% solution for injection 10ml Mini-Plasco ampoules | 20 ampoule (Pom) £10.21**

- **Sodium chloride 300 mg per 1 ml Sodium chloride 30% solution for injection 10ml ampoules | 10 ampoule (Pom) £67.46–£71.45 DT price = £69.46**

- **Sodium chloride 30% solution for injection 50ml vials | 1 vial (Pom) £12.09**

- **Drytec saline (GE Healthcare Biosciences)**

- **Sodium chloride 9 mg per 1 ml Drytec saline eluent 5ml vials | 20 vial (Pom) no price available (Hospital only) | 100 vial (Pom) no price available (Hospital only)**

- **Drytec saline eluent 10ml vials | 20 vial (Pom) no price available (Hospital only) | 100 vial (Pom) no price available (Hospital only)**

- **Infusion**

- **Sodium chloride (Non-proprietary)**

- **Sodium chloride 1.8 mg per 1 ml Polyfuisor 0 sodium chloride 0.18% infusion 500ml bottles | 1 bottle (Pom) £3.44 | 12 bottle (Pom) no price available**

- **Sodium chloride 4.5 mg per 1 ml Sodium chloride 0.45% infusion 500ml Viaflo bags | 1 bag (Pom) no price available | 20 bag (Pom) no price available**

- **Polyfuisor SB sodium chloride 0.45% infusion 500ml bottles | 1 bottle (Pom) £3.44 | 12 bottle (Pom) no price available**

- **Sodium chloride 0.45% infusion 500ml Viaflex bags | 1 bag (Pom) no price available | 20 bag (Pom) no price available**

- **Steriflex No.2 sodium chloride 0.45% infusion 500ml bags | 1 bag (Pom) £1.38 | 15 bag (Pom) no price available**

- **Sodium chloride 9 mg per 1 ml Sodium chloride 0.9% infusion 100ml bags | 1 bag (Pom) £1.27**

- **Sodium chloride 0.9% infusion 250ml Macoflex N bags | 1 bag (Pom) no price available | 30 bag (Pom) no price available**

- **Sodium chloride 0.9% infusion 1 litre Macoflex N bags | 1 bag (Pom) no price available | 10 bag (Pom) no price available**

- **Sodium chloride 0.9% infusion 100ml Viaflo bags | 1 bag (Pom) no price available | 50 bag (Pom) no price available**

- **Sodium chloride 0.9% infusion 50ml Viaflex bags | 1 bag (Pom) no price available**

- **Intravenous sodium chloride 0.9% infusion 2litre bags | 1 bag (Pom) £3.01**
Potassium chloride with calcium chloride dihydrate and sodium chloride, p. 912 - Potassium chloride with glucose and sodium chloride, p. 912 - Potassium chloride with sodium chloride, p. 913

Sodium chloride with glucose

The properties listed below are those particular to the combination only. For the properties of the components please consider, sodium chloride p. 914, glucose below.

- **INDICATIONS AND DOSE**
  - Combined water and sodium depletion
  - By intravenous infusion
  - Adult: (consult product literature)

- **MONITORING REQUIREMENTS**
  - Maintenance fluid should accurately reflect daily requirements and close monitoring is required to avoid fluid and electrolyte imbalance.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

  - Sodium chloride with glucose (Non-proprietary)
    - Sodium chloride 4.5 mg per 1 ml, Glucose anhydrous 25 mg per 1 ml
    - Sodium chloride 4.5% / Glucose 2.5% infusion 500ml Viaflex bags | 1 bag (Pom) no price available | 20 bag (Pom) no price available
    - Sodium chloride 4.5% / Glucose 2.5% infusion 500ml Viaflo bags | 1 bag (Pom) no price available | 20 bag (Pom) no price available
    - Sodium chloride 1.8 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml
      - Polyfusor T glucose 4% / sodium chloride 0.18% infusion 500ml bottles | 1 bottle (Pom) £2.40 | 12 bottle (Pom) no price available
      - Polyfusor T glucose 4% / sodium chloride 0.18% infusion 500ml Viaflex bags | 1 bag (Pom) no price available | 12 bag (Pom) no price available
      - Sodium chloride 0.18% / Glucose 4% infusion 500ml Macoflex bags | 1 bag (Pom) no price available | 12 bag (Pom) no price available
      - Sodium chloride 0.18% / Glucose 4% infusion 500ml Viaflex bags | 1 bag (Pom) no price available | 12 bag (Pom) no price available
    - Sodium chloride 4.5 mg per 1 ml, Glucose anhydrous 50 mg per 1 ml
      - Sodium chloride 4.5% / Glucose 5% infusion 500ml Viaflex bags | 1 bag (Pom) no price available | 20 bag (Pom) no price available
      - Sodium chloride 4.5% / Glucose 5% infusion 500ml Viaflo bags | 1 bag (Pom) no price available | 20 bag (Pom) no price available
      - Steriflex No.45 glucose 5% / sodium chloride 0.45% infusion 500ml bags | 1 bag (Pom) £2.02 | 15 bag (Pom) no price available
      - Sodium chloride 1.8 mg per 1 ml, Glucose anhydrous 100 mg per 1 ml
        - Steriflex No.19 glucose 10% / sodium chloride 0.18% infusion 500ml bags | 1 bag (Pom) £2.02 | 15 bag (Pom) no price available

**SUGARS**

Glucose

(Dextrose Monohydrate)

- **INDICATIONS AND DOSE**
  - Establish presence of gestational diabetes
  - By mouth
  - Adult: Test dose 75 g, anhydrous glucose to be given to the fasting patient and blood-glucose concentrations measured at intervals, to be given with 200–300 mL fluid
  - continued

**NUTRIENTS**

Blood and nutrition

Fluid and electrolyte imbalances

Sodium chloride 0.9% infusion 500ml Macoflex bags | 1 bag (Pom) no price available | 18 bag (Pom) no price available
- Sodium chloride 0.9% infusion 500ml Easyflex N bags | 1 bag (Pom) no price available | 1 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 100ml polyethylene bottles | 1 bottle (Pom) £0.55 | 20 bottle (Pom) £11.00
  - Sodium chloride 0.9% infusion 100ml Macoflex N bags | 1 bag (Pom) no price available | 60 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 250ml bags | 2 bag (Pom) £1.33
  - Sodium chloride 0.9% infusion 250ml Viaflex bags | 1 bag (Pom) no price available | 30 bag (Pom) no price available
  - Intraven sodium chloride 0.9% infusion 500ml bags | 1 bag (Pom) £1.61

- Sodium chloride 0.9% infusion 500ml Easyflex bags | 1 bag (Pom) no price available | 18 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 500ml Easyflex bags | 1 bag (Pom) no price available | 1 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 500ml Macoflex N bags | 1 bag (Pom) no price available | 70 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 500ml Macoflex N bags | 1 bag (Pom) no price available | 50 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 500ml Macoflex N bags | 1 bag (Pom) no price available | 10 bag (Pom) no price available
  - Intraven sodium chloride 0.9% infusion 500ml bags | 1 bag (Pom) £1.61

- Sodium chloride 0.9% infusion 100ml Easyflex bags | 1 bag (Pom) no price available | 1 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 100ml Easyflex bags | 1 bag (Pom) no price available | 1 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 100ml Easyflex N bags | 1 bag (Pom) no price available | 30 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 100ml Easyflex N bags | 1 bag (Pom) no price available | 1 bag (Pom) no price available
  - Intraven sodium chloride 0.9% infusion 250ml bags | 1 bag (Pom) £1.49

- Sodium chloride 0.9% infusion 1 litre bags | 1 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 1 litre bags | 1 bag (Pom) no price available | 10 bag (Pom) no price available
  - Intraven sodium chloride 0.9% infusion 100ml bags | 1 bag (Pom) £1.49

- Polyfusor S sodium chloride 0.9% infusion 500ml bottles | 1 bottle (Pom) £2.33 | 12 bottle (Pom) no price available
  - Polyfusor S sodium chloride 0.9% infusion 100ml Easyflex bags | 1 bag (Pom) no price available | 1 bag (Pom) no price available
  - Sodium chloride 0.9% infusion 250ml Easyflex N bags | 1 bag (Pom) no price available | 30 bag (Pom) no price available
  - Intraven sodium chloride 0.9% infusion 1 litre bags | 1 bag (Pom) £2.33

- Polyfusor S sodium chloride 0.9% infusion 1 litre bags | 1 bottle (Pom) £3.10 | 6 bottle (Pom) no price available
  - Sodium chloride 0.9% infusion 100ml Macoflex bags | 1 bag (Pom) no price available | 60 bag (Pom) no price available
  - Sodium chloride 18 mg per 1 ml Polyfusor S sodium chloride 1.8% infusion 500ml bottles | 1 bottle (Pom) £3.44 | 12 bottle (Pom) no price available
  - Sodium chloride 27 mg per 1 ml Polyfusor S sodium chloride 2.7% infusion 500ml bottles | 1 bottle (Pom) £3.44 | 12 bottle (Pom) no price available
  - Sodium chloride 50 mg per 1 ml Polyfusor S sodium chloride 5% infusion 500ml bottles | 1 bottle (Pom) £3.44 | 12 bottle (Pom) no price available

**Solution for infusion**

- **Sodium chloride (Non-proprietary)**
  - Sodium chloride 300 mg per 1 ml Sodium chloride 30% concentrate for solution for infusion 100ml vials | 10 vial (Pom) £44.20
  - Sodium chloride 30% concentrate for solution for infusion 50ml vials | 10 vial (Pom) £27.70
  - Sodium chloride 30% concentrate for solution for infusion 10ml ampoules | 10 ampoule (Pom) £16.40

- **Intravascular solution**
  - **Sodium chloride (Non-proprietary)**
    - Sodium chloride 9 mg per 1 ml Sodium chloride 0.9% intravascular solution 50ml bags | 1 bag (Pom) £5.00

**Combinations available:** 
- Potassium chloride with calcium chloride and sodium chloride and sodium lactate, p. 911.
Oral glucose tolerance test
▶ BY MOUTH
▶ Adult: Test dose 75 g, anhydrous glucose to be given to the fasting patient and blood-glucose concentrations measured at intervals, to be given with 200–300 mL fluid

Hypoglycaemia
▶ BY INTRAVENOUS INFUSION
▶ Child: 500 mg/kg, to be administered as Glucose 10% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs
▶ Adult: 10 g, to be administered as Glucose 20% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs

Energy source
▶ BY INTRAVENOUS INFUSION
▶ Adult: 1–3 litres daily, solution concentration of 20–50% to be administered

Water replacement
▶ BY INTRAVENOUS INFUSION
▶ Adult: The volume of glucose solution needed to replace deficits may vary (consult product literature)

Persistent cyanosis (in combination with propranolol) when blood glucose less than 3 mmol/litre (followed by morphine)
▶ BY INTRAVENOUS INFUSION
▶ Child: 200 mg/kg, to be administered as Glucose 10% intravenous infusion over 10 minutes

Management of diabetic ketoacidosis
▶ BY INTRAVENOUS INFUSION
▶ Child: Glucose 5% or 10% should be added to replacement fluid once blood-glucose concentration falls below 14 mmol/litre
▶ Adult: Glucose 10% should be given once blood-glucose concentration falls below 14 mmol/litre, to be administered into a large vein through a large-gauge needle at a rate of 125 mL/hour, in addition to the sodium chloride 0.9% infusion

DOSE EQUIVALENCE AND CONVERSION
▶ 75 g anhydrous glucose is equivalent to Glucose BP 82.5 g.

● CAUTIONS Do not give alone except when there is no significant loss of electrolytes · prolonged administration of glucose solutions without electrolytes can lead to hyponatraemia and other electrolyte disturbances
● SIDE-EFFECTS Glucose injections especially if hypertonic may have a low pH and may cause venous irritation and thrombophlebitis
● DIRECTIONS FOR ADMINISTRATION
▶ With intravenous use in children: Injections containing more than 10% glucose can be irritant and should be given into a central venous line; however, solutions containing up to 12.5% can be administered for a short period into a peripheral line.

● PRESCRIBING AND DISPENSING INFORMATION Glucose BP is the monohydrate but Glucose Intravenous Infusion BP is a sterile solution of anhydrous glucose or glucose monohydrate, potency being expressed in terms of anhydrous glucose.
● EXCEPTIONS TO LEGAL CATEGORY
▶ With intravenous use: Prescription only medicine restriction does not apply to 50% solution where administration is for saving life in emergency.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

Oral solution
▶ Rapilose OGTT (Aspire Pharma Ltd)
Glucose 250 mg per 1 ml Rapilose OGTT solution | 300 ml £3.48

Oral gel
▶ Glucose (Non-proprietary)
Glucose 400 mg per 1 gram YourGLUCO 40% gel | 75 gram £5.00 DT price = £7.16
▶ DextroGel (Neonetics Ltds)
Glucose 400 mg per 1 gram DextroGel 40% gel | 75 gram £7.16 DT price = £7.16 | 80 gram £6.84
▶ GlucoBoost (Ennogen Healthcare Ltd)
Glucose 400 mg per 1 gram GlucoBoost 40% gel | 75 gram £7.16 DT price = £7.16 | 80 gram £6.84
▶ GlucoGel (BBI Healthcare Ltd)
Glucose 400 mg per 1 gram GlucoGel 40% gel original | 75 gram £7.16 DT price = £7.16 | 80 gram £6.84
▶ Rapilose (Galen Ltd)
Glucose 400 mg per 1 gram Rapilose gel 40% gel | 75 gram £5.49 DT price = £7.16

Infusion
▶ Glucose (Non-proprietary)
Glucose anhydrous 50 mg per 1 ml Glucose 5% infusion 1 litre
Macoflex bags | 1 bag POM no price available | 12 bag POM no price available
Glucose 5% infusion 500ml bags | 1 bag POM no price available | 12 bag POM no price available
Glucose 5% infusion 500ml Macoflex N bags | 1 bag POM no price available | 18 bag POM no price available
Glucose 5% infusion 100ml bags | 1 bag POM no price available | 18 bag POM no price available
Glucose 5% infusion 1litre Easyflex N bags | 1 bag POM no price available | 10 bag POM no price available
Glucose 5% infusion 100ml Easyflex N bags | 1 bag POM no price available | 10 bag POM no price available
Glucose 5% infusion 500ml Easyflex N bags | 1 bag POM no price available | 60 bag POM no price available
Glucose 5% infusion 500ml Vialflo bags | 1 bag POM no price available | 20 bag POM no price available
Glucose 5% infusion 100ml Macoflex N bags | 1 bag POM no price available | 60 bag POM no price available
Glucose 5% infusion 500ml Vialflex bags | 1 bag POM no price available | 20 bag POM no price available
Glucose 5% infusion 250ml Macoflex N bags | 1 bag POM no price available | 30 bag POM no price available
Glucose 5% infusion 500ml Macoflex bags | 1 bag POM no price available | 30 bag POM no price available
Polyfusor D glucose 5% infusion 3 litre bottles | 1 bottle POM £3.02
Polyfusor D glucose 5% infusion 1 litre bottles | 1 bottle POM £3.02

Fluid and electrolyte imbalances

DOSE EQUIVALENCE AND CONVERSION
▶ 5 g anhydrous glucose is equivalent to Glucose BP 18.25 g.

Macoflex bags
Easyflex N bags
Macoflex N bags
Viaflex bags
Easyflex N bags
Macoflex bags
Viaflo bags
Macoflex N bags
Viaflex bags

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¢ 500 gram £
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Fluid and electrolyte loss in diarrhoea

**INDICATIONS AND DOSE**

**BY MOUTH**

- Child 1–11 months: 1–1½ times usual feed volume to be given
- Child 1–11 years: 200 mL, to be given after every loose motion
- Child 12–17 years: 200–400 mL, to be given after every loose motion, dose according to fluid loss
- Adult: 200–400 mL, to be given after every loose motion, dose according to fluid loss

**DIRECTIONS FOR ADMINISTRATION** Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na⁺ 60 mmol, K⁺ 20 mmol, Cl⁻ 60 mmol, citrate 10 mmol, and glucose 90 mmol.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral powder formulations may include black currant, citrus, or natural.

**PATIENT AND CARER ADVICE**

- After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

Medicines for Children leaflet: Oral rehydration salts  
www.medicinesforchildren.org.uk/oral-rehydration-salts

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**Potassium chloride with rice powder, sodium chloride and sodium citrate**  
(Formulated as oral rehydration salts)

**INDICATIONS AND DOSE**

**Fluid and electrolyte loss in diarrhoea**

**BY MOUTH**

- Adult: 200–400 mL, to be given after every loose motion, dose according to fluid loss

**DIRECTIONS FOR ADMINISTRATION** Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na⁺ 60 mmol, K⁺ 20 mmol, Cl⁻ 60 mmol and citrate 10 mmol.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral powder formulations may include apricot, black currant, or raspberry.

**PATIENT AND CARER ADVICE**

- Patients and carers should be advised how to reconstitute Dioralyte® Relief oral powder. After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder**

- **Dioralyte** (Sanofi)  
  Disodium hydrogen citrate 530 mg, Glucose 3.56 gram,  
  Potassium chloride 300 mg, Sodium chloride 470 mg  
  Dioralyte oral powder sachets citrus | 20 sachet (£6.72)  
  Dioralyte oral powder sachets plain | 20 sachet (£6.72)  
  Dioralyte oral powder sachets blackcurrant | 20 sachet (£6.72)

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**1.1 Calcium imbalance**

**Calcium**

Calcium supplements

Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy, and lactation, due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended amount reduces the rate of bone loss. If the actual dietary intake is less than the recommended amount, a supplement of as much as 40 mmol is appropriate.

In severe acute hypocalcaemia or hypocalcaemic tetany, an initial slow intravenous injection of calcium gluconate injection 10% p. 920 should be given, with plasma-calcium...
Blood and nutrition

Bendroflumethiazide p. 157. Reducing dietary calcium intake may be beneficial but severe restriction of calcium intake has not proved beneficial and may even be harmful.

Severe hypercalcaemia

Severe hypercalcaemia calls for urgent treatment before detailed investigation of the cause. Dehydration should be corrected first with intravenous infusion of sodium chloride 0.9% p. 914. Drugs (such as thiazides and vitamin D compounds) which promote hypercalcaemia, should be discontinued and dietary calcium should be restricted.

If severe hypercalcaemia persists drugs which inhibit mobilisation of calcium from the skeleton may have to be used. The bisphosphonates are useful and pamidronate disodium p. 665 is probably the most effective.

Corticosteroids are widely given, but may only be useful where hypercalcaemia is due to sarcoidosis or vitamin D intoxication; they often take several days to achieve the desired effect.

Calcitriol (salmon) p. 686 can be used for the treatment of hypercalcaemia associated with malignancy; it is rarely effective where bisphosphonates have failed to reduce serum calcium adequately.

After treatment of severe hypercalcaemia the underlying cause must be established. Further treatment is governed by the same principles as for initial therapy. Salt and water depletion and drugs promoting hypercalcaemia should be avoided; oral administration of a bisphosphonate may be useful.

Hyperparathyroidism

Paricalcitol p. 956 is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure.

Parathyroidectomy may be indicated for hyperparathyroidism.

Hypercalciuria

Hypercalciuria should be investigated for an underlying cause, which should be treated. Where a cause is not identified (idiopathic hypercalciuria), the condition is managed by increasing fluid intake and giving bendroflumethiazide p. 157. Reducing dietary calcium intake may be beneficial but severe restriction of calcium intake has not proved beneficial and may even be harmful.

Cinacalcet

Drug action

Cinacalcet reduces parathyroid hormone which leads to a decrease in serum calcium concentrations.

Indications and dose

Secondary hyperparathyroidism in patients with end-stage renal disease on dialysis
- By mouth
  - Adult: Initially 30 mg once daily, dose to be adjusted every 2–4 weeks; maximum 180 mg per day

Treatment of hypercalcaemia in parathyroid carcinoma

Primary hyperparathyroidism in patients where parathyroidectomy is inappropriate
- By mouth
  - Adult: Initially 30 mg twice daily (max. per dose 90 mg 4 times a day), dose to be adjusted every 2–4 weeks according to response

Dose adjustments due to interactions

Dose adjustment may be necessary if smoking started or stopped during treatment.

Caution

Treatment should not be initiated in patients with hypocalcaemia

Interactions

Appendix 1 (cinacalcet).

Side-effects

- Common or very common
  - Anorexia
  - Asthenia
  - Dizziness
  - Myalgia
  - Nausea
  - Paraesthesia
  - Rash
  - Reduced testosterone concentrations
  - Vomiting
- Uncommon
  - Diarrhoea
  - Dyspepsia
  - Seizures
- Frequency not known
  - Allergic reactions
  - Angioedema
  - Heart failure
  - Hypotension

Pregnancy

Manufacturer advises use only if potential benefit outweighs risk—no information available.

Breast feeding

Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment

Manufacturer advises caution in moderate to severe impairment. Monitor closely in hepatic impairment especially when increasing dose.

Monitoring requirements

- Measure serum-calcium concentration before initiation of treatment and within 1 week after starting treatment or adjusting dose, then monthly for secondary hyperparathyroidism, and every 2–3 months for primary hyperparathyroidism and parathyroid carcinoma.
- In secondary hyperparathyroidism measure parathyroid hormone concentration 1–4 weeks after starting treatment or adjusting dose, then every 1–3 months.

National funding/access decisions

NICE technology appraisals (TAs)

Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy (January 2007) NICE TA117

Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.

Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:
1.1b Hypocalcaemia

ELECTROLYTES AND MINERALS

Calcium salts

CONTRA-INDICATIONS Conditions associated with hypocalcaemia (e.g. some forms of malignant disease) - conditions associated with hypercalciuria (e.g. some forms of malignant disease)

CAUTIONS History of nephrolithiasis • sarcoidosis

INTERACTIONS ▶ Appendix 1 (antacids, calcium salts).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Frequency not known Hypercalcaemia

SPECIFIC SIDE-EFFECTS

With intravenous use Arrhythmias • bradycardia • fall in blood pressure • injection-site reactions • peripheral vasodilatation • severe tissue damage with extravasation • sweating

RENAL IMPAIRMENT Use with caution.

Calcium carbonate

INDICATIONS AND DOSE

Phosphate binding in renal failure and hyperphosphataemia

BY MOUTH

Adult: (consult product literature)

Calcium deficiency

BY MOUTH

Adult: (consult product literature)

PRESCRIBING AND DISPENSING INFORMATION Adcal® contains calcium carbonate 1.5 g (calcium 600 mg or Ca²⁺ 15 mmol); Calcichew® contains calcium carbonate 1.25 g (calcium 500 mg or Ca²⁺ 12.5 mmol); Calcichew Forte® contains calcium carbonate 2.5 g (calcium 1 g or Ca²⁺ 25 mmol); Cacit® contains calcium carbonate 1.25 g, providing calcium citrate when dispersed in water (calcium 500 mg or Ca²⁺ 12.5 mmol); consult product literature for details of other available products.

Calcium chloride

INDICATIONS AND DOSE

Severe acute hypocalcaemia or hypocalcaemic tetany

BY INTRAVENOUS INJECTION

Adult: Dose according to requirements

CAUTIONS Avoid in respiratory acidosis • avoid in respiratory failure

DIRECTIONS FOR ADMINISTRATION Care should be taken to avoid extravasation.

PRESCRIBING AND DISPENSING INFORMATION Non-proprietary Calcium chloride dihydrate 7.35% (calcium...
Blood and nutrition

20 mg or Ca\(^{2+}\) 500 micromol/mL; \textit{Calcium chloride dihydrate} 10\% (calcium 27.3 mg or Ca\(^{2+}\) 680 micromol/mL); \textit{Calcium chloride dihydrate} 14.7\% (calcium 40.1 mg or Ca\(^{2+}\) 1000 micromol/mL).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

**Solution for injection**
- \textit{Calcium chloride (Non-proprietary)}
  - \textit{Calcium chloride dihydrate} 73.5 mg per 1 ml Calcium chloride 7.35\% solution for injection | 10 ml ampoule | £66.38
  - \textit{Calcium chloride dihydrate} 100 mg per 1 ml Calcium chloride 10\% solution for injection | 10 ml ampoule | £95.22
- \textit{Calcium lactate (Non-proprietary)}
  - \textit{Calcium lactate} 147 mg per 1 ml Calcium lactate 14.7\% solution for injection | 10 ml ampoule | £64.69–£68.50

**INDICATIONS AND DOSE**
- **Severe acute hypocalcaemia or hypocalcaemic tetany**
  - \textit{Initially by slow intravenous injection}
  - \textit{Adult:} Initially 10–20 ml, calcium gluconate injection 10\% (providing approximately 2.25–4.5 mmol of calcium) should be administered with plasma-calcium and ECG monitoring, and either repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence, alternatively (by continuous intravenous infusion), initially 50 ml/hour, adjusted according to response, infusion to be administered using 100 ml of calcium gluconate 10\% diluted in 1 litre of glucose 5\% or sodium chloride 0.9\%.
- **Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/litre or in the presence of ECG changes)**
  - \textit{By slow intravenous injection}
  - \textit{Adult:} 10–20 ml, calcium gluconate 10\% should be administered, dose titrated and adjusted to ECG improvement

**Calcium deficiency / Mild asymptomatic hypocalcaemia**
- \textit{By mouth}
- \textit{Adult:} Dose according to requirements

**DOSE EQUIVALENT AND CONVERSION**
- 0.11 mmol/kg is equivalent to 0.5 ml/kg of calcium gluconate 10\%.

**CALCULATING ANTIDOTE DOSAGES**

**CALCULATION**

**METHOD**

1. Calculate the dose of sodium bicarbonate required

2. Divide by 6.5

3. Multiply by 100

4. Subtract from the total sodium bicarbonate required

**EXAMPLE**

**Patient:** 32 kg

**Problem:** Severe acute hypocalcaemia

**Calculation**

- **Total dose of sodium bicarbonate**
  - 10 ml of sodium bicarbonate 8.4% is 84 mmol
  - 32 kg \times 0.11 = 3.54 mmol
  - 84 mmol - 3.54 mmol = 80.46 mmol

**Solution**

- 80.46 mmol divided by 6.5 = 12.36 ml
- 12.36 ml \times 100 = 1236 ml
- 1236 ml - 10 ml = 1226 ml

**Important Safety Information**

The MHRA has advised that repeated or prolonged administration of calcium gluconate injection packaged in 10 ml glass containers is contra-indicated in children under 18 years and in patients with renal impairment owing to the risk of aluminium accumulation; in these patients the use of calcium gluconate injection packaged in plastic containers is recommended.

**MONITORING REQUIREMENTS**
- With intravenous use, Plasma-calcium and ECG monitoring required for administration by slow intravenous injection (risk of arrhythmias if given too rapidly).
- **DIRECTIONS FOR ADMINISTRATION**
- With intravenous use, For continuous intravenous infusion, dilute 100 ml of calcium gluconate 10\% in 1 litre of glucose 5\% or sodium chloride 0.9\% and give at an initial rate of 50 ml/hour adjusted according to response. Avoid bicarbonates, phosphates, or sulfates.

**PRESCRIBING AND DISPENSING INFORMATION**
Calcium gluconate 1 g contains calcium 89 mg or Ca\(^{2+}\) 2.23 mmol.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, solution for injection, solution for infusion

**Effervescent tablet**
- **CAUTIONARY AND ADVISORY LABELS**
- **ELECTROLYTES**: May contain Sodium
- **Calcium gluconate (Non-proprietary)**
  - **Calcium gluconate 1 gram** Calcium gluconate 1g effervescent tablets | 28 tablet [GSL] £15.68 DT price = £15.68

**Solution for injection**
- **Calcium gluconate (Non-proprietary)**
  - Calcium gluconate 100 mg per 1 ml Calcium gluconate 10% solution for injection | 10 ml ampoule | £7.00–£7.50 DT price = £7.25

**Calcium lactate**

**INDICATIONS AND DOSE**
- **Calcium deficiency**
  - \textit{By mouth}
  - \textit{Adult:} Dose according to requirements

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Calcium lactate (Non-proprietary)**
  - Calcium lactate 300 mg Calcium lactate 300mg tablets | 84 tablet no price available DT price = £4.57 | 84 tablet [GSL] £4.57 DT price = £4.57

**Calcium phosphate**

**INDICATIONS AND DOSE**
- **Indications listed in combination monographs (available in the UK only in combination with other drugs)**
  - **By mouth**
  - **Adult:** Doses listed in combination monographs

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
No licensed medicines listed.

1.2 Low blood volume

**BLOOD AND RELATED PRODUCTS** > **PLASMA PRODUCTS**

**Albumin solution**
- **(Human Albumin Solution)**

**INDICATIONS AND DOSE**
- **Acute or sub-acute loss of plasma volume e.g. in burns, pancreatitis, trauma, and complications of surgery (with isotonic solutions)**
- **Severe hypoalbuminaemia associated with low plasma volume and generalised oedema where salt and water restriction with plasma volume expansion are required (with concentrated solutions 20%)**
- **Paracentesis of large volume ascites associated with portal hypertension (with concentrated solutions 20%)**
  - **By intravenous infusion**
  - **Adult:** (consult product literature)**
**CONTRA-INDICATIONS** Cardiac failure • severe anaemia

**CAUTIONS** Correct dehydration when administering concentrated solution • history of cardiac disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function) • history of circulatory disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function) • increased capillary permeability

**SIDE-EFFECTS** Anaphylaxis • chills • fever • hypersensitivity reactions • hypotension • increased salivation • nausea • tachycardia • vomiting

**MONITORING REQUIREMENTS** Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

**PRESCRIBING AND DISPENSING INFORMATION** A solution containing protein derived from plasma, serum, or normal placentas; at least 95% of the protein is albumin. The solution may be isotonic (containing 3.5–5% protein) or concentrated (containing 15–25% protein).

### MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

- **Flexbumin** (Baxalta UK Ltd)
  - Albumin solution human 200 gram per 1 litre Flexbumin 20% infusion 100ml bags | 1 bag £25.50
  - Albumin 5% solution for infusion 250ml bottles | 1 vial £29.90
  - Albumin 5% solution for infusion 500ml bottles | 1 vial £51.00

- **Albunorm** (Octapharma Ltd)
  - Albumin solution human 50 mg per 1 ml Albunorm 5% solution for infusion 250ml bottles | 1 bottle £10.20
  - Albumin solution human 50 mg per 1 ml Albunorm 5% solution for infusion 500ml bottles | 1 bottle £51.00

- **AlbuReX** (CSL Behring UK Ltd)
  - Albumin solution human 50 mg per 1 ml Alburex 5% solution for infusion 500ml vials | 1 vial £42.50
  - Albumin solution human 200 mg per 1 ml Alburex 20% solution for infusion 100ml bottles | 1 bottle £40.80

- **Biotest** (Biotest (UK) Ltd)
  - Albumin solution human 50 mg per 1 ml Human Albumin Biotest 5% solution for infusion 250ml vials | 1 vial no price available
  - Albumin solution human 200 mg per 1 ml Human Albumin Biotest 20% solution for infusion 50ml vials | 1 vial £16.00

- **Grifols** (Grifols UK Ltd)
  - Albumin solution human 50 mg per 1 ml Human albumin Grifols 5% solution for infusion 500ml bottles | 1 bottle £49.50
  - Albumin solution human 50 mg per 1 ml Human albumin Grifols 5% solution for infusion 250ml bottles | 1 bottle £24.75
  - Albumin solution human 50 mg per 1 ml Human albumin Grifols 5% solution for infusion 100ml bottles | 1 bottle £19.90

- **Zenalb** (Bio Products Laboratory Ltd)
  - Albumin solution human 45 mg per 1 ml Zenalb 4.5% solution for infusion 250ml bottles | 1 bottle £26.31
  - Albumin solution human 200 mg per 1 ml Zenalb 20% solution for infusion 100ml bottles | 1 bottle £50.07

**EFFECT ON LABORATORY TESTS** Can interfere with some laboratory tests—dextran may interfere with blood group cross-matching or biochemical measurements, and these should be carried out before infusion is begun.

**PRESCRIBING AND DISPENSING INFORMATION** Dextran 70 is dextran with an average molecular weight of about 70 000.

### MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

- **Dextran 70 with sodium chloride**

- **INDICATIONS AND DOSE**
  - Initial treatment of hypovolaemia with hypotension induced by traumatic injury

  - **BY INTRAVENOUS INFUSION**
    - Adult: 250 mL, to be given over 2–5 minutes using RescueFlow®, followed immediately by administration of isotonic fluids.

- **CAUTIONS** Cardiac disease • hyperosmolality • severe hypoglycaemia • severe liver disease

- **SIDE-EFFECTS**
  - Rare • Severe anaphylactic reactions
  - **Frequency not known** Hypersensitivity reactions • transient increase in bleeding time

- **PREGNANCY** Avoid—reports of anaphylaxis in mother causing fetal anoxia, neurological damage and death.

- **HEPATIC IMPAIRMENT** Use with caution in severe impairment.

- **RENAL IMPAIRMENT** Use with caution.

- **MONITORING REQUIREMENTS**
  - Where possible, monitor central venous pressure.
  - Urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.

- Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

### Plasma Substitutes

- **Indications and dose**
  - Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

  - **By intravenous infusion**
    - Adult: Initially 500–1000 mL, use 3.5–4% solution

- **Caution** Cardiac disease • severe liver disease

- **Side-effects**
  - Rare • Severe anaphylactic reactions

- **Frequency not known** Hypersensitivity reactions • transient increase in bleeding time

- **Pregnancy** Manufacturer of Gelaplasma® advises avoid at the end of pregnancy.

- **Hepatic Impairment** Use with caution in severe impairment.

- **Renal Impairment** Use with caution in renal impairment.

### Gelatin

- **Indications and dose**
  - Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

  - **By intravenous infusion**

  - Adult: Initially 500–1000 mL, use 3.5–4% solution

- **Caution** Cardiac disease • severe liver disease

- **Side-effects**
  - Rare • Severe anaphylactic reactions

- **Frequency not known** Hypersensitivity reactions • transient increase in bleeding time

- **Pregnancy** Manufacturer of Gelaplasma® advises avoid at the end of pregnancy.

- **Hepatic Impairment** Use with caution in severe impairment.

- **Renal Impairment** Use with caution in renal impairment.
● **MONITORING REQUIREMENTS**

- Urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.
- Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

● **PRESCRIBING AND DISPENSING INFORMATION** The gelatin is partially degraded.

**Gelaspan®** contains succinylated gelatin (modified fluid gelatin, average molecular weight 26 500) 40 g. Na⁺ 151 mmol, K⁺ 4 mmol, Mg²⁺ 1 mmol, Cl⁻ 103 mmol, Ca²⁺ 1 mmol, acetate 24 mmol/litre; **Gelofusine®** contains succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 124 mmol/litre; **Geloplasma®** contains partially hydrolysed and succinylated gelatin (modified liquid gelatin) (as anhydrous gelatin) 30 g (3%), Na⁺ 150 mmol, K⁺ 5 mmol, Mg²⁺ 1.5 mmol, Cl⁻ 100 mmol, lactate 30 mmol/litre; **Isoplex®** contains succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 145 mmol, K⁺ 4 mmol, Mg²⁺ 0.9 mmol, Cl⁻ 105 mmol, lactate 25 mmol/litre; **Volplex®** contains succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 125 mmol/litre.

● **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

- **Gelaspan** (B.Braun Medical Ltd)
  - Gelatin 40 mg per 1 ml Gelaspan 4% infusion 500 ml Ecobags | 1 bag [Pack] £5.78 (Hospital only) | 20 bag [Pack] no price available (Hospital only)
- **Gelofusine** (B.Braun Medical Ltd)
  - Gelatin 40 mg per 1 ml Gelofusine 4% infusion 1 litre Ecobags | 1 bag [Pack] £9.04 | 10 bag [Pack] no price available
  - Gelofusine 4% infusion 500 ml Ecobags | 1 bag [Pack] £4.83 | 20 bag [Pack] no price available
- **Geloplasma** (Fresenius Kabi Ltd)
  - Gelatin 30 mg per 1 ml Geloplasma 3% infusion 500 ml Freeflex bags | 1 bag [Pack] £6.78 (Hospital only) | 20 bag [Pack] no price available
- **Isoplex** (Beacon Pharmaceuticals Ltd)
  - Gelatin 40 mg per 1 ml Isoplex 4% infusion 500 ml Freeflex bags | 10 bag [Pack] £75.30 (Hospital only)
  - Isoplex 4% infusion 1 litre Freeflex bags | 6 bag [Pack] £54.54 (Hospital only)
- **Volplex** (Beacon Pharmaceuticals Ltd)
  - Gelatin 40 mg per 1 ml Volplex 4% infusion 500 ml Freeflex bags | 10 bag [Pack] £47.00 (Hospital only)
  - Volplex 4% infusion 1 litre Freeflex bags | 6 bag [Pack] £54.54 (Hospital only)

**Tetrastarch**

● **INDICATIONS AND DOSE**

**VOLULYTE® INFUSION**

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient

- **BY INTRAVENOUS INFUSION**
  - **Adult:** Initially 10–20 mL, then increased to up to 30 mL/kilogram daily for a maximum duration of treatment of 24 hours, the initial dose must be given slowly and with careful monitoring of the patient to allow any anaphylactic reaction to be detected as early as possible

- **CONTRA-INDICATIONS** Burns - cerebral haemorrhage - critically ill patients - dehydration - hyperviscosity - intracranial haemorrhage - pulmonary oedema - sepsis - severe coagulopathy

- **CAUTIONS** Cardiac disease - care should be taken to avoid haematocrit concentration from falling below 25–30% - renal impairment - severe liver disease - surgery - trauma

- **SIDE-EFFECTS**
  - Rare - Severe anaphylactic reactions
  - **Frequency not known** Hypersensitivity reactions - pruritus - raised serum amylose - transient increase in bleeding time

- **HEPATIC IMPAIRMENT** Avoid in severe impairment.

- **RENAL IMPAIRMENT** Avoid.

- **MONITORING REQUIREMENTS**
  - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times. Treatment with hydroxyethyl starches should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved.
  - Monitor renal function.
  - Monitor for hypersensitivity reactions.
  - **Urine output should be monitored.**

**PRESCRIBING AND DISPENSING INFORMATION** Hydroxyethyl starch is composed of more than 90% of amylopectin that has been etherified with hydroxyethyl groups; the term tetrastarch reflects the degree of etherification. Hydroxyethyl starches should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient; they should be used at the lowest effective dose for the first 24 hours of fluid resuscitation.

**Volulyte®** contains hydroxyethyl starch 6% (average molecular weight 130 000) in sodium chloride intravenous infusion 0.6%, containing Na⁺ 137 mmol, K⁺ 4 mmol, Mg²⁺ 1.5 mmol, Cl⁻ 110 mmol, acetate 34 mmol/litre.

● **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

- **Volulyte** (Fresenius Kabi Ltd) ▼
  - Magnesium chloride hexahydrate 300 mg per 1 litre, Potassium chloride 300 mg per 1 litre, Sodium acetate trihydrate 4.63 gram per 1 litre, Sodium chloride 6.02 gram per 1 litre, Tetrastarch 60 gram per 1 litre Volulyte 6% infusion 500 ml Freeflex bags | 15 bag [Pack] £229.60

- **Voluen** (Fresenius Kabi Ltd) ▼
  - **Tetrastarch 100 mg per 1 ml** Voluen 10% infusion 500 ml Freeflex bags | 20 bag [Pack] no price available
  - **Tetrastarch 60 mg per 1 gram** Voluen 6% infusion 500 ml Freeflex bags | 1 bag [Pack] £10.63 | 15 bag [Pack] no price available
1.3 Magnesium imbalance

Magnesium

Magnesium is an essential constituent of many enzyme systems, particularly those involved in energy generation; the largest stores are in the skeleton.

Magnesium salts are not well absorbed from the gastrointestinal tract, which explains the use of magnesium sulfate as an osmotic laxative.

Magnesium is excreted mainly by the kidneys and is therefore retained in renal failure, but significant hypermagnesaemia (causing muscle weakness and arrhythmias) is rare.

Hypomagnesaemia

Since magnesium is secreted in large amounts in the gastrointestinal fluid, excessive losses in diarrhoea, stoma or fistula are the most common causes of hypomagnesaemia; deficiency may also occur in alcoholism or as a result of treatment with certain drugs. Hypomagnesaemia often causes secondary hypocalcaemia, and also hypokalaemia and hyponatraemia.

Symptomatic hypomagnesaemia is associated with a deficit of 0.5–1 mmol/kg; up to 160 mmol Mg²⁺ over up to 5 days may be required to replace the deficit (allowing for urinary losses). Magnesium is given initially by intravenous infusion or by intramuscular injection of magnesium sulfate; the intramuscular injection is painful. Plasma magnesium concentration should be measured to determine the rate and duration of infusion and the dose should be reduced in renal impairment. To prevent recurrence of the deficit, magnesium may be given by mouth, but there is limited evidence of benefit. Magnesium aspartate powder for oral solution below is available as a licensed preparation and, magnesium glycerophosphate tablets below and liquid [unlicensed] are available from ‘special-order’ manufacturers or specialist importing companies.

Arrhythmias

Magnesium sulfate injection has also been recommended for the emergency treatment of serious arrhythmias, especially in the presence of hypokalaemia (when hypomagnesaemia may also be present) and when salvos of rapid ventricular tachycardia show the characteristic twisting wave front known as torsade de pointes.

Myocardial infarction

Limited evidence that magnesium sulfate prevents arrhythmias and reperfusion injury in patients with suspected myocardial infarction has not been confirmed by large studies. Routine use of magnesium sulfate for this purpose is not recommended.

Eclampsia and pre-eclampsia

Magnesium sulfate injection is the drug of choice for the treatment of seizures and the prevention of recurrent seizures in women with eclampsia. Regimens may vary between hospitals. Calcium gluconate injection is used for the management of magnesium toxicity.

Magnesium sulfate injection is also of benefit in women with pre-eclampsia in whom there is concern about developing eclampsia. The patient should be monitored carefully.

Magnesium glycerophosphate

Prevent recurrence of magnesium deficit

Magnesium glycerophosphate powder for oral use (magnesium salts, oral). There can be variation in the licensing of different medicines imported by manufacturers or specialist importing companies.

Magnesium (as Magnesium aspartate) 243 mg (£9.97)

Magnesium aspartate powder for oral solution below and liquid [unlicensed] are available from ‘special-order’ manufacturers or specialist importing companies.

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DIRECTIONS FOR ADMINISTRATION

MONITORING REQUIREMENTS

RENAL IMPAIRMENT

Avoid or reduce dose. Increased risk of toxicity.

MONITORING REQUIREMENTS

Monitor blood pressure, respiratory rate, urine output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision, and slurred speech).

DIRECTIONS FOR ADMINISTRATION

Tablets may be dispersed in water.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, chewable tablet, capsule, oral suspension, oral solution

Tablet

Magnesium glycerophosphate (Non-proprietary)

Magnesium (as Magnesium glycerophosphate) 97.2 mg Mag-4 (magnesium 97.2mg (4mmol)) tablets | 30 tablet £84.50

Chewable tablet

Magnesium glycerophosphate (Non-proprietary)

Magnesium (as Magnesium glycerophosphate) 97.2 mg YourMAg (magnesium 97.2mg (4mmol)) chewable tablets | 50 tablet £20.00

MagnaPhate (Arjun Products Ltd)

Magnesium (as Magnesium glycerophosphate) 97.2 mg MagnaPhate (magnesium 97.2mg (4mmol)) chewable tablets sugar-free | 30 tablet £84.50

Neomag (magnesium 97mg (4mmol)) chewable tablets sugar-free | 50 tablet £20.00

Magnesium sulfate heptahydrate should not exceed 4 g, to be given over 20 minutes

Capable

Magnesium glycerophosphate (Non-proprietary)

Magnesium (as Magnesium glycerophosphate) 48.6 mg Mag-4 (magnesium 48.6mg (2mmol)) capsules | 30 capsule £85.70

Magnesium (as Magnesium glycerophosphate) 97.2 mg Mag-4 (magnesium 97.2mg (4mmol)) capsules | 30 capsule £89.30

Oral solution

LiquaMag GP (Fontus Health Ltd)

Magnesium (as Magnesium glycerophosphate) 24.25 mg per 1 ml LiquaMag GP (magnesium 121.25mg/5ml (5mmol/5ml)) oral solution sugar-free | 250 ml £55.00

Magnesium sulfate

INDICATIONS AND DOSE

Severe acute asthma | Continuing respiratory deterioration in anaphylaxis

BY INTRAVENOUS INFUSION

Child 2-17 years: 40 mg/kg (max. per dose 2 g), to be given over 20 minutes

Adult: 1.2–2 g, to be given over 20 minutes

Prevention of seizures in pre-eclampsia

INITIALLY BY INTRAVENOUS INJECTION

Adult: Initially 4 g, to be given over 5–15 minutes, followed by (by intravenous infusion) 1 gram/hour for 24 hours, if seizure occurs, additional dose of 2 g by intravenous injection to be administered

Treatment of seizures and prevention of seizure recurrence in eclampsia

INITIALLY BY INTRAVENOUS INJECTION

Adult: Initially 4 g, to be given over 5–15 minutes, followed by (by intravenous infusion) 1 gram/hour for 24 hours after seizure or delivery (whichever is later), if seizure recurs, increase the infusion rate to 1.5–2 g/hour or give an additional dose of 2 g by intravenous injection

Hypomagnesaemia

BY INTRAVENOUS INFUSION, OR BY INTRAMUSCULAR INJECTION

Adult: Up to 40 g, given over a period of up to 5 days, dose given depends on the amount required to replace the deficit (allowing for urinary losses)

Hypomagnesaemia maintenance (e.g. in intravenous nutrition)

BY INTRAVENOUS INFUSION, OR BY INTRAMUSCULAR INJECTION

Adult: 2.5–5 g daily, usual dose 3 g daily

Emergency treatment of serious arrhythmias

BY INTRAVENOUS INJECTION

Adult: 2 g, to be given over 10–15 minutes, dose may be repeated once if necessary

Rapid bowel evacuation (acts in 2–4 hours)

BY MOUTH

Adult: 5–10 g, dose to be mixed in a glass of water, taken preferably before breakfast

DOSE EQUIVALENCE AND CONVERSION

Magnesium sulfate heptahydrate 1 g equivalent to Mg2+ approx. 4 mmol.

UNLICENSED USE

With intravenous use Unlicensed indication in severe acute asthma. Continuing respiratory deterioration in anaphylaxis.

CONTRA-INDICATIONS

With oral use in rapid bowel evacuation—acute gastrointestinal conditions

CAUTIONS

With oral use in rapid bowel evacuation—elderly and debilitated patients

INTERACTIONS

Appendix 1 (magnesium, parenteral).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Arrhythmias · coma · confusion · drowsiness · flushing of skin · hypermagnesaemia associated side-effects · hypotension · loss of tendon reflexes · muscle weakness · nausea · respiratory depression · thirst · vomiting

SPECIFIC SIDE-EFFECTS

skin sensation of warmth, flushing of skin · hypermagnesaemia associated side-effects · hypotension · loss of tendon reflexes · muscle weakness · nausea · respiratory depression · thirst · vomiting

PREGNANCY

When used for Hypomagnesaemia or Arrhythmias or Prevention of seizures in pre-eclampsia or Treatment of seizures and prevention of seizure recurrence in eclampsia or Severe acute asthma or Continuing respiratory deterioration in anaphylaxis. Not known to be harmful for short-term intravenous administration in eclampsia, but excessive doses in third trimester cause neonatal respiratory depression. Sufficient amount may cross the placenta in mothers treated with high doses e.g. in pre-eclampsia, causing hypotonia and respiratory depression in newborns.

HEPATIC IMPAIRMENT

Avoid in hepatic coma if risk of renal failure.

RENAI IMPAIRMENT

Avoid or reduce dose. Increased risk of toxicity.

MONITORING REQUIREMENTS

Monitor blood pressure, respiratory rate, urine output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision, and slurred speech).

DIRECTIONS FOR ADMINISTRATION

With intravenous use in severe hypomagnesaemia administer initially via controlled infusion device (preferably syringe pump).

With intravenous use in adults. For intravenous injection, in arrhythmias, hypomagnesaemia, eclampsia, and pre-eclampsia, give continuously in Glucose 5% or Sodium chloride 0.9%. Concentration of magnesium sulfate heptahydrate should not exceed 20% (200 mg/mL or
0.8 mmol/mL Mg\(^{2+}\)); dilute 1 part of magnesium sulfate injection 50% with at least 1.5 parts of water for injections. Max. rate 150 mg/minute (0.6 mmol/minute Mg\(^{2+}\)).

**PRESCRIBING AND DISPENSING INFORMATION**

- With intramuscular use or intravenous use The BP directs that the label states the strength as the % w/v of magnesium sulfate heptahydrate and as the approximate concentration of magnesium ions (Mg\(^{2+}\)) in mmol/mL. Magnesium Sulfate Injection BP is a sterile solution of Magnesium Sulfate Heptahydrate.

**EXCEPTIONS TO LEGAL CATEGORY**

- With oral use in adults Magnesium sulfate is on sale to the public as Epsom Salts.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, solution for injection, infusion, solution for infusion

**Solution for injection**

- **Magnesium sulfate (Non-proprietary)**
  
  Magnesium sulfate heptahydrate 500 mg per 1 ml Magnesium sulfate 50% (magnesium 2mmol/ml) solution for injection 10ml ampoules | 10 ampoule £11.85–£35.25
  Magnesium sulfate 50% (magnesium 2mmol/ml) solution for injection 20ml vials | 10 vial £46.40
  Magnesium sulfate 50% (magnesium 2mmol/ml) solution for injection 5ml ampoules | 10 ampoule £21.80–£58.34
  Magnesium sulfate 50% (magnesium 2mmol/ml) solution for injection 2ml ampoules | 10 ampoule £11.72–£17.90 DT price = £11.85

**Solution for infusion**

- **Magnesium sulfate (Non-proprietary)**
  
  Magnesium sulfate heptahydrate 100 mg per 1 ml Magnesium sulfate 10% (magnesium 0.4mmol/ml) solution for injection 10ml ampoules | 10 ampoule £57.12–£60.50
  Magnesium sulfate heptahydrate 500 mg per 1 ml Magnesium sulfate 50% (magnesium 2mmol/ml) solution for infusion 50ml vials | 10 vial £66.70

**Powder**

- **Magnesium sulfate (Non-proprietary)**
  
  Magnesium sulfate dried 1 mg per 1 mg Numark Epsom Salts | 200 gram GSL £1.00
  Magnesium sulfate powder | 300 gram GSL £1.91–£2.02 | 500 gram GSL £3.20 DT price = £3.20 | 2000 gram GSL £5.60 | 5000 gram GSL £11.49
  
  Brands may include Epsom salts

### 1.4 Phosphate imbalance

**Phosphorus**

Oral phosphate supplements p. 928 may be required in addition to vitamin D in a small minority of patients with hypophosphataemic vitamin D-resistant rickets.

Phosphate infusion is occasionally needed in alcohol dependence or in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis.

For phosphate requirements in total parenteral nutrition regimens, see Intravenous nutrition p. 940.

**Phosphate-binding agents**

Calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Aluminium-containing preparations are rarely used as phosphate binding agents and can cause aluminium accumulation.

Sevelamer p. 927 is licensed for the treatment of hyperphosphataemia in patients on haemodialysis or peritoneal dialysis. Sevelamer carbonate is also licensed for the treatment of patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more.

Lanthanum p. 926 is licensed for the control of hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), and in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more that cannot be controlled by a low-phosphate diet.

Sucroferric oxyhydroxide p. 927 is licensed for the control of hyperphosphataemia in patients with chronic kidney disease on haemodialysis or peritoneal dialysis. It is used as part of a multiple therapeutic approach to control the development of renal bone disease; this could include the concomitant use of a calcium supplement, a vitamin D analogue or calcimimetics.

#### 1.4a Hyperphosphataemia

**ELECTROLYTES AND MINERALS ▶ ALUMINIUM**

**Aluminium hydroxide**

- **INDICATIONS AND DOSE**
  
  Hyperphosphataemia in renal failure
  
  ▶ BY MOUTH USING CAPSULES
  
  Adult: 4–20 capsules daily in divided doses, to be taken with meals

  Antacid
  
  ▶ BY MOUTH USING CAPSULES
  
  Adult: 475 mg 5 times a day, last dose to be taken at bedtime

- **CONTRA-INDICATIONS**
  
  Hypophosphataemia

- **INTERACTIONS** ▶ Appendix 1 (antacids).

  Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.

  Antacids may damage enteric coatings designed to prevent dissolution in the stomach.

- **SIDE-EFFECTS**
  
  Constipation - hyperaluminaemia

- **HEPATIC IMPAIRMENT**
  
  Avoid; can cause constipation which can precipitate coma.

- **RENAL IMPAIRMENT**
  
  There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics).

**CALCIUM**

**Calcium acetate**

- **INDICATIONS AND DOSE**
  
  **PHOSEX® TABLETS**

  Hyperphosphataemia
  
  ▶ BY MOUTH
  
  Adult: Initially 1 tablet 3 times a day, to be taken with meals, dose to be adjusted according to serum-phosphate concentration, usual dose continued →
4–6 tablets daily in divided doses, (1 or 2 tablets with each meal); maximum 12 tablets per day

**RENACET® TABLETS**

**Hyperphosphataemia**
- **BY MOUTH**
  - Adult: 475–950 mg, to be taken with breakfast and with snacks, 0.95–2.85 g, to be taken with main meals and 0.95–1.9 g, to be taken with supper, dose to be adjusted according to serum-phosphate concentration; maximum 6.65 g per day

**CONTRA-INDICATIONS**
- Please consider, calcium acetate p.
- Combination only. For the properties of the components see below

**PHOSPHATE BINDERS**

**Calcium acetate with magnesium carbonate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, calcium acetate p. 925, magnesium carbonate p. 67.

**INDICATIONS AND DOSE**

**Hyperphosphataemia**
- **BY MOUTH**
  - Adult: Initially 1 tablet 3 times a day, adjusted according to serum-phosphate concentration, to be taken with food; usual dose 3–10 tablets daily; maximum 12 tablets per day

**CONTRA-INDICATIONS**
- Hypercalcaemia • hypermagnesaemia • myasthenia gravis • third-degree AV block

**DIRECTIONS FOR ADMINISTRATION**
- Manufacturer advises that other drugs should be taken at least 2 hours before or 3 hours after calcium acetate with magnesium carbonate to reduce possible interference with absorption of other drugs.

**PATIENT AND CARER ADVICE**
- Patients or carers should be given advice on how to administer calcium acetate with magnesium carbonate tablets.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 25
- **Rephoren** (Vifor Fresenius Medical Care Renal Pharma UK Ltd)
  - Magnesium carbonate heavy 235 mg, Calcium acetate 435 mg
  - Osvaren 435mg/235mg tablets | 180 tablet (Pom) £24.00

**Lanthanum**

**INDICATIONS AND DOSE**

Hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) • Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more that cannot be controlled by a low-phosphate diet
- **BY MOUTH**
  - Adult: 1.5–3 g daily in divided doses, dose to be adjusted according to serum-phosphate concentration every 2–3 weeks, to be taken with or immediately after meals

**CAUTIONS**
- Acute peptic ulcer • bowel obstruction • Crohn’s disease • ulcerative colitis

**INTERACTIONS**
- → Appendix 1 (lanthanum).

**SIDE-EFFECTS**
- **Common or very common** Gastro-intestinal disturbances • headache • hypocalcaemia
- **Uncommon** Alopecia • anorexia • arthralgia • asthenia • chest pain • dizziness • dry mouth • eosinophilia • hypercalcaemia • hyperglycaemia • hyperparathyroidism • hypophosphataemia • increased appetite • malaise • myalgia • osteoporosis • peripheral oedema • stomatitis • sweating • taste disturbances • thirst • vertigo
- **Frequency not known** Accumulation of lanthanum in bone • transient changes in QT interval

**PREGNANCY**
- Manufacturer advises caution—no information available.

**BREAST FEEDING**
- Manufacturer advises caution—no information available.

**HEPATIC IMPAIRMENT**
- Lanthanum excreted in bile—possible accumulation in obstructive jaundice.

**DIRECTIONS FOR ADMINISTRATION**
- Tablets are to be chewed. Each sachet of powder to be mixed with soft food and consumed within 15 minutes.

**PATIENT AND CARER ADVICE**
- Patient and carers should be given advice on how to administer lanthanum tablets and powder.

**NATIONAL FUNDING/ACCESS DECISIONS**

*Scottish Medicines Consortium (SMC) Decisions*

The Scottish Medicines Consortium has advised (March 2007) that lanthanum (Fosrenol®) is accepted for restricted use within NHS Scotland for the control of hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis, as a second-line agent, where a non-aluminium, non-calcium phosphate binder is required.
Sevelamer

31-Oct-2016

**INDICATIONS AND DOSE**

**RENAGEL®**

Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis

- **BY MOUTH**
  - Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be given with meals and adjusted according to serum-phosphate concentration; usual dose 2.4–12 g daily in 3 divided doses

**RENVELA® 2.4G ORAL POWDER SACHETS (SANOFI)**

Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis; Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more

- **BY MOUTH**
  - Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be taken with meals and adjusted according to serum-phosphate concentration every 2–4 weeks; usual dose 6 g daily in 3 divided doses

**RENVELA® 800MG TABLETS (SANOFI)**

Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis; Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more

- **BY MOUTH**
  - Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be taken with meals and adjusted according to serum-phosphate concentration every 2–4 weeks; usual dose 6 g daily in 3 divided doses

**CONTRA-INDICATIONS** Bowel obstruction

**CAUTIONS** Gastro-intestinal disorders

**INTERACTIONS** → Appendix 1 (sevelamer).

**SIDE-EFFECTS**

- Common or very common Abdominal pain • constipation • diarrhoea • dyspepsia • flatulence • nausea • vomiting
- Frequency not known Ileus • intestinal obstruction (higher incidence with sevelamer hydrochloride salt) • intestinal perforation • pruritus • rash

**RENAVIA®** Diverticulitis

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**RENAVIA® 2.4G ORAL POWDER SACHETS (SANOFI)** Unlikely to be present in milk (however, manufacturer advises avoid).

**RENAVIA® 800MG TABLETS (SANOFI)** Unlikely to be present in milk (however, manufacturer advises avoid).

**RENAVIA®** Manufacturer advises use only if potential benefit outweighs risk.

**DIRECTIONS FOR ADMINISTRATION**

**RENAVIA® 2.4G ORAL POWDER SACHETS (SANOFI)** For powder for oral suspension, each sachet to be dispersed in 60 ml water.

**PATIENT AND CARER ADVICE**

**RENAVIA® 2.4G ORAL POWDER SACHETS (SANOFI)** Patients and carers should be advised on how to administer powder for oral suspension.

**INDICATIONS AND DOSE**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 25

**EXCIPIENTS:** May contain Propylene glycol

- **Renagel** (Sanofi)
  - Sevelamer 250 mg Renagel 250mg tablets | 10 tablets (POD) £18.60 DT price = £193.59
  - Sevelamer 500 mg Renagel 500mg tablets | 90 tablets (POD) £124.06 DT price = £124.06

- **Renvela** (Sanofi)
  - Sevelamer 800 mg Renvela 800mg tablets | 180 tablets (POD) £167.04 DT price = £74.11

Relevant medicines are available as: chewable tablets sugar-free

**Sucroferric oxyhydroxide**

16-Feb-2016

**INDICATIONS AND DOSE**

Hyperphosphataemia in patients with chronic kidney disease on haemodialysis or peritoneal dialysis

- **BY MOUTH**
  - Adult: Initially 1.5 g daily in 3 divided doses, dose to be taken with meals, then adjusted in steps of 500 mg every 2–4 weeks, dose adjusted according to serum-phosphate concentration; maintenance 1.5–2 g daily in divided doses; maximum 3 g per day

**CONTRA-INDICATIONS** Haemochromatosis • iron accumulation disorders

**CAUTIONS** Gastric disorders • hepatic disorders • major gastrointestinal surgery • peritonitis in the last 3 months

**INTERACTIONS** → Appendix 1 (iron salts).

**SIDE-EFFECTS**

- Common or very common Abdominal pain • constipation • diarrhoea • discoloration of faeces • dyspepsia • flatulence • taste disturbance • tooth discoloration • vomiting
- Uncommon Abdominal discomfort • abdominal distension • dysphagia • dysphoea • fatigue • gastritis • gastrointestinal reflux disease • headache • hypercalcaemia • hypocalcaemia • rash • tongue discoloration

**SIDE-EFFECTS, FURTHER INFORMATION**

Discoloured faeces may mask the visual signs of gastrointestinal bleeding.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**DIRECTIONS FOR ADMINISTRATION** Velphoro® tablets must be chewed or crushed, not swallowed whole.
1.4b Hypophosphataemia

**ELECTROLYTES AND MINERALS > PHOSPHATES**

**Phosphate**

**INDICATIONS AND DOSE**

Treatment of moderate to severe hypophosphatemia
- **BY INTRAVENOUS INFUSION**
- Adult: (consult product literature)

For established hypophosphataemia (with monobasic potassium phosphate)
- **BY INTRAVENOUS INFUSION**
- Adult: 9 mmol every 12 hours, increased if necessary up to 0.5 mmol/kg (max. per dose 50 mmol), dose only increased in critically ill patients; dose in critically ill patients is approximately equivalent to 30 mmol in adults, dose to be infused over 6–12 hours, according to severity

Vitamin D-resistant hypophosphataemic osteomalacia
- **BY MOUTH USING EFFERVESCENT TABLETS**
- Adult: 4–6 tablets daily, using Phosphate Sandoz®.

**SIDE-EFFECTS**

- Common or very common: Diarrhoea
- Frequency not known: Acute renal failure, hypocalcaemia, hypotension, metastatic calcification, nausea, oedema, phlebitis, tissue necrosis on extravasation

SIDE-EFFECTS, FURTHER INFORMATION

Diarrhoea is a common side-effect and should prompt a reduction in dosage.

**RENAJ IMPAIRMENT**

Reduce dose. Monitor closely in renal impairment.

**MONITORING REQUIREMENTS**

It is essential to monitor closely plasma concentrations of calcium, phosphate, potassium, and other electrolytes—excessive doses of phosphates may cause hypocalcaemia and metastatic calcification.

**PRESCRIBING AND DISPENSING INFORMATION** Phosphate Sandoz® contains sodium dihydrogen phosphate anhydrous (anhydrous sodium acid phosphate) 1.936 g, sodium bicarbonate 350 mg, potassium bicarbonate 315 mg, equivalent to phosphorus 500 mg (phosphate 16.1 mmol), sodium 468.8 mg (Na⁺ 20.4 mmol), potassium 123 mg (K⁺ 3.1 mmol); Polyfusor NA® contains Na⁺ 162 mmol/litre, K⁺ 19 mmol/litre, PO4³⁻ 100 mmol/litre; non-proprietary potassium dihydrogen phosphate injection (potassium acid phosphate) 13.6% may contain 1 mmol/mL phosphate, 1 mmol/mL potassium.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Effervescent tablet**

CAUTIONARY AND ADVISORY LABELS 13

- Phosphate Sandoz® (HK Pharma Ltd)
- Sodium dihydrogen phosphate anhydrous 1.936 gram Phosphate Sandoz effervescent tablets | 100 tablet P £16.43

**Infusion**

- Phosphate (Non-proprietary)
  - Potassium dihydrogen phosphate 1.295 gram per 1 litre, Disodium hydrogen phosphate anhydrous 5.75 gram per 1 litre Polyfusor NA phosphates infusion 500ml bottles | 1 bottle P £5.15
  - Solution for infusion
  - Phosphate (Non-proprietary)
  - Potassium dihydrogen phosphate 136 mg per 1 ml Potassium dihydrogen phosphate 13.6% (potassium 10mmol/10ml) solution for infusion 10ml ampoules | 10 ampoule P £80.25–£85.00

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1.5 Potassium imbalance

1.5a Hyperkalaemia

Other drugs used for Hyperkalaemia Calcium gluconate, p. 920 - Insulin, p. 652

**ANTIDOTES AND CHELATORS > CATION EXCHANGE RESINS**

**Calcium polystyrene sulfonate**

**INDICATIONS AND DOSE**

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
- **BY MOUTH**
  - Adult: 15 g 3–4 times a day
- **BY RECTUM**
  - Adult: 30 g, retained for 9 hours followed by irrigation to remove resin from colon

SORBITERIT® POWDER

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
- **BY MOUTH**
  - Adult: 20 g 1–3 times a day
- **BY RECTUM**
  - Adult: 40 g 1–3 times a day, retained for 6 hours followed by irrigation to remove resin from colon

**CONTRA-INDICATIONS**

Hyperparathyroidism, metastatic carcinoma, multiple myeloma, obstructive bowel disease, sarcoidosis

**INTERACTIONS** → Appendix 1 (polystyrene sulfonate resins).

**SIDE-EFFECTS**

GENERAL SIDE-EFFECTS

Anorexia, constipation (discontinue treatment—avoid magnesium-containing laxatives), diarrhoea, gastric irritation, gastro-intestinal obstruction, hypercalcaemia (including in dialysed patients and occasionally in those with renal impairment), hypomagnesaemia, intestinal necrosis (reported with concomitant sorbitol), ischaemic colitis, nausea, necrosis, ulceration, vomiting

SPECIFIC SIDE-EFFECTS

- With oral use Gastro-intestinal concretions
- With rectal use Faecal impaction

**PREGNANCY**

Manufacturers advise use only if potential benefit outweighs risk—no information available.
This document includes various sections related to the administration, monitoring, and safety information of medications. It discusses different medicinal forms and provides detailed instructions for their use. The sections covered include:

- **DIRECTIONS FOR ADMINISTRATION**
- **MONITORING REQUIREMENTS**
- **SIDE-EFFECTS**
- **INTERACTIONS**
- **CAUTIONS**
- **CONTRA-INDICATIONS**
- **CONTRARY AND ADVISORY LABELS**
- **MEDICINAL FORMS**

### Hypokalaemia

**ELECTROLYTES AND MINERALS > POTASSIUM**

#### Potassium bicarbonate with potassium acid tartrate

- **INDICATIONS AND DOSE**
  - Hyperchloraemic acidosis associated with potassium deficiency (as in some renal tubular and gastrointestinal disorders)
  - Adult: (consult product literature)

#### Contra-Indications

- Cardiac disease - elderly

#### ELECTROLYTES AND MINERALS

- **Sodium polystyrene sulfonate**
  - **INDICATIONS AND DOSE**
    - Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
      - **BY MOUTH**
        - Adult: 15 g – 4 times a day
      - **BY RECTUM**
        - Adult: 30 g, retain for 9 hours followed by irrigation to remove resin from colon
  - **CONTRA-INDICATIONS**
    - Obstructive bowel disease
  - **CAUTIONS**
    - Congestive heart failure - hypertension - oedema
  - **INTERACTIONS**
    - Appendix 1 (polystyrene sulfonate resins).
  - **SIDE-EFFECTS**
    - General Side-effects:
      - Anorexia - constipation (discontinue treatment—avoid magnesium-containing laxatives) - diarrhoea - gastric irritation - gastro-intestinal obstruction - hypocalcaemia - hypomagnesaemia - intestinal necrosis (reported with concomitant use of sorbitol) - ischaemic colitis - nausea - necrosis - sodium retention - ulceration - vomiting
    - Specific Side-effects:
      - With oral use: Gastro-intestinal concretions
      - With rectal use: Faecal impaction
  - **PREGNANCY**
    - Manufacturers advise use only if potential benefit outweighs risk—no information available.
  - **BREAST FEEDING**
    - Manufacturers advise use only if potential benefit outweighs risk—no information available.
  - **RENAAL IMPAIRMENT**
    - Use with caution.
  - **MONITORING REQUIREMENTS**
    - Monitor for electrolyte disturbances (stop if plasma-potassium concentration below 5 mmol/litre).
  - **DIRECTIONS FOR ADMINISTRATION**
    - With rectal use: Mix each 30 g of resin with 150 mL of water or 10% glucose.
    - With oral use: Administer dose (powder) in a small amount of water or honey—do not give with fruit juice or squash, which have a high potassium content.

#### Potassium chloride

- **INDICATIONS AND DOSE**
  - Prevention of hypokalaemia (patients with normal diet)
    - **BY MOUTH**
      - Adult: 2-4 g daily in divided doses
  - **Electrolyte imbalance**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Dose dependent on deficit or the daily maintenance requirements

#### Important Safety Information

- Safe Practice
  - Potassium overdose can be fatal. Ready-mixed infusion solutions containing potassium should be used. Exceptionally, if potassium chloride concentrate is used for preparing an infusion, the infusion solution should be thoroughly mixed. Local policies on avoiding...
Potassium Tablets

1 contains Kay-Cee-L 

mmol/L. Higher concentrations of potassium chloride may be given in very severe depletion, but require specialist advice. When there is no safe alternative, treatment should be started and urinary porphobilinogen excretion should be measured regularly; if it increases or symptoms occur, the drug can be withdrawn and the acute attack treated. If an acute attack of porphyria occurs during pregnancy, contact an expert porphyria service for further advice. Haem arginate from three centres (University Hospital of Wales, Addenbrooke’s Hospital, and King’s College Hospital). To access the service telephone (029) 2074 7747 and ask for the Acute Porphyria Service.

Drugs unsafe for use in acute porphyrias

The following list contains drugs on the UK market that have been classified as ‘unsafe’ in porphyria because they have

- **CONTRA-INDICATIONS** Plasma-potassium concentration above 5 mmol/litre
- **CAUTIONS**
  - With intravenous use seek specialist advice in very severe potassium depletion or difficult cases
  - With oral use
    - Cardiac disease
    - elderly
    - hiatus hernia (with modified-release preparations)
    - history of peptic ulcer (with modified-release preparations)
    - intestinal stricture (with modified-release preparations)
- **INTERACTIONS** → Appendix 1 (potassium salts).
- **SIDE-EFFECTS**
  - Common or very common
    - Nausea
    - Vomiting
    - Abdominal pain
    - Diarrhoea
    - Flatulence
  - Frequency not known
  - With intravenous use
    - Heart toxicity (with rapid infusion)
  - With oral use
    - Bleeding (with modified-release preparations)
    - Gastro-intestinal obstruction (with modified-release preparations)
    - Ulceration (with modified-release preparations)
- **RENAL IMPAIRMENT** Smaller doses must be used in the prevention of hypokalaemia, to reduce the risk of hyperkalaemia. Avoid in severe impairment. Close monitoring required in renal impairment—high risk of hyperkalaemia.
- **MONITORING REQUIREMENTS**
  - Regular monitoring of plasma-potassium concentration is essential in those taking potassium supplements.
  - With intravenous use ECG monitoring should be performed in difficult cases.
- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use
    - Potassium salts are preferably given as a liquid (or effervescent) preparation, rather than modified-release tablets; they should be given as the chloride (the use of effervescent potassium tablets BPC 1968 should be restricted to hyperchloraemic states).
  - With intravenous use
    - Potassium chloride concentrate must be diluted with not less than 50 times its volume of sodium chloride intravenous infusion 0.9% or other suitable diluent and mixed well.
    - With intravenous use
      - Ready-mixed infusion solutions should be used where possible; alternatively, potassium chloride concentrate as ampoules containing 1.5 g (K⁺ 20 mmol) in 10 mL, is thoroughly mixed with 500 mL of sodium chloride 0.9% intravenous infusion and given slowly over 2 to 3 hours with specialist advice and ECG monitoring in difficult cases. For peripheral intravenous infusion, the concentration of potassium should not usually exceed 40 mmol/L. Higher concentrations of potassium chloride may be given in very severe depletion, but require specialist advice.
- **PRESCRIBING AND DISPENSING INFORMATION** Kay-Cee-L® contains 1 mmol/mL each of K⁺ and Cl⁻. Potassium Tablets
  - With oral use
    - Do not confuse Effervescent Potassium Tablets BPC 1968 with effervescent potassium chloride tablets. Effervescent Potassium Tablets BPC 1968 do not contain chloride ions and their use should be restricted to hyperchloraemic states.
- **PATIENT AND CARER ADVICE**
  - Patient or carers should be given advice on how to administer potassium chloride modified-release tablets. Salt substitutes A number of salt substitutes which contain significant amounts of potassium chloride are readily available as health food products (e.g. LoSalt® and Ruthmol®). These should not be used by patients with renal failure as potassium intoxication may result.

- **LESS SUITABLE FOR PRESCRIBING** Modified-release tablets are less suitable for prescribing. Modified-release preparations should be avoided unless effervescent tablets or liquid preparations are inappropriate.
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release tablet, oral solution, solution for injection, infusion, solution for infusion
- **Modified-release tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 25, 27
  - Potassium chloride (Non-proprietary)
    - Potassium chloride 600 mg Kaleorid LP 600mg tablets | 30 tablet £0.48 no price available
    - Duro-K 600mg tablets | 100 tablet £0.48 no price available
- **Oral solution**
  - **CAUTIONARY AND ADVISORY LABELS** 21
  - Kay-Cee-L (Geistlich Sons Ltd)
    - Potassium chloride 75 mg per 1 ml Kay-Cee-L syrup sugar-free | 500 ml £7.95
- **Solution for infusion**
  - Potassium chloride (Non-proprietary)
    - Potassium chloride 150 mg per 1 ml Potassium chloride 15% (potassium 20mmol/10ml) solution for infusion 10ml ampoules | 10 ampoule £6.50 | 20 ampoule £6.50
    - Potassium chloride 15% (potassium 20mmol/10ml) solution for infusion 10ml Mini-Plasco ampoules | 20 ampoule £6.70
    - Potassium chloride 200 mg per 1 ml Potassium chloride 20% (potassium 13.3mmol/3ml) solution for infusion 5ml ampoules | 10 ampoule £3.64–£4.00
    - Potassium chloride 20% (potassium 27mmol/10ml) solution for infusion 10ml ampoules | 10 ampoule £11.54

### 2 Metabolic disorders

#### 2.1 Acute porphyrias

**Acute porphyrias**

**Overview**

The acute porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolaevulinic acid dehydratase deficiency porphyria) are hereditary disorders of haem biosynthesis; they have a prevalence of about 1 in 10 000 of the population.

Great care must be taken when prescribing for patients with acute porphyria, since certain drugs can induce acute porphyrin crises. Since acute porphyrias are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs.

Treatment of serious or life-threatening conditions should not be withheld from patients with acute porphyria. When there is no safe alternative, treatment should be started and urinary porphobilinogen excretion should be measured regularly; if it increases or symptoms occur, the drug can be withdrawn and the acute attack treated. If an acute attack of porphyria occurs during pregnancy, contact an expert porphyria service for further advice.

Haem arginate p. 932 is administered by short intravenous infusion as haem replacement in moderate, severe, or unremitting acute porphyria crises.

In the United Kingdom the National Acute Porphyria Service (NAPS) provides clinical support and treatment with haem arginate from three centres (University Hospital of Wales, Addenbrooke’s Hospital, and King’s College Hospital). To access the service telephone (029) 2074 7747 and ask for the Acute Porphyria Service.

**Drugs unsafe for use in acute porphyrias**

The following list contains drugs on the UK market that have been classified as ‘unsafe’ in porphyria because they have
been shown to be porphyrinogenic in animals or in vitro, or have been associated with acute attacks in patients. Absence of a drug from the following lists does not necessarily imply that the drug is safe. For many drugs no information about porphyria is available.

An up-to-date list of drugs considered safe in acute porphyrias is available at www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyria/. Further information may be obtained from: www.porphyria-europe.org and also from:

Welsh Medicines Information Centre
University Hospital of Wales
CF14 4XW
Cardiff
(029) 2074 2979/3877

Quite modest changes in chemical structure can lead to changes in porphyrinogenicity but where possible general statements have been made about groups of drugs; these should be checked first.

Unsafe Drug Groups (check first)

- Alkylating drugs (contact Welsh Medicines Information Centre for further advice)
- Anabolic steroids
- Antidepressants (includes tricyclic (and related) antidepressants and MAOIs; fluoxetine, duloxetine, venlafaxine, and trazodone thought to be safe)
- Antihistamines (alimemazine, chlorphenamine, desloratadine, fexofenadine, ketotifen, loratadine, and promethazine thought to be safe)
- Barbiturates (includes primidone and tiapentol)
- Calcium channel blockers (amlodipine, felodipine, and nifedipine thought to be safe)
- Contraceptives, hormonal (progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.)
- Ergot derivatives (includes ergometrine (oxytocin probably safe) and pergolide)
- Hormone replacement therapy (progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.)
- Imidazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure)
- Non-nucleoside reverse transcriptase inhibitors (contact Welsh Medicines Information Centre for further advice)
- Progestogens (progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.)
- Protease inhibitors (contact Welsh Medicines Information Centre for further advice)
- Sulfonamides (includes co-trimoxazole and sulfasalazine)
- Sulfonamide derivatives (glipizide and glimepiride are thought to be safe)
- Taxanes (contact Welsh Medicines Information Centre for further advice)
- Thiazolidinediones (contact Welsh Medicines Information Centre for further advice)
- Triazolone antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure)

Unsafe Drugs (check groups above first)

- Aceclofenac
- Alcohol
- Amiodarone
- Aprepitant (contact Welsh Medicines Information Centre for further advice)
- Artemether with lumefantrine
- Bexarotene
- Bosentan
- Bromocriptine
- Buspirone
- Cabergoline
- Carbamazepine
- Chloral hydrate (although evidence of hazard is uncertain, manufacturer advises avoid)
- Chloramphenicol
- Chloroform (small amounts in medicines probably safe)
- Clindamycin
- Cocaine
- Colistimethate sodium
- Danazol
- Dapsone
- Dextenfluramine
- Disopyramide
- Disulfiram
- Erythromycin
- Etamsylate
- Ethosuximide
- Etomidate
- Fenfluramine
- Flupentixol
- Flutamide
- Fosaprepitant (contact Welsh Medicines Information Centre for further advice)
- Fosphenytoin
- Griseofulvin
- Hydralazine
- Indapamide
- Isomethylenepene mucate
- Isoniazid (safety uncertain, contact Welsh Medicines Information Centre for further advice)
- Ketamine
- Mefenamic acid (may be used with caution if safer alternative not available)
- Meprobamate
- Methyldopa
- Metolazone
- Metyrapone
- Mifepristone
- Minoxidil (may be used with caution if safer alternative not available)
- Mitotane
- Mirtazapine
- Nitrazepam
- Nitrofurantoin
- Orphenadrine
- Oxcarbazepine
2.2 Carnitine deficiency

AMINO ACIDS AND DERIVATIVES

Levcarnitine (Carnitine)

- **INDICATIONS AND DOSE**
  - Primary carnitine deficiency due to inborn errors of metabolism
    - **BY MOUTH**
      - Adult: Up to 200 mg/kg daily in 2–4 divided doses; maximum 3 g per day.
    - **BY SLOW INTRAVENOUS INJECTION**
      - Adult: Up to 100 mg/kg daily in 2–4 divided doses, to be administered over 2–3 minutes.
  - Secondary carnitine deficiency in haemodialysis patients
    - **INITIALLY BY SLOW INTRAVENOUS INJECTION**
      - Adult: 20 mg/kg, to be administered over 2–3 minutes, after each dialysis session, dosage adjusted according to plasma–carnitine concentration, then (by mouth) maintenance 1 g daily, administered if benefit is gained from first intravenous course.

- **CAUTIONS**
  - Diabetes mellitus
  - **SIDE-EFFECTS**
    - Abdominal pain • body odour • diarrhoea • nausea • vomiting
    - **SIDE-EFFECTS, FURTHER INFORMATION**
      - Side-effects may be dose-related—monitor tolerance during first week and after any dose increase.
  - **PREGNANCY**
    - Appropriate use; no evidence of teratogenicity in animal studies.
  - **RENAL IMPAIRMENT**
    - Accumulation of metabolites may occur with chronic oral administration in severe impairment.
  - **MONITORING REQUIREMENTS**
    - Monitoring of free and acyl carnitine in blood and urine recommended.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule
    - **Tablet**
      - Levcarnitine (Non-proprietary)
        - L-Carnitine 1 mg Carnitine 1g chewable tablets | 10 tablet £35.00
    - **Capsule**
      - Levcarnitine (Non-proprietary)
        - L-Carnitine 250 mg Bio-Carnitine 250mg capsules | 125 capsule £11.06
        - L-Carnitine 500 mg Lambert's L-Carnitine 500mg capsules | 60 capsule £11.67

- **Solution oral**
  - Levcarnitine (Non-proprietary)
    - L-Carnitine 150 mg/5ml Carnitine oral single dose 1g solution sugar-free | 10 unit dose £35.00

- **Solution for injection**
  - Levcarnitine (Non-proprietary)
    - L-Carnitine 200 mg/1 ml Carnitine 1g/5ml solution for injection ampoules | 5 ampoule £59.50

- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for infusion**
  - Normosang (Orphan Europe (UK) Ltd)

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**Blood and related products > Haem derivatives**

Haem arginate (Human hemin)

- **INDICATIONS AND DOSE**
  - Acute porphyrias • Acute intermittent porphyria • Porphyria variegata • Hereditary coproporphyria
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 3 mg/kg once daily for 4 days, if response inadequate, repeat 4-day course with close biochemical monitoring; maximum 250 mg per day.

- **SIDE-EFFECTS**
  - Common or very common • Pain at injection site • thrombophlebitis at injection site
  - Rare • Fever • hypersensitivity reactions
  - Frequency not known • Headache

- **PREGNANCY**
  - Manufacturer advises avoid unless essential.

- **CREATININE**
  - Manufacturer advises avoid unless essential—no information available.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Normosang®), give intermittently in Sodium chloride 0.9%; dilute requisite dose in 100 mL infusion fluid in glass bottle and give over at least 30 minutes through a filter via large antibrachial or central vein; administer within 1 hour after dilution.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for infusion**
  - Normosang (Orphan Europe (UK) Ltd)

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**Blood and nutrition**
2.3 Fabry’s disease

ENZYMES

Agalsidase alfa

- **DRUG ACTION** Agalsidase alfa, an enzyme produced by recombinant DNA technology are licensed for long-term enzyme replacement therapy in Fabry’s disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

- **INDICATIONS AND DOSE**
  - **Fabry’s disease (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
    - Adult: 200 micrograms/kg every 2 weeks

- **INTERACTIONS** *Appendix 1 (agalsidase alfa and beta).
- **SIDE-EFFECTS**
  - **Common or very common** Acne, angioedema, arthralgia, asthenia, bradycardia, chest pain, cough, dizziness, dyspnoea, eye irritation, fatigue, flushing, gastrointestinal disturbances, headache, hypersensitivity reactions, hypotension, influenza-like symptoms, muscle spasms, myalgia, nasopharyngitis, neuropathic pain, oedema, palpitation, paraesthesia, pruritus, rash, rhinorrhoea, sleep disturbances, syncope, tachycardia, taste disturbances, tinnitus, tremor, urticaria
  - **Uncommon** Cold extremities, ear pain, eye swelling, injection-site reactions, parosmia, skin discoloration

SIDE-EFFECTS, FURTHER INFORMATION

- Infusion-related reactions
  - Infusion-related reactions very common; manage by slowing the infusion rate or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature.
- **PREGNANCY** Use with caution.
- **BREAST FEEDING** Use with caution—no information available.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion, given intermittently in Sodium chloride 0.9%, reconstitute initially with Water for Injections (5 mg in 1.1 mL, 35 mg in 7.2 mL) to produce a solution containing 5 mg/mL. Dilute with Sodium Chloride 0.9% (for doses less than 35 mg dilute with at least 50 mL; doses 35–70 mg dilute with at least 100 mL; doses 70–100 mg dilute with at least 250 mL; doses greater than 100 mg dilute with 500 mL) and give through an in-line low protein-binding 0.2 micron filter at an initial rate of no more than 15 mg/hour; for subsequent infusions, infusion rate may be increased gradually once tolerance has been established.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for infusion**
    - **Fabrazyme** (Genzyme Therapeutics Ltd)
      - Agalsidase beta 5 mg Fabrazyme 5mg powder for solution for infusion vials | 1 vial £1,068.64
      - Agalsidase beta 35 mg Fabrazyme 35mg powder for solution for infusion vials | 1 vial £1,962.59

Agalsidase beta

- **DRUG ACTION** Agalsidase beta, an enzyme produced by recombinant DNA technology are licensed for long-term enzyme replacement therapy in Fabry’s disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

- **INDICATIONS AND DOSE**
  - **Fabry’s disease (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
    - Adult: 1 mg/kg every 2 weeks

- **INTERACTIONS** *Appendix 1 (agalsidase alfa and beta).
- **SIDE-EFFECTS**
  - **Common or very common** Acne, angioedema, arthralgia, asthenia, bradycardia, chest pain, cough, dizziness, dyspnoea, eye irritation, fatigue, flushing, gastrointestinal disturbances, headache, hypersensitivity reactions, hypotension, influenza-like symptoms, muscle spasms, myalgia, nasopharyngitis, neuropathic pain, oedema, palpitation, paraesthesia, pruritus, rash, rhinorrhoea, sleep disturbances, syncope, tachycardia, taste disturbances, tinnitus, tremor, urticaria
  - **Uncommon** Cold extremities, ear pain, eye swelling, injection-site reactions, parosmia, skin discoloration

2.4 Gaucher’s disease

Other drugs used for Gaucher’s disease Miglustat, p. 937

ENZYMES

Imiglucerase

- **DRUG ACTION** Imiglucerase is an enzyme produced by recombinant DNA technology that is administered as enzyme replacement therapy for non-neurological manifestations of type I or type III Gaucher’s disease, a familial disorder affecting principally the liver, spleen, bone marrow, and lymph nodes.

- **INDICATIONS AND DOSE**
  - **Non-neurological manifestations of type I Gaucher’s disease (specialist use only)**
  - **Non-neurological manifestations of type III Gaucher’s disease (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 60 units/kg every 2 weeks; maintenance, adjusted according to response, doses as low as 15 units/kg once every 2 weeks may improve haematological parameters and organomegaly
934 Metabolic disorders

Betaine

- **INDICATIONS AND DOSE**
  - **Adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism (specialist use only)**
  - **BY MOUTH**
    - Adult: 3 g twice daily (max. per dose 10 g), adjusted according to response; maximum 20 g per day

- **SIDE-EFFECTS**
  - Uncommon Agitation, alopecia, anorexia, depression, gastro-intestinal disorders, personality disorder, reversible cerebral oedema, sleep disturbances, urinary incontinence, urticaria
  - **PREGNANCY** Manufacturer advises caution—no information available.
  - **BREAST FEEDING** Manufacturer advises caution—no information available.

- **MONITORING REQUIREMENTS** Monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur.

- **DIRECTIONS FOR ADMINISTRATION** Powder should be mixed with water, juice, milk, formula, or food until completely dissolved and taken immediately; measuring spoons are provided to measure 1 g, 150 mg, and 100 mg of Cystadane® powder.

- **PRESCRIBING AND DISPENSING INFORMATION** Betaine should be used in conjunction with dietary restrictions and may be given with supplements of Vitamin B₁₂, pyridoxine, and folate under specialist advice.

- **SCOTTISH MEDICINES CONSORTIUM (SMC) DECISIONS**
  - The Scottish Medicines Consortium has advised (July 2010) that betaine anhydrous (Cystadane®) is accepted for restricted use within NHS Scotland for the adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism in patients who are not responsive to pyridoxine treatment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral solution

  - **Powder**
    - Cystadane (Orphan Europe (UK) Ltd)
      - Betaine 1 gram per 1 gram Cystadane oral powder | 180 gram £347.00

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# Velaglucerase alfa

**DRUG ACTION** Velaglucerase alfa is an enzyme produced by recombinant DNA technology that is administered as enzyme replacement therapy for the treatment of type I Gaucher’s disease.

**INDICATIONS AND DOSE**

- **Type I Gaucher’s disease (specialist use only)**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 60 units/kg every 2 weeks; adjusted according to response to 15–60 units/kg every 2 weeks

**SIDE-EFFECTS** Abdominal pain, arthralgia, back pain, bone pain, dizziness, flushing, headache, hypersensitivity reactions, hypertension, hypotension, malaise, nausea, pyrexia, rash, tachycardia, urticaria

**SIDE-EFFECTS, FURTHER INFORMATION**

- Infusion-related reactions: Infusion-related reactions very common; manage by slowing the infusion rate, or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature.

**PREGNANCY** Manufacturer advises use with caution—limited information available.

**BREAST FEEDING** Manufacturer advises use with caution—no information available.

**MONITORING REQUIREMENTS** Monitor immunoglobulin G (IgG) antibody concentration in severe infusion-related reactions or if there is a lack or loss of effect with velaglucerase alfa.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (VPRIV®), give intermittently in Sodium chloride 0.9%; reconstitute each 400-unit vial with 4.3 mL water for injections to produce a 100 units/mL solution; dilute requisite dose in 100 mL infusion fluid; give over 60 minutes through a 0.22 micron filter; start infusion within 24 hours of reconstitution.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**
    - ELECTROLYTES: May contain Sodium
      - VPRIV (Shire Pharmaceuticals Ltd)
        - Velaglucerase alfa 400 unit VPRIV 400 units powder for solution for infusion vials | 1 vial £1,410.20

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## 2.5 Homocystinuria

**METHYL DONORS**

**Betaine**

**INDICATIONS AND DOSE**

- **Adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism (specialist use only)**

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**Velaglucerase alfa**

**INDICATIONS AND DOSE**

- **Type I Gaucher’s disease (specialist use only)**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 60 units/kg every 2 weeks; adjusted according to response to 15–60 units/kg every 2 weeks

**SIDE-EFFECTS** Abdominal pain, arthralgia, back pain, bone pain, dizziness, flushing, headache, hypersensitivity reactions, hypertension, hypotension, malaise, nausea, pyrexia, rash, tachycardia, urticaria

**SIDE-EFFECTS, FURTHER INFORMATION**

- Infusion-related reactions: Infusion-related reactions very common; manage by slowing the infusion rate, or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature.

**PREGNANCY** Manufacturer advises use with caution—limited information available.

**BREAST FEEDING** Manufacturer advises use with caution—no information available.

**MONITORING REQUIREMENTS** Monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur.

**DIRECTIONS FOR ADMINISTRATION** Powder should be mixed with water, juice, milk, formula, or food until completely dissolved and taken immediately; measuring spoons are provided to measure 1 g, 150 mg, and 100 mg of Cystadane® powder.

**PRESCRIBING AND DISPENSING INFORMATION** Betaine should be used in conjunction with dietary restrictions and may be given with supplements of Vitamin B₁₂, pyridoxine, and folate under specialist advice.

**SCOTTISH MEDICINES CONSORTIUM (SMC) DECISIONS**

The Scottish Medicines Consortium has advised (July 2010) that betaine anhydrous (Cystadane®) is accepted for restricted use within NHS Scotland for the adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism in patients who are not responsive to pyridoxine treatment.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral solution

  - **Powder**
    - Cystadane (Orphan Europe (UK) Ltd)
      - Betaine 1 gram per 1 gram Cystadane oral powder | 180 gram £347.00
2.6 Mucopolysaccharidosis

**ENZYMES**

### Elosulfase alfa

**DRUG ACTION** Elosulfase alfa is an enzyme produced by recombinant DNA technology that provides replacement therapy in conditions caused by N-acetylgalactosamine-6-sulfatase (GALNS) deficiency.

| CAUTIONS | Elderly—no information available • infusion-related reactions |
| CAUTIONS, FURTHER INFORMATION | Infusion-related reactions • Infusion-related reactions can occur; manufacturer advises these may be minimised by pre-treatment with an antihistamine and antipyretic, given 30–60 minutes before treatment. If reaction is severe, stop infusion and start appropriate treatment. Caution and close monitoring is advised during re-administration following a severe reaction. |
| SIDE-EFFECTS | Common or very common • Abdominal pain • chills • diarrhea • dizziness • dyspnoea • headache • hypersensitivity • infusion-related reactions • myalgia • nausea • opharyngeal pain • pyrexia • vomiting |
| unemployed | Anaphylaxis |
| PREGNANCY | Manufacturer advises avoid unless essential |
| BREAST FEEDING | Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies |
| DIRECTIONS FOR ADMINISTRATION | For intravenous infusion (Vimizim®), give intermittently in Sodium Chloride 0.9%; body-weight under 25 kg, dilute requisite dose to final volume of 100 mL infusion fluid and mix gently, give over 4 hours through in-line filter (0.2 micron) initially at a rate of 3 mL/hour, then increase to a rate of 6 mL/hour after 15 minutes, then increase gradually if tolerated every 15 minutes by 6 mL/hour to max. 36 mL/hour; body-weight 25 kg or over, dilute requisite dose to final volume of 250 mL and mix gently, give over 4 hours through in-line filter (0.2 micron) initially at a rate of 6 mL/hour, then increase to a rate of 12 mL/hour after 15 minutes, then increase gradually if tolerated every 15 minutes by 12 mL/hour to max. 72 mL/hour. |
| HANDLING AND STORAGE | Manufacturer advises store in a refrigerator at 2–8°C. After dilution use immediately or, if necessary, store at 2–8°C for max. 24 hours, followed by up to 24 hours at 23–27°C. |
| PATIENT AND CARER ADVICE | Driving and skilled tasks • Manufacturer advises patients and carers should be counselled about the effects on driving and performance of skilled tasks—increased risk of dizziness. |
| MEDICINAL FORMS | There can be variation in the licensing of different medicines containing the same drug. |

#### Solution for infusion

- **Excipients:** May contain Polysorbates, sorbitol
- **Electrolytes:** May contain Sodium
- **Elosulfase alfa (non-proprietary)**
  - Elosulfase alfa 1 mg per 1 ml Vimizim 5mg/5ml solution for infusion vials | 1 vial £982.00

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### Galsulfase

**DRUG ACTION** Galsulfase is a recombinant form of human N-acetylgalactosamine-4-sulfatase.

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th>Mucopolysaccharidosis VI (specialist use only)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY INTRAVENOUS INFUSION</strong></td>
<td>Adult: 1 mg/kg once weekly</td>
</tr>
</tbody>
</table>

| CAUTIONS | Acute febrile illness (consider delaying treatment) • acute respiratory illness (consider delaying treatment) • infusion-related reactions can occur • respiratory disease |
| SIDE-EFFECTS | Abdominal pain • anaphylaxis • arreflexia • chest pain • conjunctivitis • corneal opacity • dyspnoea • ear pain • facial oedema • gastroenteritis • hypertension • infusion-related reactions • malaise • nasal congestion • pharyngitis • rigors • umbilical hernia |

#### SIDE-EFFECTS, FURTHER INFORMATION

- Infusion-related reactions Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details. |
| PREGNANCY | Manufacturer advises avoid unless essential. |
| BREAST FEEDING | Manufacturer advises avoid—no information available. |

#### DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Naglazyme®), give intermittently in Sodium Chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and mix gently; infuse through a 0.2 micron in-line filter; give approx. 2.5% of the total volume over 1 hour, then infuse remaining volume over next 3 hours; if body-weight under 20 kg and at risk of fluid overload, dilute requisite dose in 100 mL infusion fluid and give over at least 4 hours.

---

### Idursulfase

**DRUG ACTION** Idursulfase is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in mucopolysaccharidosis II (Hunter syndrome), a lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase.

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th>Mucopolysaccharidosis II (specialist use only)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY INTRAVENOUS INFUSION</strong></td>
<td>Adult: 500 micrograms/kg once weekly</td>
</tr>
</tbody>
</table>

| CAUTIONS | Acute febrile respiratory illness (consider delaying treatment) • infusion-related reactions can occur • severe respiratory disease |
| SIDE-EFFECTS | Common or very common • Arrhythmia • arthralgia • bronchospasm • chest pain • cough • cyanosis • dizziness • dyspnoea • erythema • facial oedema • flushing • gastrointestinal disturbances • headache • hypertension • hypotension • hypoxia • infusion-site swelling • peripheral oedema • pruritus • pyrexia • rash • swollen tongue • tachycardia • tachypnoea • tremor • urticaria • wheezing |

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#### Solution for infusion

- **Naglazyme** (BioMarin Europe Ltd)
- Galsulfase 1 mg per 1 ml Naglazyme 5mg/5ml solution for infusion vials | 1 vial £982.00
- **Frequency not known** Anaphylaxis · infusion-related reactions · pulmonary embolism

### SIDE-EFFECTS, FURTHER INFORMATION

- Infusion-related reactions Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

- **CONCEPTION AND CONTRACEPTION** Contra-indicated in women of child-bearing potential.

- **PREGNANCY** Manufacturer advises avoid.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Elaprase[^3]), give intermittently in Sodium chloride 0.9%; dilute requisite dose in 100 mL infusion fluid and mix gently (do not shake); give over 3 hours (gradually reduced to 1 hour if no infusion-related reactions).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

- **Elaprase** (Shire Pharmaceuticals Ltd)  
  - Idursulfase 2 mg per 1 mL Elaprase 6mg/3ml concentrate for solution for infusion vials [1 vial](http://example.com) £1.985.00

### Laronidase

- **DRUG ACTION** Laronidase is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in the treatment of non-neurological manifestations of mucopolysaccharidosis I, a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase.

- **INDICATIONS AND DOSE**
  - Non-neurological manifestations of mucopolysaccharidosis I (specialist use only)
    - **BY INTRAVENOUS INFUSION**
      - Adult: 100 units/kg once weekly

- **CAUTIONS**
  - Infusion-related reactions can occur

- **INTERACTIONS** → Appendix 1 (laronidase).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · alopecia · anaphylaxis · angioedema · blood pressure changes · cold extremities · cough · diarrhoea · dizziness · dyspnoea · fatigue · flushing · headache · influenza-like symptoms · infusion-site reactions · musculoskeletal pain · nausea · pain in extremities · pallor · paraesthesia · pruritus · rash · restlessness · tachycardia · urticaria · vomiting
  - **Frequency not known** Bronchospasm · infusion-related reactions · respiratory arrest

### DIRECTIONS FOR ADMINISTRATION

- **For intravenous infusion** (Aldurazyme[^4]), give intermittently in Sodium chloride 0.9%; withdraw volume of infusion fluid equivalent to volume of laronidase concentrate being added; give through in-line filter (0.22 micron) initially at a rate of 2 units/kg/hour then increase gradually every 15 minutes to max. 43 units/kg/hour.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

- **Elaprase** (Genzyme Therapeutics Ltd)  
  - Laronidase 100 unit per 1 mL Aldurazyme 500units/5ml solution for infusion vials [1 vial](http://example.com) £444.70

### 2.7 Nephropathic cystinosis

#### AMINO ACIDS AND DERIVATIVES

**Mercaptamine**

(Cysteamine)

- **INDICATIONS AND DOSE**
  - Nephropathic cystinosis (specialist use only)
    - **BY MOUTH**
      - Adult (body-weight 50 kg and above): Initially one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks to avoid intolerance, maintenance 2 g daily in 4 divided doses

### DOSE EQUIVALENCE AND CONVERSION

- 1.3 g/m² is approximately equivalent to 50 mg/kg.

### IMPORTANT SAFETY INFORMATION

#### SAFE PRACTICE

Mercaptamine has been confused with mercaptopurine; care must be taken to ensure the correct drug is prescribed and dispensed.

- **CAUTIONS**
  - Dose of phosphate supplement may need to be adjusted if transferring from phosphocysteamine to mercaptamine

### SIDE-EFFECTS

- **Common or very common** Abdominal pain · anorexia · breath and body odour · diarrhoea · dyspepsia · encephalopathy · fever · gastroenteritis · headache · malaise · nausea · rash · vomiting
  - **Uncommon** Drowsiness · gastro-intestinal ulcer · hallucinations · leucopenia · nephrotic syndrome · nervousness · seizures

### ALLERGY AND CROSS-SENSITIVITY

- Contra-indicated if history of hypersensitivity to penicillamine.

#### PREGNANCY

- Avoid—teratogenic and toxic in animal studies.

#### BREAST FEEDING

- Avoid.

#### MONITORING REQUIREMENTS

- Leucocyte-cystine concentration and haematological monitoring required—consult product literature.

#### PRESCRIBING AND DISPENSING INFORMATION

Mercaptamine has a very unpleasant taste and smell, which can affect compliance.
### Pompe disease

#### ENZYMES

**Alglucosidase alfa**

- **DRUG ACTION** Alglucosidase alfa is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in Pompe disease, a lysosomal storage disorder caused by deficiency of acid alpha-glucosidase.

- **INDICATIONS AND DOSE**
  - **Pompe disease (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 20 mg/kg every 2 weeks

- **CAUTIONS** Cardiac dysfunction, infusion-related reactions—consult product literature.

- **SIDE-EFFECTS**
  - Common or very common: Agitation, anaphylaxis, antibody formation, blood pressure changes, bronchospasm, chest discomfort, cold extremities, cough, dyspnoea, dyspnoea, dyspepsia, flatulence, headache, hypoaesthesia, insomnia, malaise, muscle spasm, muscle weakness, nausea, paraesthesia, peripheral neuropathy, pruritus, pyrexia, rash, restlessness, sweating, tachycardia, tachypnoea, tremor, urticaria, vomiting
  - Frequency not known: Infusion-related reactions, necrotising skin lesions, severe skin reactions, ulcerative skin lesions

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Infusion-related reactions
  - Consult product literature for details.

- **PREGNANCY** Toxicity in animal studies, but treatment should not be withheld.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor closely if cardiac dysfunction.
  - Monitor closely if respiratory dysfunction.
  - Monitor immunoglobulin G (IgG) antibody concentration.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Myozyme®), give intermittently in Sodium chloride 0.9%; reconstitute 50 mg with 10.3 mL of water for injections to produce 5 mg/mL solution; gently rotate vial without shaking; dilute requisite dose with infusion fluid to give a final concentration of 0.5–4 mg/mL; give through a low-protein-binding in-line filter (0.2 micron) at an initial rate of 1 mg/kg/hour increased by 2 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour.

#### Niemann-Pick type C disease

**ENZYME INHIBITORS**

- **Glucosylceramide synthase inhibitors**
  - Miglustat

- **DRUG ACTION** Miglustat is an inhibitor of glucosylceramide synthase.

- **INDICATIONS AND DOSE**
  - Mild to moderate type I Gaucher’s disease for whom enzyme replacement therapy is unsuitable (under expert supervision)
    - **BY MOUTH**
      - Adult: 100 mg 3 times a day, reduced if not tolerated to 100 mg 1–2 times a day
  - Treatment of progressive neurological manifestations of Niemann-Pick type C disease (under expert supervision)
    - **BY MOUTH**
      - Adult: 200 mg 3 times a day

- **SIDE-EFFECTS** Abdominal pain, anorexia, ataxia, chills, constipation, decreased libido, depression, diarrhoea, dizziness, dyspepsia, flatulence, headache, hypoaesthesia, insomnia, malaise, muscle spasm, muscle weakness, nausea, paraesthesia, peripheral neuropathy, tachycardia, tremor, vomiting, weight changes

- **CONCEPTION AND CONTRACEPTION** Effective contraception must be used during treatment. Men should avoid fathering a child during and for 3 months after treatment.

- **PREGNANCY** Manufacturer advises avoid—tolerability in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** No information available—manufacturer advises caution.

- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m². For Gaucher’s disease initially 100 mg twice daily if eGFR 50–70 mL/minute/1.73 m². Initially 100 mg once daily if eGFR 30–50 mL/minute/1.73 m². For Niemann-Pick type C disease, initially 200 mg twice daily if eGFR 50–70 mL/minute/1.73 m². Initially 100 mg twice daily if eGFR 30–50 mL/minute/1.73 m²

- **MONITORING REQUIREMENTS**
  - Monitor cognitive and neurological function.
  - Monitor growth and platelet count in Niemann-Pick type C disease.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - Cystagon (Orphan Europe (UK) Ltd)
    - Miglustat 100 mg Cystagon 100 mg capsules | 84 capsule £3,934.17 (Hospital only)

- **PREGNANCY**
  - Monitor immunoglobulin G (IgG) antibody concentration.
  - Infusion-related reactions very common, calling for use of antihistamine, antipyretic, or corticosteroid; consult product literature for details.

- **BREAST FEEDING**
  - Manufactured advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor closely if cardiac dysfunction.
  - Monitor closely if respiratory dysfunction.
  - Monitor immunoglobulin G (IgG) antibody concentration.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Myozyme®), give intermittently in Sodium chloride 0.9%; reconstitute 50 mg with 10.3 mL of water for injections to produce 5 mg/mL solution; gently rotate vial without shaking; dilute requisite dose with infusion fluid to give a final concentration of 0.5–4 mg/mL; give through a low-protein-binding in-line filter (0.2 micron) at an initial rate of 1 mg/kg/hour increased by 2 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - Zavesca (Actelion Pharmaceuticals UK Ltd)
    - Miglustat 100 mg Zavesca 100 mg capsules | 84 capsule £3,934.17 (Hospital only)
2.10 Tyrosinaemia type I

ENZYME INHIBITORS

4-HYDROXYPHENYLPYRUVATE DIOXYGENASE INHIBITORS

Nitisinone

(NTBC)

- INDICATIONS AND DOSE
  Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only)
  - BY MOUTH
  - Adult: Initially 500 micrograms/kg twice daily, adjusted according to response; maximum 2 mg/kg per day

- SIDE-EFFECTS
  - Common or very common Conjunctivitis - corneal opacity - eye pain - granulocytopenia - keratitis - leucopenia - photophobia - thrombocytopenia
  - Uncommon Blepharitis - erythematous rash - exfoliative dermatitis - leucocytosis - pruritus
  - PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk — toxicity in animal studies.
  - BREAST FEEDING Manufacturer advises avoid — adverse effects in animal studies.
  - PRE-TREATMENT SCREENING Slit-lamp examination of eyes recommended before treatment.
  - MONITORING REQUIREMENTS
    - Monitor liver function regularly.
    - Monitor platelet and white blood cell count every 6 months.
  - DIRECTIONS FOR ADMINISTRATION Capsules can be opened and the contents suspended in a small amount of water or formula diet and taken immediately.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  - Capsule
    - Orfadin (Swedish Orphan Biovitrum Ltd)
      Nitisinone 2 mg Orfadin 2mg capsules | 60 capsule £564.00
      Nitisinone 5 mg Orfadin 5mg capsules | 60 capsule £1,127.00
      Nitisinone 10 mg Orfadin 10mg capsules | 60 capsule £2,062.00
      Nitisinone 20 mg Orfadin 20mg capsules | 60 capsule £4,512.00
  - Oral suspension
    - Orfadin (Swedish Orphan Biovitrum Ltd)
      Nitisinone 4 mg per 1 ml Orfadin 4mg/1ml oral suspension sugar-free | 90 ml £1,692.00

2.11 Urea cycle disorders

AMINO ACIDS AND DERIVATIVES

Carglumic acid

- INDICATIONS AND DOSE
  Hyperammonaemia due to N-acetylglutamate synthase deficiency (under expert supervision)
  - BY MOUTH
  - Adult: Initially 50–125 mg/kg twice daily, to be taken immediately before food, dose adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily, the total daily dose may alternatively be given in 3–4 divided doses

- INTERACTIONS
  - Appendix 1 (sodium phenylbutyrate).

- SIDE-EFFECTS
  - Common or very common Alkalosis - blood disorders - body odour - decreased appetite - depression - gastro-intestinal disturbances - headache - irritability - menstrual disorders - metabolic acidosis - oedema - rash - renal tubular acidosis - syncope - taste disturbance - weight gain
  - Uncommon Arrhythmias - pancreatitis - peptic ulcer - rectal bleeding

Hyperammonaemia due to organic acidaemia (under expert supervision)

- BY MOUTH
  - Adult: Initially 50–125 mg/kg twice daily, to be taken immediately before food, dose adjusted according to plasma-ammonia concentration, the total daily dose may alternatively be given in 3–4 divided doses

IMPORTANT SAFETY INFORMATION

EMERGENCY MANAGEMENT OF UREA CYCLE DISORDERS

For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

- SIDE-EFFECTS
  - Common or very common Sweating
  - Uncommon Bradycardia - diarrhoea - pyrexia - vomiting
  - PREGNANCY Manufacturer advises avoid unless essential — no information available.
  - BREAST FEEDING Manufacturer advises avoid — present in milk in animal studies.
  - DIRECTIONS FOR ADMINISTRATION Dispersible tablets must be dispersed in at least 5–10 mL of water and taken orally immediately, or administered via a nasogastric tube.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  - Dispersible tablet
    - Carbaglu (Orphan Europe (UK) Ltd)
      Carglumic acid 200 mg: Carbaglu 200mg dispersible tablets sugar-free | 5 tablet £299.00 sugar-free | 60 tablet £3,499.00

DRUGS FOR METABOLIC DISORDERS

AMMONIA LOWERING DRUGS

Sodium phenylbutyrate

- INDICATIONS AND DOSE
  Long-term treatment of urea cycle disorders (as adjunctive therapy in all patients with neonatal-onset disease and in those with late-onset disease who have a history of hyperammonaemic encephalopathy) (under expert supervision)
  - BY MOUTH
  - Adult: 9.9–13 g/m² daily in divided doses, with meals; maximum 20 g per day

IMPORTANT SAFETY INFORMATION

EMERGENCY MANAGEMENT OF UREA CYCLE DISORDERS

For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

- CAUTIONS Congestive heart failure (preparations contain significant amounts of sodium)
- INTERACTIONS
  - Appendix 1 (sodium phenylbutyrate).
- SIDE-EFFECTS
  - Common or very common Alkalosis - blood disorders - body odour - decreased appetite - depression - gastro-intestinal disturbances - headache - irritability - menstrual disorders - metabolic acidosis - oedema - rash - renal tubular acidosis - syncope - taste disturbance - weight gain
  - Uncommon Arrhythmias - pancreatitis - peptic ulcer - rectal bleeding
SIDE-EFFECTS, FURTHER INFORMATION
Gastro-intestinal side-effects may be reduced by giving smaller doses more frequently.

- CONCEPTION AND CONTRACEPTION Manufacturer advises adequate contraception during administration in women of child-bearing potential.
- PREGNANCY Avoid—toxicity in animal studies.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- HEPATIC IMPAIRMENT Manufacturer advises use with caution.
- RENAL IMPAIRMENT Manufacturer advises use with caution (preparations contain significant amounts of sodium).
- DIRECTIONS FOR ADMINISTRATION
  - Granules should be mixed with food before taking. Pheburane® granules must not be administered by nasogastric or gastrostomy tubes.

2.12 Wilson’s disease

Other drugs used for Wilson’s disease Penicillamine, p. 964

ANTIDOTES AND CHELATORS > COPPER CHELATORS

Zinc acetate

- INDICATIONS AND DOSE
  - Wilson’s disease (initiated under specialist supervision)
    - BY MOUTH
    - Adult: 50 mg 3 times a day (max. per dose 50 mg 5 times a day), adjusted according to response

DOSE EQUIVALENCE AND CONVERSION
- Doses expressed as elemental zinc.

PHARMACOKINETICS
Symptomatic Wilson’s disease patients should be treated initially with a chelating agent because zinc has a slow onset of action. When transferring from chelating treatment to zinc maintenance therapy, chelating treatment should be co-administered for 2–3 weeks until zinc produces its maximal effect.

- CAUTIONS Portal hypertension (risk of hepatic decompensation when switching from chelating agent)
- INTERACTIONS → Appendix 1 (zinc)
- SIDE-EFFECTS
  - Common or very common Gastric irritation (usually transient)
  - Uncommon Leucopenia · sideroblastic anaemia

SIDE-EFFECTS, FURTHER INFORMATION
Transient gastric irritation may be reduced if first dose is taken mid-morning or with a little protein.

- PREGNANCY Reduce dose to 25 mg 3 times daily adjusted according to plasma-copper concentration and urinary copper excretion.
- BREAST FEEDING Manufacturer advises avoid; present in milk—may cause zinc-induced copper deficiency in infant.
- MONITORING REQUIREMENTS Monitor full blood count and serum cholesterol.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  Capsule
  - CAUTIONARY AND ADVISORY LABELS 23
  - Wilson (Orphan Europe (UK) Ltd)
    - Zinc (as Zinc acetate) 25 mg Wilzin 25mg capsules | 250 capsule POM £132.00
    - Zinc (as Zinc acetate) 50 mg Wilzin 50mg capsules | 250 capsule POM £242.00

ANTIDOTES AND CHELATORS > COPPER CHELATORS

Trientine dihydrochloride

- INDICATIONS AND DOSE
  - Wilson’s disease in patients intolerant of penicillamine
    - BY MOUTH
    - Adult: 1.2–2.4 g daily in 2–4 divided doses, adjusted according to response, to be taken before food

- INTERACTIONS → Appendix 1 (trientine).
- SIDE-EFFECTS
  - Common or very common Nausea · rash
  - Very rare Anaemia
  - Frequency not known Colitis · duodenitis
- PREGNANCY Teratogenic in animal studies—use only if benefit outweighs risk. Monitor maternal and neonatal serum-copper concentrations.
- PRESCRIBING AND DISPENSING INFORMATION Trientine is not an alternative to penicillamine for rheumatoid arthritis or cystinuria. Penicillamine-induced systemic lupus erythematosus may not resolve on transfer to trientine.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  Capsule
  - CAUTIONARY AND ADVISORY LABELS 6, 22
  - Trientine dihydrochloride (Non-proprietary)
    - Trientine dihydrochloride 300 mg Trientine dihydrochloride 300mg capsules | 100 capsule POM no price available

3  Mineral and trace elements deficiencies

3.1 Selenium deficiency

Selenium deficiency can occur as a result of inadequate diet or prolonged parenteral nutrition. A selenium supplement should not be given unless there is good evidence of deficiency.
VITAMINS AND TRACE ELEMENTS

Selenium

- **INDICATIONS AND DOSE**
  - Selenium deficiency
    - By mouth, or by intramuscular injection, or by intravenous injection
    - Adult: 100–500 micrograms daily
  - **INTERACTIONS** → Appendix 1 (selenium).

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Selenium (Non-proprietary)
      - Selenium (as L-Selenomethionine) 100 microgram Solgar Selenium 100microgram tablets | 100 tablet no price available
      - L-Selenomethionine 200 microgram Solgar Selenium 200microgram tablets | 50 tablet no price available
      - 250 tablet no price available
      - EN-Selenium 200microgram tablets | 30 tablet £88.60
      - HealthAid Selenium 200microgram tablets | 60 tablet £3.90
      - Lamberts Selenium 200microgram tablets | 60 tablet £4.08
  - SelenoPrecise (Pharma Nord (UK) Ltd)
    - Selenium (as L-Selenomethionine) 100 microgram SelenoPrecise 100microgram tablets | 60 tablet £6.75
    - L-Selenomethionine 200 microgram SelenoPrecise 200microgram tablets | 60 tablet £4.02
  - **Capsule**
    - Selenium (Non-proprietary)
      - L-Selenomethionine 200 microgram Selenium 200microgram capsules | 30 capsule £3.20 | 60 capsule £5.79
  - **Oral solution**
    - Selense (Baxter Healthcare Ltd)
      - Selenium (as Sodium selenite) 50 microgram per 1 ml Selense 100micrograms/2ml oral solution 2ml unit-dose ampoules | 20 unit dose [P] no price available
      - Selense 500micrograms/10ml oral solution unit dose vials | 10 unit dose [P] no price available
  - **Solution for injection**
    - Selense (Baxter Healthcare Ltd)
      - Selenium (as Sodium selenite) 50 microgram per 1 ml Selense 100micrograms/2ml solution for injection ampoules | 10 ampoule [P] no price available
      - Selense 500micrograms/10ml solution for injection vials | 10 vial [P] no price available

3.2 Zinc deficiency

Zinc supplements should not be given unless there is good evidence of deficiency (hypoproteinaemia spuriously lowers plasma-zinc concentration) or in zinc-losing conditions. Zinc deficiency can occur as a result of inadequate diet or malabsorption; excessive loss of zinc can occur in trauma, burns, and protein-losing conditions. A zinc supplement is given until clinical improvement occurs, but it may need to be continued in severe malabsorption, metabolic disorders, or in zinc-losing states.

Zinc is used in the treatment of Wilson’s disease and acrodermatitis enteropathica, a rare inherited abnormality of zinc absorption.

Parenteral nutrition regimens usually include trace amounts of zinc. If necessary, further zinc can be added to intravenous feeding regimens.

Electrolytes and minerals → Zinc

Zinc sulfate

- **INDICATIONS AND DOSE**
  - Zinc deficiency or supplementation in zinc-losing conditions
    - By mouth using effervescent tablets
    - Child (body-weight up to 10 kg): 22.5 mg daily, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
    - Child (body-weight 10–30 kg): 22.5 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
    - Child (body-weight 31 kg and above): 45 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
    - Adult (body-weight 31 kg and above): 45 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
  - Additional elemental zinc for intravenous nutrition
    - By intravenous injection
      - Adult: 6.5 mg daily (Zn²⁺ 100 micromol)
  - **INTERACTIONS** → Appendix 1 (zinc).
  - **SIDE-EFFECTS** Abdominal pain, diarrhoea, dyspepsia, gastric irritation, gastritis, headache, irritability, lethargy, nausea, vomiting
  - **PREGNANCY** Crosses placenta; risk theoretically minimal, but no information available.
  - **BREAST FEEDING** Present in milk; risk theoretically minimal, but no information available.
  - **RENAL IMPAIRMENT** Accumulation may occur in acute renal failure.
  - **PRESCRIBING AND DISPENSING INFORMATION** Each Solvazinc® tablet contains zinc sulfate monohydrate 125 mg (45 mg zinc).
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection
  - **Effervescent tablet**
    - CAUTIONARY AND ADVISORY LABELS 13, 21
    - Solvazinc (Galen Ltd)
      - Zinc sulfate monohydrate 125 mg Solvazinc 125mg effervescent tablets sugar-free | 90 tablet [P] £16.45 DT price + £16.45

4 Nutrition (intravenous)

Intravenous nutrition

Overview

When adequate feeding through the alimentary tract is not possible, nutrients may be given by intravenous infusion. This may be in addition to ordinary oral or tube feeding—supplemental parenteral nutrition, or may be the sole source of nutrition—total parenteral nutrition (TPN). Indications for this method include preparation of undernourished patients for surgery, chemotherapy, or radiation therapy; severe or prolonged disorders of the gastro-intestinal tract; major surgery, trauma, or burns; prolonged coma or refusal to eat; and some patients with renal or hepatic failure. The composition of proprietary preparations available is given under Proprietary Infusion Fluids for Parenteral Feeding p. 941.
## Proprietary Infusion Fluids for Parenteral Feeding

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>12 Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>K⁺</td>
<td>Mg²⁺</td>
<td>Na⁺</td>
</tr>
<tr>
<td>Aminoven 25 (Fresenius Kabi Ltd)</td>
<td>25.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clinimix N9G20E (Baxter Healthcare Ltd)</td>
<td>4.6</td>
<td>1680</td>
<td>30.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Clinimix N14G30E (Baxter Healthcare Ltd)</td>
<td>7.0</td>
<td>2520</td>
<td>30.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Clin Oleic 20% (Baxter Healthcare Ltd)</td>
<td>-</td>
<td>8360</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperamine 30 (B. Braun Medical Ltd)</td>
<td>30.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intralipid 10% (Fresenius Kabi Ltd)</td>
<td>-</td>
<td>4600</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intralipid 20% (Fresenius Kabi Ltd)</td>
<td>-</td>
<td>8400</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intralipid 30% (Fresenius Kabi Ltd)</td>
<td>-</td>
<td>12600</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kabiven (Fresenius Kabi Ltd)</td>
<td>5.3</td>
<td>3275</td>
<td>23.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Kabiven peripheral (Fresenius Kabi Ltd)</td>
<td>3.75</td>
<td>2625</td>
<td>17.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Lipidem (B. Braun Medical Ltd)</td>
<td>-</td>
<td>7900</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Lipofundin MCT/LCT 10% (B. Braun Medical Ltd)</td>
<td>-</td>
<td>4430</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lipofundin MCT/LCT 20% (B. Braun Medical Ltd)</td>
<td>-</td>
<td>8000</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1. 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy.
## Nutrition (intravenous)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>$^{12}$ Energy KJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutriflex basal (B.Braun Medical Ltd)</td>
<td>4.6</td>
<td>2095</td>
<td>30.0 5.7 49.9 35.0 50.0</td>
<td>Ca(^{2+}) 3.6 mmol, acid phosphate 12.8 mmol, anhydrous glucose 125 g</td>
</tr>
<tr>
<td>Nutriflex peri (B.Braun Medical Ltd)</td>
<td>5.7</td>
<td>1340</td>
<td>15.0 4.0 27.0 19.5 31.6</td>
<td>Ca(^{2+}) 2.5 mmol, acid phosphate 5.7 mmol, anhydrous glucose 80 g</td>
</tr>
<tr>
<td>Nutriflex plus (B.Braun Medical Ltd)</td>
<td>6.8</td>
<td>2510</td>
<td>25.0 5.7 37.2 22.9 35.5</td>
<td>Ca(^{2+}) 3.6 mmol, acid phosphate 20 mmol, anhydrous glucose 150 g</td>
</tr>
<tr>
<td>Nutriflex special (B.Braun Medical Ltd)</td>
<td>10.0</td>
<td>4020</td>
<td>25.7 5.0 40.5 22.0 49.5</td>
<td>Ca(^{2+}) 4.1 mmol, acid phosphate 14.7 mmol, anhydrous glucose 240 g</td>
</tr>
<tr>
<td>NuTRIflex Lipid peri (B.Braun Medical Ltd)</td>
<td>4.56</td>
<td>2664</td>
<td>24.0 2.4 40.0 32.0 38.4</td>
<td>Ca(^{2+}) 2.4 mmol, Zn(^{2+}) 24 micromol, phosphate 6 mmol, anhydrous glucose 64 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>NuTRIflex Lipid plus (B.Braun Medical Ltd)</td>
<td>5.44</td>
<td>3600</td>
<td>28.0 3.2 40.0 36.0 36.0</td>
<td>Ca(^{2+}) 3.2 mmol, Zn(^{2+}) 24 micromol, phosphate 12 mmol, anhydrous glucose 120 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>NuTRIflex Lipid plus without Electrolytes (B.Braun Medical Ltd)</td>
<td>5.44</td>
<td>3600</td>
<td>- - - - -</td>
<td>anhydrous glucose 120 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>NuTRIflex Lipid special (B.Braun Medical Ltd)</td>
<td>8.0</td>
<td>4004</td>
<td>37.6 4.24 53.6 48.0 48.0</td>
<td>Ca(^{2+}) 4.24 mmol, Zn(^{2+}) 32 micromol, phosphate 16 mmol, anhydrous glucose 144 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>NuTRIflex Lipid special without Electrolytes (B.Braun Medical Ltd)</td>
<td>8.0</td>
<td>4004</td>
<td>- - - - -</td>
<td>anhydrous glucose 144 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
</tbody>
</table>

1. 1000 kcal = 4200kJ; 1000 KJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy.
<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1,2 Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>NuTRIflex Omega plus (B.Braun Medical Ltd)</td>
<td></td>
<td>5.4</td>
<td>3600</td>
<td>Ca²⁺ 3.2 mmol, Zn²⁺ 24 micromol, phosphate 12 mmol, anhydrous glucose 120 g, refined soya oil 16 g, medium-chain triglycerides 20 g, omega-3-acid triglycerides 4 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids 500 mL, 750 mL or 1000 mL; glucose 500 mL, 750 mL or 1000 mL; lipid emulsion 250 mL, 375 mL or 500 mL) 1.25 litre = £47.43; Net price 1.875 litre = £60.57; Net price 2.5 litre = £69.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NuTRIflex Omega special (B.Braun Medical Ltd)</td>
<td></td>
<td>8.0</td>
<td>4004</td>
<td>Ca²⁺ 4.24 mmol, Zn²⁺ 30 micromol, phosphate 16 mmol, anhydrous glucose 144 g, refined soya oil 16 g, medium-chain triglycerides 20 g, omega-3-acid triglycerides 4 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids 250 mL, 500 mL, 750 mL or 1000 mL; glucose 250 mL, 500 mL, 750 mL or 1000 mL; lipid emulsion 125 mL, 250 mL, 375 mL or 500 mL) 625 ml = £43.62; Net price 1.25 litre = £58.01; Net price 1.875 litre = £76.01; Net price 2.5 litre = £89.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N4-550E (Baxter Healthcare Ltd)</td>
<td></td>
<td>3.6</td>
<td>2184</td>
<td>Ca²⁺ 2 mmol, phosphate 8.5 mmol, refined olive and soya oil 20 g, anhydrous glucose 80 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids with electrolytes 1000 mL; glucose 20% 1000 mL; lipid emulsion 10% 500 mL) 2.5 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N4-720E (Baxter Healthcare Ltd)</td>
<td></td>
<td>3.64</td>
<td>3024</td>
<td>Ca²⁺ 1.8 mmol, phosphate 8 mmol, refined olive and soya oil 40 g, anhydrous glucose 80 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids with electrolytes 1000 mL; glucose 20% 1000 mL; lipid emulsion 20% 500 mL) 2.5 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N5-800E (Baxter Healthcare Ltd)</td>
<td></td>
<td>4.6</td>
<td>3360</td>
<td>Ca²⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 100 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids with electrolytes 800 mL or 1000 mL; glucose 25% 800 mL or 1000 mL; lipid emulsion 20% 400 mL or 500 mL) 2 litre: no price available; Net price 2.5 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N6-900E (Baxter Healthcare Ltd)</td>
<td></td>
<td>5.6</td>
<td>3696</td>
<td>Ca²⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 120 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids with electrolytes 800 mL or 1000 mL; glucose 30% 800 mL or 1000 mL; lipid emulsion 20% 400 mL or 500 mL) 2 litre: no price available; Net price 2.5 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N7-1000 (Baxter Healthcare Ltd)</td>
<td></td>
<td>6.6</td>
<td>4368</td>
<td>phosphate 3 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids 600 mL; glucose 40% 600 mL; lipid emulsion 20% 300 mL) 1.5 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N7-1000E (Baxter Healthcare Ltd)</td>
<td></td>
<td>6.6</td>
<td>4368</td>
<td>Ca²⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids with electrolytes 800 mL; glucose 40% 800 mL; lipid emulsion 20% 400 mL) 2 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OliClinomel N8-800 (Baxter Healthcare Ltd)</td>
<td></td>
<td>8.25</td>
<td>3360</td>
<td>phosphate 2.25 mmol, refined olive and soya oil 30 g, anhydrous glucose 125 g</td>
</tr>
<tr>
<td>Net price (triple compartment bag of amino acids 800 mL; glucose 31.25% 800 mL; lipid emulsion 15% 400 mL) 2 litre: no price available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy.
<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>Energy 12kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omegaven (Fresenius Kabi Ltd) Net price 100 ml: no price available</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plasma-Lyte 148 (water) (Baxter Healthcare Ltd) Net price 1 litre: no price available</td>
<td>-</td>
<td>4700</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plasma-Lyte 148 (dextrose 5%) (Baxter Healthcare Ltd) Net price 1 litre: no price available</td>
<td>-</td>
<td>840</td>
<td>5.0</td>
<td>140.0</td>
</tr>
<tr>
<td>Plasma-Lyte M (dextrose 5%) (Baxter Healthcare Ltd) Net price 1 litre: no price available</td>
<td>-</td>
<td>840</td>
<td>16.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Synthamin 9 (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>9.1</td>
<td>-</td>
<td>60.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Synthamin 9 EF (electrolyte-free) (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>9.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Synthamin 14 (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>14.0</td>
<td>-</td>
<td>60.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Synthamin 14 EF (electrolyte-free) (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>14.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Synthamin 17 (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>16.5</td>
<td>-</td>
<td>60.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Synthamin 17 EF (electrolyte-free) (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 3 litre: no price available</td>
<td>16.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vamin 9 Glucose (Fresenius Kabi Ltd) Net price 100 ml = £3.90; Net price 500 ml = £7.95; Net price 1 litre = £13.80</td>
<td>9.4</td>
<td>1700</td>
<td>20.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Vamin 14 (Fresenius Kabi Ltd) Net price 500 ml = £9.48; Net price 1 litre = £16.02</td>
<td>13.5</td>
<td>-</td>
<td>50.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Vamin 14 (electrolyte-free) (Fresenius Kabi Ltd) Net price 500 ml = £9.48; Net price 1 litre = £16.02</td>
<td>13.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vamin 18 (electrolyte-free) (Fresenius Kabi Ltd) Net price 500 ml = £11.99; Net price 1 litre = £23.38</td>
<td>18.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2 Excludes protein- or amino acid-derived energy.
Parenteral nutrition requires the use of a solution containing amino acids, glucose, fat, electrolytes, trace elements, and vitamins. This is now commonly provided by the pharmacy in the form of a 3-litre bag. A single dose of vitamin B₁₂, as hydroxocobalamin p. 899, is given by intramuscular injection; regular vitamin B₁₂ injections are not usually required unless total parenteral nutrition continues for many months. Folic acid p. 898 is given in a dose of 15 mg once or twice each week, usually in the nutrition solution. Other vitamins are usually given daily; they are generally introduced in the parenteral nutrition solution. Alternatively, if the patient is able to take small amounts by mouth, vitamins may be given orally.

The nutrition solution is infused through a central venous catheter inserted under full surgical precautions. Alternatively, infusion through a peripheral vein may be used for supplementary as well as total parenteral nutrition for periods of up to a month, depending on the availability of peripheral veins; factors prolonging cannula life and preventing thrombophlebitis include the use of soft polyurethane paediatric canulas and use of feeds of low osmolality and neutral pH. Only nutritional fluids should be given by the dedicated intravenous line.

Before starting, the patient should be well oxygenated with a near normal circulating blood volume and attention should be given to renal function and acid-base status. Appropriate biochemical tests should have been carried out beforehand and serious deficits corrected. Nutritional and electrolyte status must be monitored throughout treatment. Complications of long-term parenteral nutrition include gall bladder sludging, gall stones, cholestasis and abnormal liver function tests. For details of the prevention and management of parenteral nutrition complications, specialist literature should be consulted.

Protein is given as mixtures of essential and non-essential synthetic L-amino acids. Ideally, all essential amino acids should be included with a wide variety of nonessential ones to provide sufficient nitrogen together with electrolytes. Solutions vary in their composition of amino acids; they often contain an energy source (usually glucose p. 915) and electrolytes. Energy is provided in a ratio of 0.6 to 1.1 megajoules (150–250 kcal) per gram of protein nitrogen. Energy requirements must be met if amino acids are to be utilised for tissue maintenance. A mixture of carbohydrate and fat energy sources (usually 30–50% as fat) gives better utilisation of amino acids than glucose alone.

Glucose is the preferred source of carbohydrate, but if more than 180 g is given per day frequent monitoring of blood glucose is required, and insulin may be necessary. Glucose in various strengths from 10 to 50% must be infused through a central venous catheter to avoid thrombosis.

In parenteral nutrition regimens, it is necessary to provide adequate phosphate in order to allow phosphorylation of glucose and to prevent hypophosphataemia; between 20 and 30 mmol of phosphate is required daily. Fructose and sorbitol have been used in an attempt to avoid the problem of hyperosmolar hyperglycaemic non-ketotic acidosis but other metabolic problems may occur, as with xylitol and ethanol which are now rarely used.

Fat emulsions have the advantages of a high energy to fluid volume ratio, neutral pH, and iso-osmolarity with plasma, and provide essential fatty acids. Several days of adaptation may be required to attain maximal utilisation. Reactions include occasional febrile episodes (usually only with 20% emulsions) and rare anaphylactic responses. Interference with biochemical measurements such as those for blood gases and calcium may occur if samples are taken before fat has been cleared. Daily checks are necessary to ensure complete clearance from the plasma in conditions where fat metabolism may be disturbed. Additives should not be mixed with fat emulsions unless compatibility is known.

Administration Because of the complex requirements relating to parenteral nutrition full details relating to administration have been omitted. In all cases product literature and other specialist literature should be consulted.

**NUTRIENTS > PARENTERAL NUTRITION**

### Parenteral nutrition supplements

#### INDICATIONS AND DOSE

**Dipeptiven 20g/100ml Concentrate for Solution for Infusion Bottles**

**Amino acid supplement for hypercatabolic or hypermetabolic states**

- **BY INTRAVENOUS INFUSION**
- Adult: 300–400 mg/kg daily, dose not to exceed 20% of total amino acid intake

#### CAUTIONS

**Peditrave Solution for Infusion 10ml Vials** Reduced biliary excretion; reduced biliary excretion in cholestatic liver disease; reduced biliary excretion in markedly reduced urinary excretion (careful biochemical monitoring required) - total parenteral nutrition exceeding one month

#### DIRECTIONS FOR ADMINISTRATION

Because of the complex requirements relating to parenteral nutrition, full details relating to administration have been omitted. In all cases specialist pharmacy advice, product literature, and other specialist literature should be consulted. Compatibility with the infusion solution must be ascertained before adding supplementary preparations. Additives should not be mixed with fat emulsions unless compatibility is known.

**Cernevit Solution for Injection Vials and Diluent** Dissolve in 5 mL water for injections.

**Peditrave Solution for Infusion 10ml Vials** For addition to Vaminolact®, Vamin® 14 Electrolyte-Free solutions, and glucose intravenous infusions.

**Tracutil® Ampoules** For addition to infusion solutions.

**Decan Concentrate for Solution for Infusion 40mL Bottles** For addition to infusion solutions.

**Addiphos® Vials** For addition to Vamin® solutions and glucose intravenous infusions.

**Dipeptiven 20g/100ml Concentrate for Solution for Infusion Bottles** For addition to infusion solutions containing amino acids.

**Additrace Solution for Infusion 10ml Ampoules** For addition to Vamin® solutions and glucose intravenous infusions.

**Glycophos® Vials** For addition to Vamin® and Vaminolact® solutions, and glucose intravenous infusions.

**Solviton Powder for Solution for Infusion Vials** Dissolve in water for injections or glucose intravenous infusion for adding to glucose intravenous infusion or Intralipid®; dissolve in Vitlipid N® or Intralipid® for adding to Intralipid® only.

**Vitlipid N Infant Emulsion for Injection 10ml Ampoules** For addition to Intralipid®.

**Vitlipid N Adult Emulsion for Injection 10ml Ampoules** For addition to Intralipid®.
PRESCRIBING AND DISPENSING INFORMATION

Cernevit® solution contains dl-alpha tocopherol 11.2 units, ascorbic acid 125 mg, Biotin 69 micrograms, colecalciferol 220 units, cyanocobalamin 6 micrograms, folic acid 414 micrograms, glycine 250 mg, nicotinamide 46 mg, pantethionic acid (as dexpantethanol) 17.25 mg, pyridoxine hydrochloride 5.5 mg, retinol (as palmitate) 3500 units, riboflavin (as dilyhydrated sodium phosphate) 4.14 mg, thiamine (as cocarcocobale tetrahydride) 3.51 mg.

PEDITRACE SOLUTION FOR INFUSION 10ML VIALS

Peditrace® solution contains traces of Zn²⁺, Cu²⁺, Mn²⁺, Se⁶⁻, I⁻, F⁻.

TRACUTIL® AMPULES

Tractuit® solution contains trace elements Fe²⁺, Zn²⁺, Mn²⁺, Cu²⁺, Cr³⁺, Se⁶⁻, Mo⁶⁻, Cr³⁺.

DECAN CONCENTRATE FOR SOLUTION FOR INFUSION 40ML BOTTLES

For patients over 40 kg. Decan® solution contains trace elements Fe²⁺, Zn²⁺, Cu²⁺, Mn²⁺, F⁻, Co²⁺, I⁻, Se⁶⁻, Mo⁶⁻, Cr³⁺.

ADDIPHOS® VIALS

Addiphos® sterile solution contains phosphate 40 mmol, K⁺ 30 mmol, Na⁺ 30 mmol/20 mL.

Dipeptiven 20G/100ML CONCENTRATE FOR SOLUTION FOR INFUSION BOTTLES

Dipeptiven® solution contains N(2)-L-alanyl-L-glutamine 200 mg/mL (providing L-alanine 82 mg, L-glutamine 134.6 mg).

ADDITRACE SOLUTION FOR INFUSION 10ML VIALS

Additrace solution contains traces of Fe²⁺, Zn²⁺, Cu²⁺, Cr³⁺, Se⁶⁻, Mo⁶⁻, F⁻.

GLYCOPHOS® VIALS

Glycophos® Sterile Concentrate Solution contains phosphate 20 mmol, Na⁺ 40 mmol/20 mL.

SOLIVITO N POWDER FOR SOLUTION FOR INFUSION VIALS

Solivito N® powder for reconstitution contains Biotin 60 micrograms, Cyanocobalamin 5 micrograms, Folic acid 400 micrograms, glycine 300 mg, Nicotinamide 40 mg, Pyridoxine hydrochloride 4.9 mg, riboflavin sodium phosphate 4.9 mg, sodium ascorbate 113 mg, sodium pantothenate 113 mg, thiamine mononitrate 3.1 mg.

VITLIPID N INFANT EMULSION FOR INJECTION 10ML AMPULES

Vitlipid N® infant emulsion contains vitamin A 230 units, ergocalciferol 40 units, dl-alpha tocopherol 0.7 unit, phytomenadione 20 micrograms/mL.

VITLIPID N ADULT EMULSION FOR INJECTION 10ML AMPULES

Vitlipid N® adult emulsion contains vitamin A 330 units, ergocalciferol 20 units, dl-alpha tocopherol 1 unit, phytomenadione 15 micrograms/mL. For adults and children over 11 years.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

Solution for injection

Cernevit® (Baxter Healthcare Ltd)

Alpha tocopherol 11.2 unit. Ascorbic acid 125 mg. Biotin 69 micrograms, Colecalciferol 220 unit. Cyanocobalamin 6 micrograms, Thiamine 3.51 mg, Riboflavin (as Riboflavin sodium phosphate) 4.14 mg, Pantothenic acid (as Dexpantethanol) 17.25 mg, Folic acid 414 micrograms, Pyridoxine (as Pyridoxine hydrochloride) 4.53 mg, Nicotinamide 46 mg, Retinol 3500 unit. Cernevit solution for injection vials and diluent | 10 vial | no price available

Emulsion for injection

Vitlipid N Adult (Fresenius Kabi Ltd)

Alpha tocopherol 910 microgram per 1 mL. Ergocalciferol 500 nanogram per 1 mL. Phytomenadione 15 microgram per 1 mL. Retinol palmitate 99 microgram per 1 mL. Vitlipid N Adult emulsion for injection 10ml ampoules | 1 ampoule | £1.97 | 10 ampoules | no price available

Vitlipid N Infant (Fresenius Kabi Ltd)

Ergocalciferol 1 microgram per 1 mL. Phytomenadione 20 microgram per 1 mL. Retinol palmitate 69 microgram per 1 mL. Alpha tocopherol 640 microgram per 1 mL. Vitlipid N Infant emulsion for injection 10ml ampoules | 1 ampoule | £1.97 | 10 ampoules | no price available

Solution for infusion

Parenteral nutrition supplements (Non-proprietary)

Sodium glycerophosphate 216 mg per 1 mL. Glycerophosphate 4.32g/20ml concentrate for solution for infusion vials | 1 vial | £4.83 | 10 vial | no price available

Additrace (Fresenius Kabi Ltd)

Sodium molydate 0.85 microgram per 1 mL. Chronic chloride 5.33 microgram per 1 mL. Sodium selenite 10.5 microgram per 1 mL. Potassium iodide 16.6 microgram per 1 mL. Manganese chloride 99 microgram per 1 mL. Sodium fluoride 210 microgram per 1 mL. Copper chloride 340 microgram per 1 mL. Ferric chloride 544 microgram per 1 mL. Zinc chloride 1.36 mg per 1 mL. Additrace solution for infusion 10ml ampoules | 1 ampoule | £1.96 | 20 ampoules | no price available

Dipeptiven (Fresenius Kabi Ltd)

N(2)-L-alanyl-L-glutamine 200 mg per 1 mL. Dipeptiven 20G/100ML concentrate for solution for infusion bottles | 1 bottle | £25.93 | 10 bottle | no price available

Additrace (Fresenius Kabi Ltd)

Sodium molybdate dihydrate 2.42 microgram per 1 mL. Chronic chloride 5.3 microgram per 1 mL. Sodium selenite pentahydrate 7.89 microgram per 1 mL. Potassium iodide 16.6 microgram per 1 mL. Sodium fluoride 126 microgram per 1 mL. Manganese chloride 1979 microgram per 1 mL. Copper chloride 204.6 microgram per 1 mL. Zinc chloride 681.5 microgram per 1 mL. Ferrous chloride 695.8 microgram per 1 mL. Tracutil concentrate for solution for infusion 10ml ampoules | 5 ampoule | £7.96

Powder for solution for infusion

Solivito (Fresenius Kabi Ltd)

Cyanocobalamin 5 microgram, Biotin 60 microgram, Folic acid 400 microgram, Thiamine nitrate 3.1 mg, Pyridoxine hydrochloride 4.9 mg, riboflavin sodium phosphate 4.9 mg, Sodium pantothenate 16.5 mg, Nicotinamide 40 mg, Sodium ascorbate 113 mg. Solivito N powder for solution for infusion vials | 1 vial | £1.97 | 10 vial | no price available

5 Nutrition (oral)

Enteral nutrition

Overview

The body’s reserves of protein rapidly become exhausted in severely ill patients, especially during chronic illness or in those with severe burns, extensive trauma, pancreatitis, or intestinal fistula. Much can be achieved by frequent meals and by persuading the patient to take supplementary snacks of ordinary food between the meals.

However, extra calories, protein, other nutrients, and vitamins are often best given by supplementing ordinary meals with enteral sip or tube feeds.

When patients cannot feed normally, for example, patients with severe facial injury, oesophageal obstruction, or coma, a nutritionally complete diet of enteral feeds must be given. The advice of a dietitian should be sought to determine the protein and total energy requirement of the patient and the form and relative contribution of carbohydrate and fat to the energy requirements.

Most enteral feeds contain protein derived from cows’ milk or soya. Elemental feeds containing protein hydrolysates or
free amino acids can be used for patients who have diminished ability to break down protein, for example in inflammatory bowel disease or pancreatic insufficiency.

Even when nutritionally complete feeds are given, water and electrolyte balance should be monitored. Haematological and biochemical parameters should also be monitored, particularly in clinically unstable patients. Extra minerals (e.g. magnesium and zinc) may be needed in patients where gastro-intestinal secretions are being lost. Additional vitamins may also be needed.

**Enteral nutrition in children**

Children have special requirements and in most situations liquid feeds prepared for adults are totally unsuitable—the advice of a paediatric dietitian should be sought.

### 5.1 Special diets

#### Nutrition in special diets

**Overview**

These are preparations that have been modified to eliminate a particular constituent from a food or that are nutrient mixtures formulated as food substitutes for patients who either cannot tolerate or cannot metabolise certain common constituents of food. In certain clinical conditions, some food preparations are regarded as drugs and can be prescribed within the NHS if they have been approved by the Advisory Committee on Borderline Substances (ACBS).

**Coeliac disease**

Coeliac disease is caused by an abnormal immune response to gluten. For management and further information, see Coeliac disease p. 34.

**Phenylketonuria**

Phenylketonuria (hyperphenylalaninaemia, PKU), which results from the inability to metabolise phenylalanine, is managed by restricting dietary intake of phenylalanine to a small amount sufficient for tissue building and repair.

Sapropterin dihydrochloride, a synthetic form of tetrahydrobiopterin, is licensed as an adjunct to dietary restriction of phenylalanine in the management of patients with phenylketonuria and tetrahydrobiopterin deficiency.

Aspartame (used as a sweetener in some foods and medicines) contributes to the phenylalanine intake and may affect control of phenylketonuria. Where the presence of aspartame is specified in the product literature this is indicated in the BNF against the preparation; the patient should be informed of this.

#### 5.1a Phenylketonuria

**DRUGS FOR METABOLIC DISORDERS ➔ TETRAHYDROBIOPTERIN AND DERIVATIVES**

<table>
<thead>
<tr>
<th><strong>Sapropterin dihydrochloride</strong></th>
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<tbody>
<tr>
<td><strong>INDICATIONS AND DOSE</strong></td>
</tr>
<tr>
<td>Phenylketonuria (adjunct to dietary restriction of phenylalanine) (specialist use only)</td>
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<tr>
<td>➔ BY MOUTH</td>
</tr>
<tr>
<td>Adult: Initially 10 mg/kg once daily, adjusted according to response; usual dose 5–20 mg/kg once daily, dose to be taken preferably in the morning</td>
</tr>
</tbody>
</table>

**Tetrahydrobiopterin deficiency (adjunct to dietary restriction of phenylalanine) (specialist use only)**

- **BY MOUTH**
- **Adult:** Initially 2–5 mg/kg once daily, adjusted according to response, dose to be taken preferably in the morning, the total daily dose may alternatively be given in 2–3 divided doses; maximum 20 mg/kg per day

- **CAUTIONS** History of convulsions
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain • cough • diarrhoea • headache • nasal congestion • pharyngolaryngeal pain • vomiting
  - **Frequency not known** Hypersensitivity reactions
- **PREGNANCY** Manufacturer advises caution—consider only if strict dietary management inadequate.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution—no information available.
- **RENAL IMPAIRMENT** Manufacturer advises caution—no information available.
- **MONITORING REQUIREMENTS**
  - Monitor blood-phenylalanine concentration before and after first week of treatment—if unsatisfactory response increase dose at weekly intervals to max. dose and monitor blood-phenylalanine concentration weekly; discontinue treatment if unsatisfactory response after 1 month.
  - Monitor blood-phenylalanine and tyrosine concentrations 1–2 weeks after dose adjustment and during treatment.

- **DIRECTIONS FOR ADMINISTRATION** Tablets should be dissolved in water and taken within 20 minutes.
- **PRESCRIBING AND DISPENSING INFORMATION** Sapropterin is a synthetic form of tetrahydrobiopterin.
- **PATIENT AND CARER ADVICE** Patient or carers should be given advice on how to administer sapropterin dihydrochloride dispersible tablets.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th><strong>SoluTable</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>CAUTIONARY AND ADVISORY LABELS</strong> 13, 21</td>
</tr>
<tr>
<td><strong>Kuvan</strong> (BioMarin Europe Ltd)</td>
</tr>
<tr>
<td><strong>Sapropterin dihydrochloride 100 mg</strong> Kuvan 100mg soluble tablets sugar-free</td>
</tr>
</tbody>
</table>

### 6 Vitamin deficiency

**Vitamins**

**Overview**

Vitamins are used for the prevention and treatment of specific deficiency states or where the diet is known to be inadequate; they may be prescribed in the NHS to prevent or treat deficiency but not as dietary supplements.

Their use as general ‘pick-me-ups’ is of unproven value and, in the case of preparations containing vitamin A or D, may actually be harmful if patients take more than the prescribed dose. The ‘fad’ for mega-vitamin therapy with water-soluble vitamins, such as ascorbic acid p. 952 and pyridoxine hydrochloride p. 950, is unscientific and can be harmful.

Dietary reference values for vitamins are available in the Department of Health publication:

Dietary Reference Values for Food Energy and Nutrients for the United Kingdom: Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of
Dental patients
It is unjustifiable to treat stomatitis or glossitis with mixtures of vitamin preparations; this delays diagnosis and correct treatment.
Most patients who develop a nutritional deficiency despite an adequate intake of vitamins have malabsorption and if this is suspected the patient should be referred to a medical practitioner.

Vitamin A
Deficiency of vitamin A p. 949 (retinol) is associated with ocular defects (particularly xerophthalmia) and an increased susceptibility to infections, but deficiency is rare in the UK (even in disorders of fat absorption).

Vitamin B group
Deficiency of the B vitamins, other than vitamin B₁₂, is rare in the UK and is usually treated by preparations containing thiamine (B₁) p. 950, riboflavin (B₂), and nicotinamide, which is used in preference to nicotinic acid, as it does not cause vasodilatation. Other members (or substances traditionally classified as members) of the vitamin B complex such as aminobenzoic acid, biotin, choline, inositol nicotinate, and pantotheneic acid or panthenol may be included in vitamin B preparations but there is no evidence of their value.
The severe deficiency states Wernicke’s encephalopathy and Korsakoff’s psychosis, especially as seen in chronic alcoholism, are best treated initially by the parenteral administration of B vitamins (Parabinex®), followed by oral administration of thiamine in the longer term. Anaphylaxis has been reported with parenteral B vitamins.
As with other vitamins of the B group, pyridoxine hydrochloride (B₆) deficiency is rare, but it may occur during isoniazid p. 541 therapy or penicillamine p. 964 treatment in Wilson’s disease and is characterised by peripheral neuritis. High doses of pyridoxine hydrochloride are given in some metabolic disorders, such as hyperoxaluria, and it is also used in sideroblastic anaemia. There is evidence to suggest that pyridoxine hydrochloride may provide some benefit in premenstrual syndrome. It has been tried for a wide variety of other disorders, but there is little sound evidence to support the claims of efficacy.
Nicotinic acid inhibits the synthesis of cholesterol and triglyceride. Folic acid p. 886 and vitamin B₁₂ are used in the treatment of megaloblastic anaemia. Folinic acid p. 838 (available as calcium folinate) is used in association with cytotoxic therapy.

Vitamin C
Vitamin C (ascorbic acid) therapy is essential in scurvy, but less florid manifestations of vitamin C deficiency are commonly found, especially in the elderly.
Severe scurvy causes gingival swelling and bleeding margins as well as petechiae on the skin. This is, however, exceedingly rare and a patient with these signs is more likely to have leukaemia. Investigation should not be delayed by a trial period of vitamin treatment.
Claims that vitamin C ameliorates colds or promotes wound healing have not been proven.

Vitamin D
The term Vitamin D is used for a range of compounds which possess the property of preventing or curing rickets. They include ergocalciferol (calciferol, vitamin D₂) p. 955, colecalciferol (vitamin D₃) p. 953, dihydrotachysterol p. 955, alfalcacidol (1α-hydroxycolecalciferol) p. 952, and calcitriol (1,25-dihydroxycolecalciferol) p. 953.
Simple vitamin D deficiency can be prevented by taking an oral supplement of ergocalciferol (calciferol, vitamin D₂) or colecalciferol (vitamin D₃) daily. Vitamin D deficiency can occur in people whose exposure to sunlight is limited and in those whose diet is deficient in vitamin D. In these individuals, ergocalciferol or colecalciferol daily by mouth may be given to treat vitamin D deficiency; higher doses may be necessary for severe deficiency. Patients who do not respond should be referred to a specialist.
Preparations containing colecalciferol with calcium carbonate p. 954 are available for the management of combined calcium and vitamin D deficiency, or for those at high risk of deficiency.
Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease usually requires vitamin D in pharmacological doses.
Vitamin D requires hydroxylation by the kidney to its active form, therefore the hydroxylated derivatives alfalcacidol or calcitriol should be prescribed if patients with severe renal impairment require vitamin D therapy. Calcitriol is also licensed for the management of postmenopausal osteoporosis.
Paricalcitol p. 956, a synthetic vitamin D analogue, is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure.

Vitamin E
The daily requirement of vitamin E (tocopherol) has not been well defined but is probably 3 to 15 mg daily. There is little evidence that oral supplements of vitamin E are essential in adults, even where there is fat malabsorption secondary to cholestasis. In young children with congenital cholestasis, abnormally low vitamin E concentrations may be found in association with neuromuscular abnormalities, which usually respond only to the parenteral administration of vitamin E.
Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

Vitamin K
Vitamin K is necessary for the production of blood clotting factors and proteins necessary for the normal calcification of bone.
Because vitamin K is fat soluble, patients with fat malabsorption, especially in biliary obstruction or hepatic disease, may become deficient. Menadiol sodium phosphate p. 957 is a water-soluble synthetic vitamin K derivative that can be given orally to prevent vitamin K deficiency in malabsorption syndromes.
Oral coumarin anticoagulants act by interfering with vitamin K metabolism in the hepatic cells and their effects can be antagonised by giving vitamin K.

Other compounds
Potassium aminobenzoate p. 949 has been used in the treatment of various disorders associated with excessive fibrosis such as scleroderma and Peyronie’s disease. In Peyronie’s disease there is some evidence to support efficacy in reducing progression when given early in the disease; however, there is no evidence for reversal of the condition. The therapeutic value of potassium aminobenzoate in scleroderma is doubtful.
VITAMINS AND TRACE ELEMENTS

MULTIVITAMINS

Vitamin A and D

- **INDICATIONS AND DOSE**
  - Prevention of vitamin A and D deficiency
  - **BY MOUTH**
    - Child: 1 capsule daily, 1 capsule contains 4000 units vitamin A and 400 units (10 micrograms) vitamin D
    - Adult: (consult product literature)

- **UNLICENSED USE** Not licensed in children under 6 months of age.
- **INTERACTIONS** → Appendix 1 (vitamins).
- **SIDE-EFFECTS**
  - **OVERDOSE**
    - Excessive ingestion: Prolonged excessive ingestion of vitamins A and D can lead to hypervitaminosis.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - This drug contains vitamin D; consult individual vitamin D monographs.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Capsule**
      - Vitamins a and d (Non-proprietary)
      - **Vitamin D 400 unit** capsule £0.71 [28 capsule £2.11] 84 capsule £6.58-£8.42 DT price = £7.47

Vitamins A, C and D

The properties listed below are those particular to the combination only. For the properties of the components please consider, vitamin A below, ascorbic acid p. 952.

- **INDICATIONS AND DOSE**
  - Prevention of vitamin deficiency
  - **BY MOUTH**
    - Child 1 month–4 years: 5 drops daily, 5 drops contain vitamin A approx. 700 units, vitamin D approx. 300 units (7.5 micrograms), ascorbic acid approx. 20 mg

- **PRESCRIBING AND DISPENSING INFORMATION**
  - This drug contains vitamin D; consult individual vitamin D monographs.
  - Available free of charge to children under 4 years in families on the Healthy Start Scheme, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

  - Healthy Start Vitamins for women (containing ascorbic acid, vitamin D, and folic acid) are also available free of charge to women on the Healthy Start Scheme during pregnancy and until their baby is one year old, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Oral drops**
      - Healthy Start Children’s Vitamin (Secretary of State for Health)
        - Vitamin A and D3 concentrate.55 mg per 1 ml, Sodium ascorbate 18.58 mg per 1 ml, Ascorbic acid 150 mg per 1 ml, Vitamin D 2000 iu per 1 ml, Vitamin A 5000 iu per 1 ml Healthy Start Children’s Vitamin drops | 10 ml no price available

- **VITAMINS AND TRACE ELEMENTS**
  - **VITAMIN A**
    - **INDICATIONS AND DOSE**
      - Vitamin A deficiency
      - **BY MOUTH**
        - Child 1–11 months: 5000 units daily, to be taken with or after food, higher doses may be used initially for treatment of severe deficiency
        - Child 1–17 years: 10 000 units daily, to be taken with or after food, higher doses may be used initially for treatment of severe deficiency

- **UNLICENSED USE** Preparations containing only vitamin A are not licensed.
- **INTERACTIONS** → Appendix 1 (vitamins).
- **SIDE-EFFECTS**
  - **OVERDOSE**
    - Massive overdose can cause rough skin, dry hair, an enlarged liver, and a raised erythrocyte sedimentation rate and raised serum calcium and serum alkaline phosphatase concentrations.

- **PREGNANCY** Excessive doses may be teratogenic. In view of evidence suggesting that high levels of vitamin A may cause birth defects, women who are (or may become) pregnant are advised not to take vitamin A supplements (including tablets and fish liver oil drops), except on the advice of a doctor or an antenatal clinic; nor should they eat liver or products such as liver paté or liver sausage.

- **BREAST FEEDING** Theoretical risk of toxicity in infants of mothers taking large doses.
- **MONITORING REQUIREMENTS** Treatment is sometimes initiated with very high doses of vitamin A and the child should be monitored closely; very high doses are associated with acute toxicity.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: drops
    - **Drops**
      - Vitamin a (Non-proprietary)
      - Vitamin A 50000 unit per 1 ml Arovit 150,000 units/ml drops | 7.5 ml [Potaba] no price available

  - Combinations available: *Vitamins A, C and D*, above

Potassium aminobenzoate

- **INDICATIONS AND DOSE**
  - Peyronie's disease | Scleroderma
  - **BY MOUTH**
    - Adult: 12 g daily in divided doses, to be taken after food

- **INTERACTIONS** → Appendix 1 (potassium aminobenzoate).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Capsule**
      - CAUTIONARY AND ADVISORY LABELS 21
      - Potaba (Cheplapharm Arzneimittel GmbH)
        - Potassium aminobenzoate 500 mg Potaba 500mg capsules | 240 capsule [Potaba] £44.75
    - **Powder**
      - CAUTIONARY AND ADVISORY LABELS 13, 21
      - Potaba (Cheplapharm Arzneimittel GmbH)
        - Potassium aminobenzoate 3 gram Potaba 3g sachets | 40 sachet [Potaba] £34.31
Pyridoxine hydrochloride
(Vitamin B₆)

- **INDICATIONS AND DOSE**
  - **Deficiency states**
    - **BY MOUTH**
      - Adult: 20–50 mg 1–3 times a day
  - **Isoniazid-induced neuropathy (prophylaxis)**
    - **BY MOUTH**
      - Adult: 10–20 mg daily
  - **Isoniazid-induced neuropathy (treatment)**
    - **BY MOUTH**
      - Adult: 50 mg 3 times a day
  - **Idiopathic sideroblastic anaemia**
    - **BY MOUTH**
      - Adult: 100–400 mg daily in divided doses
  - **Prevention of penicillamine-induced neuropathy in Wilson’s disease**
    - **BY MOUTH**
      - Adult: 20 mg daily
  - **Premenstrual syndrome**
    - **BY MOUTH**
      - Adult: 50–100 mg daily


**INTERACTIONS** → Appendix 1 (vitamins).

**SIDE-EFFECTS** Sensory neuropathy (with high doses when given for extended periods)

**Overdose** Overdosage induces toxic effects.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution, solution for injection, cream

**Tablet**

- **Pyridoxine hydrochloride (Non-proprietary)**
  - Pyridoxine hydrochloride 10 mg
    - Tablet [GSL] no price available | 28 tablet £0.50 | 50 tablet £1.90
  - Pyridoxine hydrochloride 20 mg
    - Tablet [GSL] no price available | 28 tablet £1.00 | 50 tablet £2.00
  - Pyridoxine hydrochloride 50 mg
    - Tablet [GSL] no price available | 28 tablet £2.00
  - **Pyridine** (Ennogen Healthcare Ltd)
    - Pyridine hydrochloride 10 mg
      - Tablet [GSL] no price available | 30 tablet £1.00
    - Pyridine hydrochloride 20 mg
      - Tablet [GSL] no price available | 30 tablet £1.40

**Capsule**

- **Pyridoxine hydrochloride (Non-proprietary)**
  - Pyridoxine hydrochloride 100 mg
    - Vitamin B6 100mg capsules | 100 capsule no price available
  - Solution for injection
    - Pyridoxine hydrochloride 50 mg per 1 ml
      - Vitamin B6 Streuli 100mg/2ml solution for injection ampoules | 10 ampoule [POM] no price available

Thiamine
(Vitamin B₁)

- **INDICATIONS AND DOSE**
  - **Mild deficiency**
    - **BY MOUTH**
      - Adult: 25–100 mg daily
  - **Severe deficiency**
    - **BY MOUTH**
      - Adult: 200–300 mg daily in divided doses

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (SEPTEMBER 2007)

Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:

- This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;
- Intravenous administration should be by infusion over 30 minutes;
- Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.

- **CAUTIONS** Anaphylaxis may occasionally follow injection
- **BREAST FEEDING** Severely thiamine-deficient mothers should avoid breast-feeding as toxic methylglyoxal present in milk.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Thiamine (Non-proprietary)**
  - Thiamine hydrochloride 50 mg
    - Thiamine 50mg tablets | 28 tablet | £1.80–2.00 | 100 tablet | £7.14
  - Thiamine hydrochloride 100 mg
    - Thiamine 100mg tablets | 28 tablet | £2.00–2.80 | 100 tablet | £10.00
  - Thiamine hydrochloride 200 mg
    - Thiamine 200mg tablets | 100 tablet | £6.99
  - **Tyvera (Audent McKenzie (Pharma Division) Ltd)**
    - Thiamine hydrochloride 50 mg
      - Tyvera 50mg tablets | 100 tablet | £4.99
    - Thiamine hydrochloride 100 mg
      - Tyvera 100mg tablets | 100 tablet | £6.99

**Modified-release tablet**

- **Thiamine (Non-proprietary)**
  - Thiamine hydrochloride 100 mg
    - HealthAid Vitamin B1 100mg modified-release tablets | 90 tablet £4.18

**Vitamin B complex**

- **INDICATIONS AND DOSE**
  - **Treatment of deficiency**
    - **BY MOUTH USING TABLETS**
      - Adult: 1–2 tablets 3 times a day, this dose is for vitamin B compound strong tablets
  - **Prophylaxis of deficiency**
    - **BY MOUTH USING TABLETS**
      - Adult: 1–2 tablets daily, this dose is for vitamin B compound tablets

- **LESS SUITABLE FOR PRESCRIBING** Vitamin B compound tablets and vitamin B compound strong tablets are less suitable for prescribing.
DIRECTIONS FOR ADMINISTRATION

UNLICENSED USE

Pabrinex® doses in BNF may differ from those in product literature.

DIRECTIONS FOR ADMINISTRATION

Give (Pabrinex® I/V High Potency) intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Ampoules contents should be mixed, diluted, and administered without delay; give over 30 minutes.

PRESCRIBING AND DISPENSING INFORMATION

Some formulations of Pabrinex® may contain benzyl alcohol. Pabrinex® I/V High Potency Injection is for intramuscular use only. Pabrinex® I/V High Potency injection is for intravenous use only.

Vitamin B substances with ascorbic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, thiamine p. 950, ascorbic acid p. 952.

INDICATIONS AND DOSE

Parenteral vitamins B and C for rapid correction of severe depletion or malabsorption (e.g. in alcoholism, after acute infections, postoperatively, or in psychiatric states) Maintenance of vitamins B and C in chronic intermittent haemodialysis

▶ BY INTRAVENOUS INFUSION
▶ Adult: See MHRA/CHM advice in thiamine monograph (consult product literature).

Treatment of Wernicke’s encephalopathy

▶ INITIALLY BY INTRAVENOUS INFUSION
▶ Adult: 2 – 3 pairs 3 times a day for 2 days, discontinue if no response, continue treatment if symptoms respond after 2 days; (by intravenous infusion or by deep intramuscular injection) 1 pair once daily for 5 days or for as long as improvement continues, give deep intramuscular injection into the gluteal muscle

Prophylaxis of Wernicke’s encephalopathy in alcohol dependence

▶ BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION
▶ Adult: 1 pair once daily for at least 3 – 5 days, give deep intramuscular injection into the gluteal muscle

Psychosis following narcosis or electroconvulsive therapy

▶ TOXICITY FROM ACUTE INFECTIONS
▶ BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION
▶ Adult: 1 pair twice daily for up to 7 days, give deep intramuscular injection into the gluteal muscle

Haemodialysis

▶ BY INTRAVENOUS INFUSION
▶ Adult: 1 pair every 2 weeks

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for Injection

EXCIPIENTS: May contain Benzyl alcohol

Pabrinex Intramuscular High Potency (Kyowa Kirin Ltd)

Pabrinex Intravenous High Potency solution for injection 5ml and 2ml ampoules | 20 ampoule Pot £22.53 DT price = £22.53

Pabrinex Intravenous High Potency (Kyowa Kirin Ltd)

Pabrinex Intravenous High Potency solution for injection 5ml and 5ml ampoules | 20 ampoule Pot £22.53 DT price = £22.53

Solution for Injection

There can be variation in the licensing of different medicines containing the same drug.

Vitamin deficiency

951

Vitamin and mineral deficiency and as adjunct in synthetic diets

▶ BY MOUTH
▶ Adult: 1 capsule daily, one hour after a meal

KETOVITE® LIQUID

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism | Adjunct in restricted, specialised, or synthetic diets

▶ BY MOUTH
▶ Adult: 5 mL daily, use with Ketovite® Tablets for complete vitamin supplementation.

KETOVITE® TABLETS

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism | Adjunct in restricted, specialised, or synthetic diets

▶ BY MOUTH
▶ Adult: 1 tablet 3 times a day, use with Ketovite® Liquid for complete vitamin supplementation.

PRESCRIBING AND DISPENSING INFORMATION

To avoid potential toxicity, the content of all vitamin preparations, particularly vitamin A, should be considered when used together with other supplements.

PATIENT AND CARER ADVICE

KETOVITE® LIQUID Ketovite® liquid may be mixed with milk, cereal, or fruit juice.

KETOVITE® TABLETS Tablets may be crushed immediately before use.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

Ketovite (Essential Pharmaceuticals Ltd)

Acetomenaphthone 500 microgram, Riboflavin 1 mg, Thiamine hydrochloride 1 mg, Alpha tocopherol acetate 5 mg, Ascorbic acid 16.6 mg, Biotin 170 microgram, Calcium pantothenate 1.16 mg, Folic acid 250 microgram, Nicotinamide 3.3 mg, Inositol 50 mg, Pyridoxine hydrochloride 330 microgram Ketovite tablets | 100 tablet Pot £5.21

Capsule

Forceval (Alliance Pharmaceuticals Ltd)

Ascorbic acid 60 mg, Biotin 100 microgram, Riboflavin 1.6 mg, Calcium 100 mg, Selenium 50 microgram, Chromium 200 microgram, Copper 2 mg, Cyanocobalamin 3 microgram, Ergocalciferol 400 unit, Iodine 140 microgram, Folic acid 400 microgram, Thiamine 1.2 mg, Pyridoxine 2 mg, Manganese 3 mg, Pantothenic acid 4 mg, Potassium 4 mg, Tocopheryl acetate 10 mg, Iron 12 mg, Magnesium 30 mg, Molybdenum 250 microgram, Zinc 15 mg, Nicotinamide 18 mg, Phosphorus 77 mg, Vitamin A 2500 unit Forceval capsules | 15 capsule Pot £4.42 | 30 capsule Pot £7.71 | 90 capsule Pot £23.13
**952** Vitamin deficiency

Oral emulsion
- Ketovite (Essential Pharmaceuticals Ltd)
  Choline chloride 30 mg per 1 ml, Cyanocobalamin 2.5 microgram per 1 ml, Ergocalciferol 80 unit per 1 ml, Vitamin A 500 unit per 1 ml Ketovite liquid sugar-free | 150 ml £19.10

**VITAMINS AND TRACE ELEMENTS** > **VITAMIN C**

**Ascorbic acid**
**(Vitamin C)**

- **INDICATIONS AND DOSE**
  - **Prevention of scurvy**
    - **Adult:** 25–75 mg daily
  - **Treatment of scurvy**
    - **Adult:** Not less than 250 mg daily in divided doses

- **INTERACTIONS** > Appendix 1 (vitamins).
- **PRESCRIBING AND DISPENSING INFORMATION** It is rarely necessary to prescribe more than 100 mg daily except early in the treatment of scurvy.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**EXCIPIENTS:** May contain Aspartame
- **Ascorbic acid (Non-proprietary)**
  - Ascorbic acid 50 mg Ascorbic acid 50mg tablets | 28 tablet GSL £15.05 DT price = £15.05 | 28 tablet no price available DT price = £15.05 | 500 tablet GSL no price available
  - Ascorbic acid 100 mg Ascorbic acid 100mg tablets | 28 tablet GSL £14.30 DT price = £14.30 | 28 tablet no price available DT price = £14.30
  - Ascorbic acid 200 mg Ascorbic acid 200mg tablets | 28 tablet no price available DT price = £19.86 | 28 tablet GSL £19.86 DT price = £19.86 | 100 tablet GSL no price available
  - Ascorbic acid 250 mg Ascorbic acid 250mg tablets | 1000 tablet GSL no price available
  - Ascorbic acid 500 mg Ascorbic acid 500mg tablets | 28 tablet GSL £26.87 DT price = £26.87 | 28 tablet no price available DT price = £26.87 | 100 tablet GSL no price available

**Chewable tablet**

**CAUTIONARY AND ADVISORY LABELS** 24
**EXCIPIENTS:** May contain Aspartame
- **Ascorbic acid (Non-proprietary)**
  - Ascorbic acid 60 mg Vitamin C 60mg chewable tablets | 60 tablet no price available | 180 tablet no price available
  - Ascorbic acid 500 mg Vitamin C 500mg chewable tablets | 25 tablet £0.90
  - Ascorbic acid (as Sodium ascorbate) 500 mg Lloyd’s pharmacy Vitamin C 500mg chewable tablets sugar-free | 60 tablet no price available
  - Ascorbic acid 1 gram Vitamin C 1000mg chewable tablets | 30 tablet £2.35 | 60 tablet £4.29
  - Ascur (Emmogen Healthcare Ltd)
    - Ascorbic acid 100 mg Ascur 100mg chewable tablets | 30 tablet £3.95
  - Ascorbic acid (as Sodium ascorbate) 500 mg Ascur 500mg chewable tablets sugar-free | 30 tablet £2.99

**Capsule**

- **Ascorbic acid (Non-proprietary)**
  - Ascorbic acid 1 gram Vitamin C 1000mg capsules | 100 capsule no price available | 250 capsule no price available
  - Ascorbic acid 500 mg Vitamin C 500mg capsules | 100 capsule no price available

**Combinations available:** *Vitamin B substances with ascorbic acid*, p. 951 - *Vitamins A, C and D*, p. 949

**VITAMINS AND TRACE ELEMENTS** > **VITAMIN D AND ANALOGUES**

**Vitamin D and analogues**
**(systemic)**

- **CONTRA-INDICATIONS** Hypercalcaemia · metastatic calcification
- **INTERACTIONS** > Appendix 1 (vitamins).
- **SIDE-EFFECTS**
  - Overdose
    - Symptoms of overdose include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.
  - **PREGNANCY** High doses teratogenic in *animals* but therapeutic doses unlikely to be harmful.
  - **BREAST FEEDING** Caution with high doses; may cause hypercalcaemia in infant—monitor serum-calcium concentration.
  - **MONITORING REQUIREMENTS** Important: All patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occurs.

**Alfacalcidol**
**(1α-Hydroxycholecalciferol)**

- **INDICATIONS AND DOSE**
  - **Patients with severe renal impairment requiring vitamin D therapy**
    - **BY MOUTH, OR BY INTRAVENOUS INJECTION**
      - **Adult:** Initially 1 microgram daily, dose to be adjusted to avoid hypercalcaemia; maintenance 0.25–1 microgram daily
      - **Elderly:** Initially 500 nanograms daily, dose adjusted to avoid hypercalcaemia; maintenance 0.25–1 microgram daily
  - **Hypophosphataemic rickets | Persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism**
    - **BY MOUTH, OR BY INTRAVENOUS INJECTION**
      - **Child 1 month–11 years:** 25–50 nanograms/kg once daily, dose to be adjusted as necessary; maximum 1 microgram per day
      - **Child 12–17 years:** 1 microgram once daily, dose to be adjusted as necessary
  - **Prevention of vitamin D deficiency in renal or cholestatic liver disease**
    - **BY MOUTH, OR BY INTRAVENOUS INJECTION**
      - **Child 1 month–11 years (body-weight up to 20 kg):** 15–30 nanograms/kg once daily (max. per dose 500 nanograms)
      - **Child 1 month–11 years (body-weight 20 kg and above):** 250–500 nanograms once daily, dose to be adjusted as necessary
      - **Child 12–17 years:** 250–500 nanograms once daily, dose to be adjusted as necessary
  - **DOSE EQUIVALENCE AND CONVERSION**
    - One drop of alfacalcidol 2 microgram/mL oral drops contains approximately 100 nanograms alfacalcidol.

- **CAUTIONS** Nephrolithiasis · take care to ensure correct dose in infants
- **SIDE-EFFECTS**
  - Rare Nephrocalcinosis · pruritus · rash · urticaria
Monitor plasma-calcium concentration in renal impairment.

**MONITORING REQUIREMENTS**  Monitor plasma-calcium concentration in patients receiving high doses.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use: For injection, shake ampoule for at least 5 seconds before use, and give over 30 seconds.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

- **Calcitriol (Non-proprietary)**
  - Calcitriol 250 nanogram capsules | 30 capsule (Pom) £5.20 DT price = £2.49
  - Calcitriol 500 nanogram capsules | 30 capsule (Pom) £10.00 DT price = £5.66
  - Calcitriol 1 microgram capsules | 30 capsule no price available DT price = £7.10
  - **One-Alfa (LEO Pharma)**
    - Calcitriol 250 nanogram capsules | 30 capsule (Pom) £3.37 DT price = £2.49
    - Calcitriol 500 nanogram capsules | 30 capsule (Pom) £6.27 DT price = £5.66
  - Calcitriol 1 microgram capsules | 30 capsule (Pom) £8.75 DT price = £7.10

**Oral drops**

- **Calcitriol 2 microgram per 1 ml** One-Alfa 2 micrograms/ml oral drops sugar-free | 10 ml (Pom) £21.30 DT price = £21.30

**Solution for injection**

- **Calcitriol 2 microgram per 1 ml** One-Alfa 2 micrograms/ml oral solution for injection ampoules | 10 ampoule (Pom) £41.13

**Colecalciferol**  

(Cholecalciferol; Vitamin D₃)

**INDICATIONS AND DOSE**

**Prevention of vitamin D deficiency**

- **BY MOUTH**
  - Adult: 400 units daily

**Treatment of vitamin D deficiency**

- **BY MOUTH**
  - Adult: 800 units daily, higher doses may be necessary for severe deficiency

**RENAL IMPAIRMENT**  Monitor plasma-calcium concentration in patients receiving high doses.

**MONITORING REQUIREMENTS**  Monitor plasma-calcium concentration in patients receiving high doses.

**DIRECTIONS FOR ADMINISTRATION**

- Contents of capsule may be administered by oral syringe.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

- **Calcitriol (Non-proprietary)**
  - Calcitriol 250 nanogram capsules | 30 capsule (Pom) £18.04 DT price + £18.04
  - Calcitriol 500 nanogram capsules | 30 capsule (Pom) £32.25 DT price + £32.25
- **Rocaltrol (Roche Products Ltd)**
  - Calcitriol 250 nanogram capsules | 100 capsule (Pom) £16.04 DT price + £18.04
  - Calcitriol 500 nanogram capsules | 100 capsule (Pom) £32.25 DT price = £32.25

**Oral solution**

- **Calcitriol (Non-proprietary)**
  - Calcitriol 1 microgram per 1 ml Rocaltrol micrograms/ml oral solution sugar-free | 10 ml (Pom) no price available

**Calcitriol**  

(1,25-Dihydroxycholecalciferol)

**INDICATIONS AND DOSE**

**Renal osteodystrophy**

- **BY MOUTH**
  - Adult: Initially 250 nanograms daily, adjusted in steps of 250 nanograms every 2–4 weeks if required; usual dose 0.5–1 microgram daily

**Renal osteodystrophy (in patients with normal or only slightly reduced plasma-calcium concentration)**

- **BY MOUTH**
  - Adult: Initially 250 nanograms once daily on alternate days, adjusted in steps of 250 nanograms every 2–4 weeks if required; usual dose 0.5–1 microgram daily

**Established postmenopausal osteoporosis**

- **BY MOUTH**
  - Adult: 250 nanograms twice daily, plasma-calcium concentration and creatinine to be monitored (consult product literature)

**HEPATIC IMPAIRMENT**  Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT**  Manufacturer advises avoid—no information available. Monitor plasma-calcium concentration in renal impairment.

**MONITORING REQUIREMENTS**

- Monitor plasma calcium, phosphate, and creatinine during dosage titration.

**Blood and nutrition**
### 954 Vitamin deficiency

- **Stexerol-D3** (Kyowa Kirin Ltd)
  - Colecalciferol 1000 unit: Stexerol-D3 1,000 unit tablets | 28 tablet (PoM) £2.95 DT price = £2.95
  - Colecalciferol 25000 unit: Stexerol-D3 25,000 unit tablets | 12 tablet (PoM) £17.00 DT price = £17.00

- **Chewable tablet**
  - **Colecalciferol** (Non-proprietary)
    - Colecalciferol 280 unit: Vitamin D3 280 unit chewable tablets | 180 tablet £5.00
    - Colecalciferol 1000 unit: Vitamin D3 1,000 unit chewable tablets | 100 tablet no price available

- **Orodispersible tablet**
  - **Colecalciferol** (Non-proprietary)
    - Colecalciferol 2000 unit: Vitamin D3 2,000 unit sugar-free | 120 tablet £4.88

### Capsule

CAUTIONARY AND ADVISORY LABELS 25

- **Colecalciferol** (Non-proprietary)
  - Colecalciferol 400 unit: Colecalciferol 400 unit capsules | 30 capsule no price available
  - Colecalciferol 500 unit: Vitamin D3 500 unit capsules | 90 capsule (GSP) £3.50
  - Colecalciferol 600 unit: Colecalciferol 600 unit capsules | 30 capsule no price available
  - Colecalciferol 800 unit: Colecalciferol 800 unit capsules | 30 capsule £3.60 DT price = £3.60
  - Colecalciferol 100 unit: Vitamin D3 100 unit capsules | 28 capsule £36.50 | 30 capsule £29.50
  - Colecalciferol 2200 unit: Colecalciferol 2,200 unit capsules | 30 capsule no price available
  - Colecalciferol 2500 unit: Colecalciferol 2,500 unit capsules | 30 capsule no price available
  - Colecalciferol 3000 unit: Colecalciferol 3,000 unit capsules | 30 capsule no price available
  - Colecalciferol 4000 unit: Vitamin D3 4,000 unit capsules | 60 capsule no price available | 120 capsule no price available
  - Colecalciferol 5000 unit: Colecalciferol 5,000 unit capsules | 30 capsule no price available | 100 capsule (PoM) no price available
  - Colecalciferol 10000 unit: Colecalciferol 10,000 unit capsules | 30 capsule no price available
  - Colecalciferol 20000 unit: Colecalciferol 20,000 unit capsules | 20 capsule £37.99 | 30 capsule £39.99 DT price = £29.00 | 30 capsule (PoM) £29.00 DT price = £29.00
  - Colecalciferol 30000 unit: Colecalciferol 30,000 unit capsules | 10 capsule no price available
  - Colecalciferol 50000 unit: Colecalciferol 50,000 unit capsules | 10 capsule £56.00 | 100 capsule (PoM) no price available
  - **Aciferol D3** (Rhodes Pharma Ltd)
    - Colecalciferol 30000 unit: Aciferol D3 30,000 unit capsules | 10 capsule £19.99
    - Colecalciferol 50000 unit: Aciferol D3 50,000 unit capsules | 10 capsule £19.99
  - **Aviticol** (Colenis Pharma Ltd)
    - Colecalciferol 800 unit: Aviticol 800 unit capsules | 30 capsule (PoM) £3.60
    - Colecalciferol 1000 unit: Aviticol 1,000 unit capsules | 30 capsule (PoM) £3.16
    - Colecalciferol 2000 unit: Aviticol 2,000 unit capsules | 30 capsule (PoM) £29.00 DT price = £29.00
  - **Fultium-D3** (Internis Pharmaceuticals Ltd)
    - Colecalciferol 800 unit: Fultium-D3 800 unit capsules | 30 capsule (PoM) £3.60 DT price = £3.60 | 90 capsule (PoM) £13.50
    - Colecalciferol 3200 unit: Fultium-D3 3,200 unit capsules | 30 capsule (PoM) £13.32 DT price = £13.32 | 90 capsule (PoM) £39.96
    - Colecalciferol 2000 unit: Fultium-D3 2,000 unit capsules | 15 capsule (PoM) £17.04 DT price = £17.04 | 30 capsule (PoM) £29.00 DT price = £29.00
  - **Plenachol** (Austen McKenzie (Pharma Division) Ltd)
    - Colecalciferol 2000 unit: Plenachol 2,000 unit capsules | 10 capsule (PoM) £9.00
    - Colecalciferol 40000 unit: Plenachol 40,000 unit capsules | 10 capsule (PoM) £15.00 DT price = £15.00
  - **Strivit-D3** (Strides Arcolab International Ltd)
    - Colecalciferol 800 unit: Strivit-D3 800 unit capsules | 30 capsule (PoM) £2.34 DT price = £2.34

### Oral solution

CAUTIONARY AND ADVISORY LABELS 21

- **Colecalciferol** (Non-proprietary)
  - Colecalciferol 3000 unit per 1 ml: Colecalciferol 3,000 units/ml oral solution | 100 ml (PoM) £144.00 DT price = £144.00
  - Colecalciferol 10000 unit per 1 ml: Colecalciferol 10,000 units/ml oral solution | 10 ml no price available

- **InVita D3** (Consilient Health Ltd)
  - Colecalciferol 25000 unit per 1 ml: InVita D3 25,000 units/1 ml oral solution sugar-free | 3 ampoule (PoM) £4.45 DT price = £4.45
  - Colecalciferol 50000 unit per 1 ml: InVita D3 50,000 units/1 ml oral solution sugar-free | 3 ampoule (PoM) £6.25 DT price = £6.25

- **Thoren** (Galen Ltd)
  - Colecalciferol 10000 unit per 1 ml: Thoren 25,000 units/2.5 ml oral solution sugar-free | 2.5 ml (PoM) £1.55 DT price = £1.55 sugar-free | 10 ml (PoM) £5.85 DT price = £5.85

### Oral drops

- **Colecalciferol** (Non-proprietary)
  - Colecalciferol 20000 unit per 1 ml: Colecalciferol 20,000 units/ml oral drops | 10 ml no price available
  - Colecalciferol 2000 unit per 1 drop: Vitamin D3 2,000 units/drop for infants and children oral drops sugar-free | 50 ml £3.86
  - Colecalciferol 2500 unit per 1 drop: Nature’s Aid Vitamin D 2,500 units/drop oral drops sugar-free | 50 ml £6.64

- **Fultium-D3** (Internis Pharmaceuticals Ltd)
  - Colecalciferol 2740 unit per 1 ml: Fultium-D3 2.74 units/1 ml oral drops sugar-free | 25 ml (PoM) £10.70 DT price = £10.70

- **InVita D3** (Consilient Health Ltd)
  - Colecalciferol 2400 unit per 1 ml: InVita D3 2,400 units/ml oral drops sugar-free | 10 ml (PoM) £3.60

- **Thoren** (Galen Ltd)
  - Colecalciferol 10000 unit per 1 ml: Thoren 10,000 units/ml oral drops sugar-free | 10 ml (PoM) £5.85 DT price = £5.85

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### Colecalciferol with calcium carbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, colecalciferol p. 953, calcium carbonate p. 919.

#### INDICATIONS AND DOSE

Prevention and treatment of vitamin D and calcium deficiency

- **By mouth**
  - Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

#### PRESCRIBING AND DISPENSING INFORMATION

**Accrete D3®** contains calcium carbonate 1.5 g (calcium 600 mg or Ca2+ 15 mmol), colecalciferol 10 micrograms (400 units); **Adcal-D3®** tablets contain calcium carbonate 1.5 g (calcium 600 mg or Ca2+ 15 mmol), colecalciferol 10 micrograms (400 units); **CalcitD® D3** contains calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 11 micrograms (440 units/sachet); **Calcios®** contains calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 10 micrograms (400 units); **Calcichew-D3® Tablets** contain calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 5 micrograms (200 units); **Calcichew-D3® Forte Tablets** contain calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 10 micrograms (400 units); **Calcichew-D3® 500 mg/400 unit caplets contain calcium carbonate (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 10 micrograms (400 units); **Kalcinos-D®** contains calcium carbonate (calcium 500 mg or Ca2+ 15 mmol), colecalciferol 20 micrograms (800 units); **Natecal D3®** contains calcium carbonate 1.5 g (calcium 600 mg or Ca2+ 15 mmol), colecalciferol 10 micrograms (400 units); consult product literature for details of other available products.

Flavours of chewable and soluble forms may include orange, lemon, aniseed, peppermint, molasses, or tutti-frutti.
**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

### Table

**EXCIPIENTS:** May contain Propylene glycol
- **Calcioferril with calcium carbonate (Non-proprietary)**
  - Calcium carbonate 400 mg, Calcioferril 100 unit
  - Calcium carbonate 2.5 gram, Calcioferril 220 unit
  - Calcium carbonate 1 gram, Calcioferril 112 unit

### Chewable tablet

**CAUTIONARY AND ADVISORY LABELS** 24
EXCIPIENTS: May contain Aspartame

- **Calcioferril with calcium carbonate (Non-proprietary)**
  - Calcium carbonate 1.5 gram, Calcioferril 400 unit
  - Calcium carbonate 1.5 gram, Calcioferril 400 unit / Calcium carbonate 1.5g chewable tablets
  - Calcium carbonate 1.5 gram, Calcioferril 400 unit / Calcium carbonate 1.5g chewable tablets

### Oral solution

**CAUTIONARY AND ADVISORY LABELS** 13

- **Calcioferril with calcium carbonate (Non-proprietary)**
  - Calcium carbonate 2.5 gram, Calcioferril 880 unit
  - Calcium carbonate 2.5 gram, Calcioferril 440 unit

### Effervescent granules

**CAUTIONARY AND ADVISORY LABELS** 13

- **Calcioferril with calcium carbonate (Non-proprietary)**
  - Calcium carbonate 2.5 gram, Calcioferril 880 unit
  - Calcium carbonate 2.5 gram, Calcioferril 440 unit

### Dihydrotachysterol

**INDICATIONS AND DOSE**

**Acute, chronic, and latent forms of hypocalcaemic tetany due to hypoparathyroidism**
- **BY MOUTH**
- **Adult:** (consult product literature)

**RENAL IMPAIRMENT** Monitor plasma-calcium concentration in renal impairment.

**MONITORING REQUIREMENTS** Monitor plasma-calcium concentration in patients receiving high doses.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Oral solution

**EXCIPIENTS:** May contain Arachis (peanut) oil

- **AT10 (Intrapharm Laboratories Ltd)**
  - Dihydrotachysterol 250 microgram per 1 ml
  - AT10 250micrograms/ml oral solution sugar-free

### Ergocalciferol (Calciferol; Vitamin D₂)

**INDICATIONS AND DOSE**

**Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease**
- **BY MOUTH**
- **Adult:** Up to 40 000 units daily

**Hypocalcaemia of hypoparathyroidism to achieve normocalcaemia**
- **BY MOUTH**
- **Adult:** Up to 100 000 units daily

**Prevention of vitamin D deficiency**
- **BY MOUTH**
- **Adult:** 400 units daily

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**Colecalfirop with calcium phosphate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, colecalciferol p. 953, calcium phosphate p. 920.

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**Colecalfirop with calcium carbonate**

- **BY MOUTH**
- **Adult:** (consult product literature)

**REMEDIAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Powder

**CAUTIONARY AND ADVISORY LABELS** 13

- **Calcioferril D3 (A. Menarini Farmaceutica Internazionale SRL)**
  - Calcium phosphate 3.1 gram, Calcioferril 800 unit
  - Calcioferril D3 oral powder sachets

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Oral solution

**EXCIPIENTS:** May contain Arachis (peanut) oil

- **AT10 (Intrapharm Laboratories Ltd)**
  - Dihydrotachysterol 250 microgram per 1 ml
  - AT10 250micrograms/ml oral solution sugar-free
Treatment of vitamin D deficiency

- **BY MOUTH**
- **Adult:** 800 units daily, higher doses may be necessary for severe deficiency

- **RENAL IMPAIRMENT** Monitor plasma-calcium concentration in renal impairment.
- **MONITORING REQUIREMENTS** Monitor plasma-calcium concentration in patients receiving high doses.
- **PRESCRIBING AND DISPENSING INFORMATION** The BP directs that when calciferol is prescribed or demanded, colecalciferol or ergocalciferol should be dispensed or supplied. When the strength of the tablets ordered or prescribed is not clear, the intention of the prescriber with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution.

  **Tablet**
  - Ergocalciferol (Non-proprietary)
  - Ergocalciferol 12.5 microgram (Calcium and vitamin D) Ergocalciferol 12.5 microgram tablets | 30 tablet no price available
  - Ergoral (Cubic Pharmaceuticals Ltd)
  - Ergocalciferol 125 microgram (Calcium and vitamin D) Ergoral D2 5,000 unit tablets | 30 tablet £19.95
  - Ergocalciferol 250 microgram (Calcium and vitamin D) Ergoral D2 10,000 unit tablets | 30 tablet £23.95

  **Capsule**
  - Ergocalciferol (Non-proprietary)
  - Ergocalciferol 1.25 mg (Calcium and vitamin D) Ergocalciferol 1.25 mg capsules | 30 capsule £55.00 no price available | 50 capsule £93.00
  - Eciferol (Rhodes Pharma Ltd)
  - Ergocalciferol 1.25 mg (Calcium and vitamin D) Eciferol D2 50,000 unit capsules | 10 capsule £29.99
  - Ergoral (Cubic Pharmaceuticals Ltd)
  - Ergocalciferol 1.25 mg (Calcium and vitamin D) Ergoral D2 50,000 unit capsules | 10 capsule £19.95

  **Oral solution**
  - Ergocalciferol (Non-proprietary)
  - Ergocalciferol 1500 unit per 1 ml (Calcium and vitamin D) Ergocalciferol D 1,500 units/ml oral solution sugar-free | 20 ml £2.40 no price available
  - Ergocalciferol 20000 unit per 1 ml (Calcium and vitamin D) Ergocalciferol 100,000 units/5ml oral solution | 20 ml £25.00 no price available DT price = £185.19
  - Eciferol (Rhodes Pharma Ltd)
  - Ergocalciferol 3000 unit per 1 ml (Calcium and vitamin D) Eciferol D2 3,000 units/ml liquid | 60 ml £55.00 DT price = £107.95

### Ergocalciferol with calcium lactate and calcium phosphate

(Calcium and vitamin D)

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergocalciferol p. 955, calcium lactate p. 920.

- **INDICATIONS AND DOSE**
  - Prevention of calcium and vitamin D deficiency
  - Treatment of calcium and vitamin D deficiency
  - **BY MOUTH**
  - **Adult:** (consult product literature)

- **DIRECTIONS FOR ADMINISTRATION** Tablets may be crushed before administration, or may be chewed.

- **PRESCRIBING AND DISPENSING INFORMATION** Each tablet contains calcium lactate 300 mg, calcium phosphate 150 mg (calcium 57 mg or Ca²⁺ 2.4 nmol), ergocalciferol 10 micrograms (400 units).

- **PATIENT AND CARER ADVICE** Patient or carers should be given advice on how to administer calcium and ergocalciferol tablets.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Ergocalciferol with calcium lactate and calcium phosphate (Non-proprietary)
  - Calcium phosphate 150 mg, Calcium lactate 300 mg, Ergocalciferol 10 microgram (Calcium and vitamin D) Calcium and Ergocalciferol tablets | 28 tablet no price available DT price = £15.43 | 28 tablet £15.43

### Paricalcitol

- **INDICATIONS AND DOSE**
  - For prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure
  - **BY MOUTH**
  - **Adult:** (consult product literature)

- **SIDE-EFFECTS** Acne, breast tenderness, dyspepsia, pruritus, rash, taste disturbance

- **PREGNANCY** Toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises caution—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor plasma calcium and phosphate during dose titration and at least monthly when stabilised.
  - Monitor parathyroid hormone concentration.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - Zemplar (AbbVie Ltd)
  - Paricalcitol 1 microgram (Calcium and vitamin D) Zemplar 1 microgram capsules | 28 capsule £69.44
  - Paricalcitol 2 microgram (Calcium and vitamin D) Zemplar 2 microgram capsules | 28 capsule £138.88

### Solution for injection

EXCIPIENTS: May contain Propylene glycol

- **Zemplar (AbbVie Ltd)**
  - Paricalcitol 5 microgram per 1 ml (Calcium and vitamin D) Zemplar 5 micrograms/1ml solution for injection ampoules | 5 ampoule £62.00 (Hospital only)
  - Zemplar 5 micrograms/1ml solution for injection vials | 5 vial £138.88 (Hospital only)

### Vitamins and trace elements

**Alpha tocopherol** (Tocopherol)

- **INDICATIONS AND DOSE**
  - Vitamin E deficiency because of malabsorption in congenital or hereditary chronic cholestatics
  - **BY MOUTH USING ORAL SOLUTION**
  - **Child:** 17 mg/kg daily, dose to be adjusted as necessary

- **CAUTIONS** Predisposition to thrombosis

- **INTERACTIONS** → Appendix 1 (Vitamin E).
Alpha tocopheryl acetate
(Tocopherol)

**INDICATIONS AND DOSE**

**Vitamin E deficiency**
- **BY MOUTH**
  - Child: 2–10 mg/kg daily, increased if necessary up to 20 mg/kg daily

**Malabsorption in cystic fibrosis**
- **BY MOUTH**
  - Child 1-11 months: 50 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
  - Child 1-11 years: 100 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
  - Child 12-17 years: 100–200 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
  - Adult: 100–200 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes

**Vitamin E deficiency in cholestasis and severe liver disease**
- **BY MOUTH**
  - Child 1 month-11 years: Initially 100 mg daily, adjusted according to response, increased if necessary up to 200 mg/kg daily
  - Child 12-17 years: Initially 200 mg daily, adjusted according to response, increased if necessary up to 200 mg/kg daily

**Malabsorption in abetalipoproteinemia**
- **BY MOUTH**
  - Adult: 50–100 mg/kg once daily

**CAUTIONS**
- Predisposition to thrombosis

**INTERACTIONS**
- Appendix 1 (Vitamins).

**SIDE-EFFECTS**
- Abdominal pain (particularly with high doses) · diarrhoea (particularly with high doses)

**PREGNANCY**
- No evidence of safety of high doses.

**BREAST FEEDING**
- Excreted in milk; minimal risk, although caution with large doses.

**MONITORING REQUIREMENTS**
- Increased bleeding tendency in vitamin-K deficient patients or those taking anticoagulants (prothrombin time and INR should be monitored).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: chewable tablet

<table>
<thead>
<tr>
<th>Chewable tablet</th>
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<tbody>
<tr>
<td>Alpha tocopheryl acetate (Non-proprietary)</td>
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<tr>
<td>Alpha tocopheryl acetate 100 mg</td>
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<tr>
<td>E-Tabs (Ennogen Healthcare Ltd)</td>
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<tr>
<td>Alpha tocopheryl acetate 100 mg E-Tabs 100mg chewable tablets</td>
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<tr>
<td>Eephyral (Imported (Italy))</td>
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<tr>
<td>Alpha tocopheryl acetate 100 mg Ephyral 100mg chewable tablets</td>
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<th>Capsule</th>
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<tr>
<td>Alpha tocopheryl acetate (Non-proprietary)</td>
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<td>Alpha tocopherol 100 unit</td>
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<td>Alpha tocopherol 200 unit</td>
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<td>E-Caps (Ennogen Healthcare Ltd)</td>
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<td>Alpha tocopherol 1000 unit E-Caps 1000unit capsules</td>
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<td>Vita-E (Typharm Ltd)</td>
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<td>Alpha tocopherol 75 unit Vita-E 75unit capsules</td>
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<td>Alpha tocopherol 200 unit Vita-E 200unit capsules</td>
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<td>Alpha tocopherol 400 unit Vita-E 400unit capsules</td>
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<tr>
<th>Oral suspension</th>
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<tr>
<td>EXCIPIENTS: May contain Sucrose</td>
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<tr>
<td>Alpha tocopheryl acetate (Non-proprietary)</td>
</tr>
<tr>
<td>Alpha tocopheryl acetate 100 mg per 1 ml Alpha tocopheryl acetate 500mg/5ml oral suspension</td>
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</tbody>
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**Menadiol sodium phosphate**

**INDICATIONS AND DOSE**

**Prevention of Vitamin K deficiency in malabsorption syndromes**
- **BY MOUTH**
  - Adult: 10–40 mg daily, dose to be adjusted as necessary

**CAUTIONS**
- G6PD deficiency (risk of haemolysis) · vitamin E deficiency (risk of haemolysis)

**INTERACTIONS**
- Appendix 1 (Vitamins).

**PREGNANCY**
- Avoid in late pregnancy and labour unless benefit outweighs risk of neonatal haemolytic anaemia, hyperbilirubinaemia, and kernicterus in neonate.
Phytonadione (Vitamin K₃)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Menadion sodium phosphate (Non-proprietary)
- Menadion as (Menadion sodium phosphate)

**INDICATIONS AND DOSE**

**Major bleeding in patients on warfarin** (in combination with dried prothrombin complex or fresh frozen plasma)
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5 mg for 1 dose, stop warfarin treatment

**INR > 8.0 with minor bleeding in patients on warfarin**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 1–3 mg, stop warfarin treatment, dose may be repeated if INR still too high after 24 hours, restart warfarin treatment when INR < 5

**INR > 8.0 with no bleeding in patients on warfarin**
- **BY MOUTH**
  - Adult: 1–5 mg, intravenous preparation to be used orally, stop warfarin treatment, repeat dose if INR still too high after 24 hours, restart warfarin treatment when INR < 5

**INR 5.0–8.0 with minor bleeding in patients on warfarin**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 1–3 mg, stop warfarin treatment, restart warfarin treatment when INR < 5

**Reversal of anticoagulation prior to elective surgery (after warfarin stopped)**
- **BY MOUTH**
  - Adult: 1–5 mg, intravenous preparation to be used orally, dose to be given the day before surgery if INR ≥ 1.5

**Reversal of anticoagulation prior to emergency surgery (when surgery can be delayed 6–12 hours)**
- **BY INTRAVENOUS INJECTION**
  - Adult: 5 mg as a single dose, if surgery cannot be delayed, dried prothrombin complex can be given in addition to phytonadione and the INR checked before surgery

**UNLICENSED USE**
Oral use of intravenous preparations is unlicensed.

**CAUTIONS**
Intravenous injections should be given very slowly—risk of vascular collapse

KONAKION® MM Reduce dose in elderly

**INTERACTIONS**
→ Appendix 1 (Vitamins).

**SIDE-EFFECTS**

KONAKION® MM Anaphylactoid reactions

**PREGNANCY**
Use if potential benefit outweighs risk.

**BREAST FEEDING**
Present in milk.

**HEPATIC IMPAIRMENT**
KONAKION® MM Caution—glycocholic acid may displace bilirubin.

**DIRECTIONS FOR ADMINISTRATION**

KONAKION® MM PAEDIATRIC KONAKION® MM Paediatric may be administered by mouth or by intramuscular injection or by intravenous injection.
- For intravenous injection, may be diluted with Glucose 5%; note for intramuscular injection. For intravenous infusion (Konakion® MM), give intermittently in Glucose 5%; dilute with 55 mL; may be injected into lower part of infusion apparatus.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution, drops

**Solution for injection**

EXCIPIENTS: May contain Glycocholic acid, lecithin
- Konakion MM (Roche Products Ltd)
  - Phytonadione 10 mg per 1 ml Konakion MM Paediatric
    - 2mg/0.2ml solution for injection ampoules | 5 ampoule (P) £4.71
    - Konakion MM 10mg/1ml solution for injection ampoules | 10 ampoule (P) £3.78 DT price = £3.78

6.1 Neural tube defects (prevention in pregnancy)

**Neural tube defects (prevention in pregnancy)**

**Prevention in pregnancy**
Folic acid supplements p. 898 taken before and during pregnancy can reduce the occurrence of neural tube defects. The risk of a neural tube defect occurring in a child should be assessed and folic acid given as follows:

- Women at a low risk of conceiving a child with a neural tube defect should be advised to take folic acid as a medicinal or food supplement daily (at low-risk group dose) before conception and until week 12 of pregnancy. Women who have not been taking folic acid and who suspect they are pregnant should start at once and continue until week 12 of pregnancy.

- Couples are at a high risk of conceiving a child with a neural tube defect if either partner has a neural tube defect (or either partner has a family history of neural tube defects), if they have had a previous pregnancy affected by a neural tube defect, or if the woman has coeliac disease (or other malabsorption state), diabetes mellitus, sickle-cell anemia, or is taking antiepileptic medicines.

- Women in the high-risk group who wish to become pregnant (or who are at risk of becoming pregnant) should be advised to take folic acid daily (at high-risk group dose) and continue until week 12 of pregnancy (women with sickle-cell disease should continue taking their normal dose of folic acid (or to increase the dose to high-risk group daily dose) and continue this throughout pregnancy).

There is no justification for prescribing multiple-ingredient vitamin preparations containing vitamin B₁₂ or folic acid.

Glucose 5%; not for intramuscular injection. For intravenous infusion (Konakion® MM), give intermittently in Glucose 5%; dilute with 55 mL; may be injected into lower part of infusion apparatus.
Chapter 10
Musculoskeletal system

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5.2 Soft tissue disorders .......... 1013

1 Arthritis

Arthritis

Rheumatoid arthritis and other inflammatory disorders

A non-steroidal anti-inflammatory drug (NSAID) is indicated for pain and stiffness resulting from inflammatory rheumatic disease; analgesics such as paracetamol p. 414 or codeine phosphate p. 421 can also be used.

Drugs are also used to influence the rheumatic disease process itself. For rheumatoid arthritis these disease-modifying anti-rheumatic drugs (DMARDs) include methotrexate p. 817, cytokine modulators, azathioprine p. 765, ciclosporin p. 766, cyclophosphamide p. 802, leflunomide p. 963, penicillamine p. 964, gold, antimalarials (chloroquine p. 569 and hydroxychloroquine sulfate p. 962), and sulfasalazine p. 39. Corticosteroids also have a significant role in the management of rheumatoid arthritis.

Drugs which may affect the disease process in psoriatic arthritis include sulfasalazine, gold, azathioprine, methotrexate, leflunomide, and cytokine modulators.

Osteoarthritis and soft-tissue disorders

For pain relief in osteoarthritis and soft-tissue disorders, paracetamol should be used first and may need to be taken regularly. A topical NSAID or topical capsaicin 0.025% p. 446 should also be considered, particularly in knee or hand osteoarthritis. An oral NSAID can be substituted for, or used in addition to, paracetamol. If further pain relief is required in osteoarthritis, then the addition of an opioid analgesic may be considered, but with a substantial risk of adverse effects; however, an opioid analgesic should be considered before a NSAID in patients taking low-dose aspirin.

Intra-articular corticosteroid injections may produce temporary benefit in osteoarthritis, especially if associated with soft-tissue inflammation.

Non-drug measures, such as weight reduction and exercise, should also be encouraged.

Glucosamine p. 961 and rubefacients are not recommended for the treatment of osteoarthritis.

Hyaluronic acid and its derivatives are available for osteoarthritis of the knee, but are not recommended. Sodium hyaluronate (Durospan®️, Euflexxa®️, Fermaphon®️, Hyalgan®️, Orthovisc®️, Ostenil®, Ostenil Plus®, RenehaVis®️, Suplasyn®️, Synocrom®️, Synopsis®️️) or hylan G-F 20 (Synvisc®️️) is injected intra-articularly to supplement natural hyaluronic acid in the synovial fluid. These injections may reduce pain over 1–6 months, but are associated with a short-term increase in knee inflammation. Sodium hyaluronate (SportVis®️️) is also licensed for the relief of pain and optimisation of recovery following ankle sprain, and for the relief of chronic pain and disability associated with tennis elbow.

Rheumatic disease, suppressing drugs

Overview

Certain drugs such as those affecting the immune response can suppress the disease process in rheumatoid arthritis and psoriatic arthritis; gold, penicillamine p. 964, hydroxychloroquine sulfate p. 962, chloroquine p. 569, and sulfasalazine p. 39 can also suppress the disease process in rheumatoid arthritis while sulfasalazine and possibly gold can suppress the disease process in psoriatic arthritis. Unlike NSAIDs, which are used only for symptom control, disease-modifying anti-rheumatic drugs (DMARDs) can affect the progression of disease but may require 2–6 months of treatment for a full therapeutic response. Response to DMARDs may allow the NSAID dose to be reduced or withdrawn. All patients with suspected inflammatory joint disease should be referred to a specialist as soon as possible to confirm diagnosis and evaluate disease activity; early initiation of DMARDs is recommended to control the signs and symptoms, and to limit joint damage.

Choice

The choice of a disease-modifying anti-rheumatic drug should take into account co-morbidity and patient preference. Methotrexate p. 817, sulfasalazine, intramuscular gold, and penicillamine are similar in efficacy. However, methotrexate or sulfasalazine may be better tolerated.

A combination of DMARDs (including methotrexate and at least one other DMARD) and a short-term corticosteroid, should be given to patients with newly diagnosed active rheumatoid arthritis, ideally within 3 months of the onset of persistent symptoms. If the use of particular DMARDs is contra-indicated and combination therapy is not possible, monotherapy with a suitable DMARD should be given and the dose rapidly increased until clinically effective. In patients with established and stable rheumatoid arthritis, cautiously reduce drug doses to the lowest that are clinically effective. Response to drug treatment often produces a reduction in requirements of both corticosteroids and other drugs.

Gold and penicillamine are effective in palindromic rheumatism. Systemic and discoid lupus erythematosus are
sometimes treated with chloroquine or hydroxychloroquine sulfate.

If a disease-modifying anti-rheumatic drug does not lead to an objective benefit within 6 months, it should be replaced by a different one.

**Gold**

Gold can be given as sodium aurothiomalate p. 965 for active progressive rheumatoid arthritis; it must be given by deep intramuscular injection and the area gently massaged. A test dose must be given followed by doses at weekly intervals until there is definite evidence of remission. In patients who do respond, the interval between injections is then gradually increased to 4 weeks and treatment is continued for up to 5 years after complete remission. If relapse occurs the dosage frequency may be immediately increased and only once control has been obtained again should the dosage frequency be decreased; if no response is seen within 2 months, alternative treatment should be sought. It is important to avoid complete relapse since second courses of gold are not usually effective.

**Penicillamine**

Penicillamine has a similar action to gold. More patients are able to continue treatment with gold but side-effects are common.

Patients should be warned not to expect improvement for at least 6 to 12 weeks after treatment is initiated. Penicillamine should be discontinued if there is no improvement within 1 year.

**Sulfasalazine**

Sulfasalazine has a beneficial effect in suppressing the inflammatory activity of rheumatoid arthritis. Sulfasalazine may also be used by specialists, in the management of psoriatic arthritis affecting peripheral joints [unlicensed indication]. Haematological abnormalities occur usually in the first 3 to 6 months of treatment and are reversible on cessation of treatment.

**Antimalarials**

The antimalarial hydroxychloroquine sulfate is used to treat rheumatoid arthritis of moderate inflammatory activity; chloroquine is also licensed for treating inflammatory disorders but is used much less frequently and is generally reserved for use if other drugs have failed.

Chloroquine and hydroxychloroquine sulfate are effective for mild systemic lupus erythematosus, particularly involving the skin and joints. These drugs should not be used for psoriatic arthritis. Chloroquine and hydroxychloroquine sulfate are better tolerated than gold or penicillamine.

Retinopathy rarely occurs provided that the recommended doses are not exceeded; in the elderly it is difficult to distinguish drug-induced retinopathy from changes of ageing.

Mepacrine hydrochloride is sometimes used in discoid lupus erythematosus [unlicensed].

**Drugs affecting the immune response**

Methotrexate is a disease-modifying anti-rheumatic drug suitable for moderate to severe rheumatoid arthritis.

Azathioprine p. 765, ciclosporin p. 766, cyclophosphamide p. 802, leflunomide p. 963, and the **cytokine modulators** are considered more toxic and they are used in cases that have not responded to other disease-modifying drugs.

Methotrexate is usually given by mouth once a week, adjusted according to response. In patients who experience mucosal or gastro-intestinal side-effects with methotrexate, folic acid p. 898 given every week [unlicensed indication], on a different day from the methotrexate, may help to reduce the frequency of such side-effects.

Leflunomide acts on the immune system as a disease-modifying anti-rheumatic drug. Its therapeutic effect starts after 4–6 weeks and improvement may continue for a further 4–6 months. Leflunomide, which is similar in efficacy to sulfasalazine and methotrexate, may be chosen when these drugs cannot be used.

Ciclosporin is licensed for severe active rheumatoid arthritis when conventional second-line therapy is inappropriate or ineffective. There is some evidence that ciclosporin may retard the rate of erosive progression and improve symptom control in those who respond only partially to methotrexate.

Cyclophosphamide may be used for rheumatoid arthritis with severe systemic manifestations [unlicensed indication]; it is toxic and regular blood counts (including platelet counts) should be carried out. Cyclophosphamide can also be given for severe systemic rheumatoid arthritis and for other connective tissue diseases (especially with active vasculitis).

Drugs that affect the immune response are also used in the management of severe cases of systemic lupus erythematosus and other connective tissue disorders. They are often given in conjunction with corticosteroids for patients with severe or progressive renal disease. They may be used in cases of polymyositis that are resistant to corticosteroids. They are used for their corticosteroid-sparing effect in patients whose corticosteroid requirements are excessive. Azathioprine is usually used.

In the specialist management of psoriatic arthritis affecting peripheral joints, leflunomide, methotrexate, or azathioprine [unlicensed indication] may be used.

**Juvenile idiopathic arthritis**

Many children with juvenile idiopathic arthritis (juvenile chronic arthritis) do not require disease-modifying anti-rheumatic drugs. Methotrexate is effective; sulfasalazine is an alternative [unlicensed indication] but it should be avoided in systemic-onset juvenile idiopathic arthritis. Gold and penicillamine are no longer used. Cytokine modulators have a role in juvenile idiopathic arthritis.

**Cytokine modulators**

Cytokine modulators should be used under specialist supervision.

Adalimumab p. 969, certolizumab pegol p. 971, etanercept p. 973, golimumab p. 974, and infliximab p. 976 inhibit the activity of tumour necrosis factor alpha (TNF-α).

Adalimumab is licensed for moderate to severe active rheumatoid arthritis when response to other disease modifying anti-rheumatic drugs (including methotrexate p. 817) has been inadequate; it is also licensed for severe, active, and progressive disease in adults not previously treated with methotrexate. In the treatment of rheumatoid arthritis, adalimumab should be used in combination with methotrexate, but it can be given alone if methotrexate is inappropriate. Adalimumab is also licensed for the treatment of active and progressive psoriatic arthritis and severe active ankylosing spondylitis that have not responded adequately to other disease-modifying anti-rheumatic drugs. It is also licensed for the treatment of severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs. Adalimumab also has a role in inflammatory bowel disease and plaque psoriasis.

Certolizumab pegol is licensed for use in patients with moderate to severe active rheumatoid arthritis when response to disease-modifying anti-rheumatic drugs (including methotrexate) has been inadequate. Certolizumab pegol can be used in combination with methotrexate, or as a monotherapy if methotrexate is not tolerated or is contra-indicated. Certolizumab pegol is also licensed for the treatment of severe active ankylosing spondylitis in patients
who have had an inadequate response to, or are intolerant of NSAIDs. It is also licensed for the treatment of severe active axial spondyloarthritis, without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs.

Etanercept is licensed for the treatment of moderate to severe active rheumatoid arthritis either alone or in combination with methotrexate when the response to other disease-modifying antirheumatic drugs is inadequate and in severe, active and progressive rheumatoid arthritis in patients not previously treated with methotrexate. It is also licensed for the treatment of active and progressive psoriatic arthritis inadequately responsive to other disease-modifying antirheumatic drugs, and for severe ankylosing spondylitis inadequately responsive to conventional therapy. Etanercept also has a role in plaque psoriasis.

Golimumab is licensed in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis when response to disease-modifying antirheumatic drug (DMARD) therapy (including methotrexate has been inadequate; it is also licensed in combination with methotrexate for patients with severe, active, and progressive rheumatoid arthritis not previously treated with methotrexate. Golimumab is also licensed for the treatment of active and progressive psoriatic arthritis, as monotherapy or in combination with methotrexate, when response to DMARD therapy has been inadequate; it is also licensed for the treatment of severe active ankylosing spondylitis when there is an inadequate response to conventional treatment. Infliximab is licensed for the treatment of active rheumatoid arthritis in combination with methotrexate when the response to other disease-modifying antirheumatic drugs, including methotrexate, is inadequate; it is also licensed in combination with methotrexate for patients not previously treated with methotrexate or other DMARDs who have severe, active, and progressive rheumatoid arthritis. Infliximab is also licensed for the treatment of ankylosing spondylitis, in patients with severe axial symptoms who have not responded adequately to conventional therapy, and in combination with methotrexate (or alone if methotrexate is not tolerated or is contra-indicated) for the treatment of active and progressive psoriatic arthritis which has not responded adequately to disease-modifying antirheumatic drugs.

Rituximab p. 792 is licensed in combination with methotrexate for the treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them. Rituximab has a role in malignant disease.

Abatacept p. 968 prevents the full activation of T-lymphocytes. It is licensed for moderate to severe active rheumatoid arthritis in combination with methotrexate, in patients unresponsive to other disease-modifying antirheumatic drugs (including methotrexate or a tumour necrosis factor (TNF) inhibitor). Abatacept is not recommended for use in combination with TNF inhibitors.

Anakinra p. 965 inhibits the activity of interleukin-1. Anakinra (in combination with methotrexate) is licensed for the treatment of rheumatoid arthritis which has not responded to methotrexate alone. Anakinra is not recommended for the treatment of rheumatoid arthritis except when used in a controlled long-term clinical study. Patients who are already receiving anakinra for rheumatoid arthritis should continue treatment until they and their specialist consider it appropriate to stop.

Belimumab p. 773 inhibits the activity of B-lymphocyte stimulator. Belimumab is licensed as adjunctive therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy.

Secukinumab p. 966 inhibits the activity of interleukin-17A. Secukinumab is licensed for the treatment of active psoriatic arthritis, in combination with methotrexate or alone, which has not responded adequately to disease-modifying antirheumatic drugs; it is also licensed for the treatment of ankylosing spondylitis, in patients who have not responded adequately to conventional therapy. Secukinumab also has a role in plaque psoriasis.

Tocilizumab p. 966 antagonises the actions of interleukin-6. Tocilizumab is licensed for use in patients with moderate to severe active rheumatoid arthritis when response to at least one disease-modifying antirheumatic drug or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs. Tocilizumab can be used in combination with methotrexate, or as monotherapy if methotrexate is not tolerated or is contra-indicated.

Ustekinumab p. 967 inhibits the activity of interleukins 12 and 23. It is licensed for the treatment of active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs.

CHONDROPROTECTIVE DRUGS

Glucosamine

- **DRUG ACTION** Glucosamine is a natural substance found in mucopolysaccharides, mucoproteins, and chitin.

- **INDICATIONS AND DOSE**

  **ALATERIS®**

  **Symptomatic relief of mild to moderate osteoarthritis of the knee**

  - **BY MOUTH**
  - Adult: 1250 mg once daily, review treatment if no benefit after 2–3 months

  **DOLENIO®**

  **Symptomatic relief of mild to moderate osteoarthritis of the knee**

  - **BY MOUTH**
  - Adult: 1500 mg once daily, review treatment if no benefit after 2–3 months

  **GLUSARTEL®**

  **Symptomatic relief of mild to moderate osteoarthritis of the knee**

  - **BY MOUTH**
  - Adult: 1500 mg once daily, dose to be dissolved in at least 250 mL of water, review treatment if no benefit after 2–3 months

- **CAUTIONS** Asthma · impaired glucose tolerance · predisposition to cardiovascular disease

- **INTERACTIONS** → Appendix 1 (glucosamine).

- **SIDE-EFFECTS**

  ▶ Common or very common Abdominal pain · constipation · diarrhoea · drowsiness · dyspepsia · fatigue · flatulence · headache · nausea

  ▶ Uncommon Flushing · pruritus · rash

Other drugs used for Arthritis

- Aceclofenac, p. 988
- Acemetacin, p. 989
-Celecoxib, p. 990
- Derivations, p. 990
- Diclofenac potassium, p. 992
- Diclofenac sodium, p. 993
- Etorofibin, p. 995
- Etoricoxib, p. 996
- Fenoprofen, p. 997
- Flurbiprofen, p. 998
- Ibuprofen, p. 999
- Indomethacin, p. 1001
- Ketoprofen, p. 1002
- Mefenamic acid, p. 1004
- Meloxicam, p. 1004
- Nabumetone, p. 1005
- Naprofen, p. 1006
- Piroxicam, p. 1007
- Prednisone, p. 623
- Sulindac, p. 1009
- Tenoxicam, p. 1009
- Tiaprofenic acid, p. 1010
Hydroxychloroquine sulfate

**INDICATIONS AND DOSE**
Active rheumatoid arthritis (administered on expert advice) Systemic and discoid lupus erythematosus (administered on expert advice) Dermatological conditions caused or aggravated by sunlight (administered on expert advice)

- **BY MOUTH**
  - Adult: 200–400 mg daily, daily maximum dose to be based on ideal body-weight; maximum 6.5 mg/kg per day

**CAUTIONS** Acute porphyrias p. 930 · elderly · G6PD deficiency · may aggravate myasthenia gravis · may exacerbate psoriasis · neurological disorders (especially in those with a history of epilepsy) · severe gastro-intestinal disorders

**Screening for ocular toxicity** A review group convened by the Royal College of Ophthalmologists has updated guidelines for screening to prevent ocular toxicity on long-term treatment with chloroquine and hydroxychloroquine (Hydroxychloroquine and Ocular Toxicity: Recommendations on Screening 2009). The following recommendations relate to hydroxychloroquine, which is only rarely associated with toxicity.

**Before treatment:**
- Assess renal and liver function (adjust dose if impaired)
- Ask patient about visual impairment (not corrected by glasses). If impairment or eye disease present, assessment by an optometrist is advised and any abnormality should be referred to an ophthalmologist
- Record near visual acuity of each eye (with glasses where appropriate) using a standard reading chart
- Initiate hydroxychloroquine treatment if no abnormality detected (at a dose not exceeding hydroxychloroquine sulfate 6.5 mg/kg daily)

**During treatment:**
- Ask patient about visual symptoms and monitor visual acuity annually using the standard reading chart
- Refer to ophthalmologist if visual acuity changes or if vision blurred and warn patient to seek prescribing doctor’s advice about stopping treatment
- If long-term treatment is required (more than 5 years), individual arrangement should be agreed with the local ophthalmologist

**INTERACTIONS** ▶ Appendix 1 (hydroxychloroquine). Concurrent use of hepatotoxic drugs should be avoided.

**SIDE-EFFECTS** ▶ Common or very common Gastro-intestinal disturbances · headache · pruritus · rashes · skin reactions
- Uncommon Convulsions · discoloration of skin, nails, and mucous membranes · ECG changes · hair depigmentation · hair loss · keratopathy · otoxicity · retinal damage · visual changes
- Rare Acute generalised exanthematous pustulosis · agranulocytosis · angioedema · aplastic anaemia · blood disorders · cardiomyopathy · emotional disturbances · exfoliative dermatitis · hepatic damage · mental changes · myopathy · neuromyopathy · photosensitivity · psychosis · Stevens–Johnson syndrome · thrombocytopenia

**Frequency not known** Bronchospasm · diffuse parenchymal lung disease · drug rash with eosinophilia and systemic symptoms

**Overdose** Hydroxychloroquine is very toxic in overdosage; overdosage is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

**PRECAUTIONS** It is not necessary to withdraw an antimalarial drug during pregnancy if the rheumatic disease is well controlled; however, the manufacturer of hydroxychloroquine advises avoiding use.

**BREAST FEEDING** Avoid—risk of toxicity in infant.

**HEPATIC IMPAIRMENT** Caution in moderate to severe hepatic impairment.

**RENAL IMPAIRMENT** Manufacturer advises caution. Monitor plasma-hydroxychloroquine concentration in severe renal impairment.

**MONITORING REQUIREMENTS** Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory (see advice of the Royal College of Ophthalmologists).

**PRESCRIBING AND DISPENSING INFORMATION** To avoid excessive dosage in obese patients, the dose of hydroxychloroquine should be calculated on the basis of ideal body-weight.

**PATIENT AND CARER ADVICE** Do not take antacids for at least 4 hours before or after hydroxychloroquine to reduce possible interference with hydroxychloroquine absorption.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
ELECTROLYTES: May contain Sodium
- Alateris (MKW Healthcare Ltd)
  - Glucosamine (as Glucosamine hydrochloride) 625 mg · Alateris 625mg tablets 60 tablet [P] £18.40 DT price + £18.40
- Dolenio (Allisa Healthcare Research Ltd)
  - Dolenio 1500mg tablets 30 tablet [P] £18.20 DT price + £18.20

Powder
CAUTIONARY AND ADVISORY LABELS 13
EXCIPIENTS: May contain Aspartame
- Glucosamine (Non-proprietary)
  - Glucosamine sulfate 1.5g oral powder sachets sugar free sugar-free 30 sachet [P] £30.09

**DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS**

**SCREENING FOR OCULAR TOXICITY** A review group convened by the Royal College of Ophthalmologists has updated guidelines for screening to prevent ocular toxicity on long-term treatment with chloroquine and hydroxychloroquine (Hydroxychloroquine and Ocular Toxicity: Recommendations on Screening 2009). The following recommendations relate to hydroxychloroquine, which is only rarely associated with toxicity.

**PRECAUTIONS** It is not necessary to withdraw an antimalarial drug during pregnancy if the rheumatic disease is well controlled; however, the manufacturer of hydroxychloroquine advises avoiding use.

**BREAST FEEDING** Avoid—risk of toxicity in infant.

**HEPATIC IMPAIRMENT** Caution in moderate to severe hepatic impairment.

**RENAL IMPAIRMENT** Manufacturer advises caution. Monitor plasma-hydroxychloroquine concentration in severe renal impairment.

**MONITORING REQUIREMENTS** Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory (see advice of the Royal College of Ophthalmologists).

**PRESCRIBING AND DISPENSING INFORMATION** To avoid excessive dosage in obese patients, the dose of hydroxychloroquine should be calculated on the basis of ideal body-weight.

**PATIENT AND CARER ADVICE** Do not take antacids for at least 4 hours before or after hydroxychloroquine to reduce possible interference with hydroxychloroquine absorption.
**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21**

- **Hydroxychloroquine sulfate (Non-proprietary)**
  
- **Plaquenil** (Sanofi)
  
- **Quinoric** (Bristol Laboratories Ltd)

**Hepatotoxicity** Potentially life-threatening hepatotoxicity reported usually in the first 6 months. Discontinue treatment (and institute washout procedure—consult product literature) or reduce dose according to liver-function abnormality; if liver-function abnormality persists after dose reduction, discontinue treatment and institute washout procedure.

**CONCEPTION AND CONTRACEPTION** Effective contraception **essential** during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (plasma concentration monitoring required; waiting time before conception may be reduced with washout procedure—consult product literature). The concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception—consult product literature.

**PREGNANCY** Avoid—active metabolite teratogenic in animal studies.

**BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Avoid—active metabolite may accumulate.

**RENAI IMPAIRMENT** Manufacturer advises avoid in moderate or severe impairment—no information available.

**PRE-TREATMENT SCREENING** Exclude pregnancy before treatment.

**MONITORING REQUIREMENTS**
- Monitor full blood count (including differential white cell count and platelet count) before treatment and every 2 weeks for 6 months then every 8 weeks.
- Monitor liver function before treatment and every 2 weeks for first 6 months then every 8 weeks.
- Monitor blood pressure.

**TREATMENT CESSION**
Washout Procedure The active metabolite persists for a long period; to aid drug elimination in case of serious adverse effect, or before starting another disease-modifying antirheumatic drug, or before conception, stop treatment and give either colestyramine p. 186 or charcoal, activated p. 1211. Procedure may be repeated as necessary.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 4**

- **Leflunomide (Non-proprietary)**
  
- **Arava** (Sanofi)

**SIDE-EFFECTS, FURTHER INFORMATION**
Discontinue treatment and institute washout procedure in case of serious side-effect (consult product literature).

**Leflunomide**

**INDICATIONS AND DOSE**

**Moderate to severe active rheumatoid arthritis (specialist use only)**

- **BY MOUTH**
  
- **Adult:** Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily

**Active psoriatic arthritis (specialist use only)**

- **BY MOUTH**
  
- **Adult:** Initially 100 mg once daily for 3 days, then reduced to 20 mg once daily

**CONTRA-INDICATIONS** Serious infection · severe hypoproteinaemia · severe immunodeficiency

**CAUTIONS** Anaeemia (avoid if significant and due to causes other than rheumatoid arthritis) · history of tuberculosis · impaired bone-marrow function (avoid if significant and due to causes other than rheumatoid arthritis) · leucopenia (avoid if significant and due to causes other than rheumatoid arthritis) · thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis)

**INTERACTIONS**

- Appendix 1 (leflunomide).

Increased risk of toxicity with other haematotoxic and hepatotoxic drugs.

Caution if recent treatment with other hepatotoxic disease-modifying anti-rheumatic drugs.

Caution if recent treatment with other myelotoxic disease-modifying anti-rheumatic drugs.

Caution—washout procedures recommended before switching to other disease-modifying antirheumatic drugs (consult product literature).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · alopecia · anorexia · asthenia · diarrhea · dizziness · dry skin · headache · increased blood pressure · leucopenia · nausea · oral mucosal disorders · paraesthesia · pruritus · rash · tenosynovitis · vomiting

- **Uncommon** Anaemia · anxiety · hyperlipidaemia · hypokalaemia · hypophosphataemia · taste disturbance · tendon rupture · thrombocytopenia

- **Rare** Hepatitis · eosinophilia · interstitial lung disease · jaundice · pancytopenia · severe infection

- **Very rare** Hepatic failure · pancreatitis · peripheral neuropathy · progressive multifocal leucoencephalopathy · Stevens-Johnson syndrome · toxic epidermal necrolysis · vasculitis

- **Frequency not known** Bone-marrow toxicity · hypouricaemia · malignancy · reduced sperm count · renal failure

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21**

- **Leflunomide 10 mg** Leflunomide 10mg tablets | 30 tablet £46.00 DT price £4.70

- **Leflunomide 15 mg** Leflunomide 15mg tablets | 30 tablet £61.36 DT price £4.59

- **Arava** (Sanofi)

- **Leflunomide 10 mg** Arava 10mg tablets | 30 tablet £51.13 DT price £4.70

- **Leflunomide 20 mg** Arava 20mg tablets | 30 tablet £61.36 DT price £4.59

- **Leflunomide 100 mg** Arava 100mg tablets | 3 tablet £30.67
Penicillamine

- **DRUG ACTION**  Penicillamine aids the elimination of copper ions in Wilson’s disease (hepatolenticular degeneration).

- **INDICATIONS AND DOSE**
  - **Severe active rheumatoid arthritis (administered on expert advice)**
    - **BY MOUTH**
      - Adult: Initially 125–250 mg daily for 1 month, then increased in steps of 125–250 mg, at intervals of not less than 4 weeks; maintenance 500–750 mg daily in divided doses, then reduced in steps of 125–250 mg every 12 weeks; dose reduction attempted only if remission sustained for 6 months; maximum 1.5 g per day
      - Elderly: Initially up to 125 mg daily for 1 month, then increased in steps of up to 125 mg, at intervals of at least 4 weeks; maximum 1 g per day
  - **Wilson’s disease**
    - **BY MOUTH**
      - Adult: 1.5–2 g daily in divided doses, adjusted according to response, to be taken before food; maintenance 0.75–1 g daily, a dose of 2 g daily should not be continued for more than one year; maximum 2 g per day
      - Elderly: 20 mg/kg daily in divided doses, adjusted according to response
  - **Autoimmune hepatitis (used rarely; after disease controlled with corticosteroids)**
    - **BY MOUTH**
      - Adult: Initially 500 mg daily in divided doses, to be increased slowly over 3 months; maintenance 1.25 g daily
  - **Cystinuria, therapeutic**
    - **BY MOUTH**
      - Adult: 1–3 g daily in divided doses, to be adjusted to maintain urinary cystine below 200 mg/litre, to be taken before food
  - **Cystinuria, prophylactic**
    - **BY MOUTH**
      - Adult: 0.5–1 g daily, maintain urinary cystine below 300 mg/litre and adequate fluid intake (at least 3 litres daily), to be taken at bedtime
      - Elderly: Minimum dose to maintain urinary cystine below 200 mg/litre is recommended

- **CONTRA-INDICATIONS**  Lupus erythematosus
- **CAUTIONS**  Neurological involvement in Wilson’s disease
- **INTERACTIONS**  Appendix 1 (penicillamine). Caution with concomitant nephrotoxic drugs (increased risk of toxicity). Caution with gold treatment (avoid concomitant use if adverse reactions to gold).
- **SIDE-EFFECTS**
  - **Common or very common**  Anorexia · fever · nausea · proteinuria · rash · thrombocytopenia
  - **Rare**  Alopecia · breast enlargement (male and female) · elastosis perforans · haematuria (withdraw immediately if cause unknown) · mouth ulceration · pseudoxanthoma elasticum · skin laxity · stomatitis
  - **Frequency not known**  Agranulocytosis · aplastic anaemia · blood disorders · bronchitis · cholestatic jaundice · dermatomyositis · glomerulonephritis · Goodpasture’s syndrome · haemolytic anaemia · haemolytic leucopenia · late rashes (consider dose reduction) · lupus erythematosus · myasthenia gravis · nephrotic syndrome · neuropathy (especially if neurological involvement in Wilson’s disease—prophylactic pyridoxine recommended) · neutropenia · pancreatitis · pemphigus · pneumonitis · polyneuropathy · pulmonary haemorrhage · rheumatoid arthritis · septic arthritis (in patients with rheumatoid arthritis) · Stevens-Johnson syndrome · taste loss (mineral supplements not recommended) · urticaria · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - **Proteinuria**  Proteinuria, associated with immune complex nephritis, occurs in up to 30% of patients, but may resolve despite continuation of treatment; treatment may be continued provided that renal function tests remain normal, oedema is absent, and the 24-hour urinary excretion of protein does not exceed 2 g.
  - **Rash**  Rashes are a common side-effect. Those that occur in the first few months of treatment disappear when the drug is stopped and treatment may then be re-introduced at a lower dose level and gradually increased.
  - **Taste loss**  Loss of taste can occur about 6 weeks after treatment is started but usually returns 6 weeks later irrespective of whether treatment is discontinued.
  - **Nausea**  Nausea may occur but is not usually a problem provided that penicillamine is taken before food or on retiring and that low initial doses are used and only gradually increased.

- **ALLERGY AND CROSS-SENSITIVITY**  Patients who are hypersensitive to penicillin may react rarely to penicillamine.
- **PREGNANCY**  Fetal abnormalities reported rarely; avoid if possible.
- **BREAST FEEDING**  Manufacturer advises avoid unless potential benefit outweighs risk—no information available.
- **RENAL IMPAIRMENT**  Reduce dose and monitor renal function or avoid (consult product literature).
- **MONITORING REQUIREMENTS**
  - Consider withdrawal if platelet count falls below 120 000/mm³ or white blood cells below 2500/mm³ or if 3 successive falls within reference range (can restart at reduced dose when counts return to within reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia). Blood counts, including platelets, and urine examinations should be carried out before starting treatment and then every 1 or 2 weeks for the first 2 months then every 4 weeks to detect blood disorders and proteinuria (they should also be carried out in the week after any dose increase).
  - A reduction in platelet count calls for discontinuation with subsequent re-introduction at a lower dosage and then, if possible, gradual increase.
  - Longer intervals may be adequate in cystinuria and Wilson’s disease.
- **PATIENT AND CARER ADVICE**  Counselling on the symptoms of blood disorders is advised. Warn patient and carers to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**  6, 22

- **Penicillamine (Non-proprietary)**
  - **Penicillamine 125 mg**  Penicillamine 125mg tablets | 56 tablet £45.00 DT price = £44.97
  - **Penicillamine 250 mg**  Penicillamine 250mg tablets | 56 tablet £88.84 DT price = £88.72
  - **Distamine (Alliance Pharmaceuticals Ltd)**
    - **Penicillamine 125 mg**  Distamine 125mg tablets | 100 tablet £10.34
    - **Penicillamine 250 mg**  Distamine 250mg tablets | 100 tablet £17.78
Sodium aurothiomalate

INDICATIONS AND DOSE

Active progressive rheumatoid arthritis (administered on expert advice)

- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: Test dose 10 mg, followed by 50 mg once weekly until there is definite evidence of remission, then reduced to 50 mg every 4 weeks continued for up to 5 years after complete remission, dose to be reduced gradually. Benefit is not expected until 300–500 mg has been given; it should be discontinued if there is no remission after 1 g has been given.

Relapse in patients who have previously received sodium aurothiomalate therapy for active progressive rheumatoid arthritis (administered on expert advice)

- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: 50 mg once weekly until control has been obtained again, then reduced to 50 mg every 4 weeks continued for up to 5 years after complete remission, if no response is seen within 2 months, alternative treatment should be sought.

CONTRA-INDICATIONS Exfoliative dermatitis · history of blood disorders · history of bone marrow aplasia · necrotising enterocolitis · pulmonary fibrosis · systemic lupus erythematosus

CAUTIONS Colitis · eczema · elderly · history of urticaria

Sodium aurothiomalate should be discontinued in the presence of blood disorders, gastro-intestinal bleeding (associated with ulcerative enterocolitis), or unexplained proteinuria (associated with immune complex nephritis) which is repeated above 300 mg/litre.

INTERACTIONS → Appendix 1 (sodium aurothiomalate).

SIDE-EFFECTS Alopecia · blood disorders (sometimes sudden and fatal) · colitis · gold deposits in eye · hepatotoxicity with cholestatic jaundice · irreversible pigmentation in sun-exposed areas (on prolonged parenteral treatment) · mouth ulcers · nephrotic syndrome · peripheral neuropathy · proteinuria · pulmonary fibrosis · severe anaphylactic reactions · skin reactions · stomatitis · taste disturbances

SIDE-EFFECTS, FURTHER INFORMATION

Rashes with pruritus often occur after 2 to 6 months of treatment and may necessitate discontinuation.

PREGNANCY Consider reducing dose and frequency. Manufacturer advises avoid but limited data suggests usually not necessary to withdraw if condition well controlled.

BREAST FEEDING Manufacturer advises avoid—present in milk; theoretical possibility of rashes and idiosyncratic reactions.

HEPATIC IMPAIRMENT Caution in mild to moderate impairment. Avoid in severe impairment.

RENAL IMPAIRMENT Caution in mild to moderate impairment. Avoid in severe impairment.

MONITORING REQUIREMENTS

- Urine tests and full blood counts (including total and differential white cell and platelet counts) must be performed before starting treatment and before each intramuscular injection.
- Monitor for pulmonary fibrosis with annual chest X-ray.

PATIENT AND CARER ADVICE Patients should be advised to seek prompt medical attention if diarrhoea, sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, metallic taste, rash, breathlessness, or cough develop.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

solution for injection

- Myocrisin (Sanofi)
  - Sodium aurothiomalate 20 mg per 1 ml Myocrisin 10mg/0.5ml solution for injection ampoules | 10 ampoule £45.55
  - Sodium aurothiomalate 100 mg per 1 ml Myocrisin 50mg/0.5ml solution for injection ampoules | 10 ampoule £134.80

IMMUNOSUPPRESSANTS → INTERLEUKIN INHIBITORS

Anakinra

INDICATIONS AND DOSE

Treatment of rheumatoid arthritis (in combination with methotrexate) which has not responded to methotrexate alone

- BY SUBCUTANEOUS INJECTION
  - Adult: 100 mg once daily

CONTRA-INDICATIONS Neutropenia

CAUTIONS History of asthma (risk of serious infection) · predisposition to infection

INTERACTIONS → Appendix 1 (anakinra).

SIDE-EFFECTS

Common or very common Neutropenia

Frequency not known Antibody formation · headache · infections · injection-site reactions · malignancy

SIDE-EFFECTS, FURTHER INFORMATION

Blood disorders. Neutropenia reported commonly—discontinue if neutropenia develops.

CONCEPTION AND CONTRACEPTION Effective contraception must be used during treatment.

PREGNANCY Manufacturer advises avoid.

BREAST FEEDING Manufacturer advises avoid—no information available.

RENAL IMPAIRMENT Caution if eGFR 30–50 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS Monitor neutrophil count before treatment, then every month for 6 months, then every 3 months.

PATIENT AND CARER ADVICE

Blood disorders. Patients should be instructed to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat, bruising or, bleeding) develop.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (July 2002) that anakinra is not recommended for the treatment of rheumatoid arthritis within NHS Scotland.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Kineret (Swedish Orphan Biovitrum Ltd)
  - Anakinra 150 mg per 1 ml Kineret 100mg/0.67ml solution for injection pre-filled syringes | 28 pre-filled disposable injection £734.44

Arthritis 965

Musculoskeletal system
Secukinumab

16-Mar-2016

**INDICATIONS AND DOSE**

Psoriatic arthritis / Ankylosing spondylitis

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 150 mg every week for 5 doses, then maintenance 150 mg every month, review treatment if no response within 16 weeks of initial dose

Psoriatic arthritis with concomitant moderate to severe plaque psoriasis or if inadequate response to anti-TNF treatment / Plaque psoriasis

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 300 mg every week for 5 doses, then maintenance 300 mg every month, review treatment if no response within 16 weeks of initial dose

**CONTRA-INDICATIONS**

Severe active infection

**CAUTIONS**

Chronic infection - Crohn’s disease (monitor for exacerbations) - history of recurrent infection - predisposition to infection (discontinue if new serious infection develops)

**INTERACTIONS** → Appendix 1 (secukinumab).

**SIDE-EFFECTS**

- Common or very common Diarrhoea - oral herpes - rhinorrhea - upper respiratory tract infections
- Uncommon Conjunctivitis - neutropenia (usually mild and reversible) - oral candidiasis - otitis externa - tinea pedis
- Rare Anaphylactic reactions

**CONCEPTION AND CONTRACEPTION**

Manufacturer advises that women of childbearing potential should complete anti-tuberculosis therapy before starting secukinumab.

**PREGNANCY**

Manufacturer advises avoid—no information available.

**BREAST FEEDING**

Manufacturer advises avoid during treatment and for up to 20 weeks after discontinuing treatment—no information available.

**DIRECTIONS FOR ADMINISTRATION**

Manufacturer advises to take the syringe or pen out of the refrigerator 20 minutes before administration and to avoid injecting into areas of the skin that show psoriasis. Patients may self-administer Cosentyx® pre-filled pen.

**PATIENT AND CARER ADVICE**

Self-administration Patients and their carers should be given training in subcutaneous injection technique. Infection Patients and their carers should be advised to seek immediate medical attention if symptoms of infection develop during treatment with secukinumab.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Secukinumab for treating moderate to severe plaque psoriasis (July 2015) NICE TA350

Secukinumab is recommended as an option for the treatment of moderate to severe plaque psoriasis in adults if:

- the disease has failed to respond to standard systemic treatments (including ciclosporin, methotrexate, and PUVA), or when standard treatments are contra-indicated or not tolerated; and
- the manufacturer provides secukinumab with the discount agreed in the patient access scheme

Secukinumab should be withdrawn in patients whose psoriasis has not responded adequately within 12 weeks of initial dose; further treatment cycles are not recommended.

Patients whose treatment with secukinumab was started before this guidance was published, but does not meet these criteria, should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA350

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (May 2015) that secukinumab (Cosentyx®) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), or when standard treatments cannot be used because of intolerance or contra-indications.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Cosentyx** (Novartis Pharmaceuticals UK Ltd) ▼
  - Secukinumab 150 mg per 1 ml Cosentyx 150mg/1ml solution for injection pre-filled pens | 2 pre-filled disposable injection | £218.78
  - Cosentyx 150mg/1ml solution for injection pre-filled syringes | 2 pre-filled disposable injection | £218.78

Tocilizumab

31-May-2016

**INDICATIONS AND DOSE**

Moderate to severe active rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate) when response to at least one disease-modifying antirheumatic drug or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs

- **BY INTRAVENOUS INFUSION**
  - Adult: 8 mg/kg every 4 weeks (max. per dose 800 mg), for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count, consult product literature

**CONTRA-INDICATIONS**

Do not initiate if absolute neutrophil count less than 2 × 10^9/litre - severe active infection

**CAUTIONS**

History of diverticulitis - history of intestinal ulceration - history of recurrent or chronic infection (interrupt treatment if serious infection occurs) - low absolute neutrophil count - low platelet count - predisposition to infection (interrupt treatment if serious infection occurs)

**INTERACTIONS** → Appendix 1 (tocilizumab).

**SIDE-EFFECTS**

- Common or very common Abdominal pain - antibody formation - dizziness - gastritis - headache - hypercholesterolaemia - hypersensitivity - hypertension - infection - leucopenia - mouth ulceration - neutropenia - peripheral oedema - pruritus - raised hepatic transaminases - rash - upper respiratory tract infection
- Uncommon Anaphylaxis - gastric ulcer - gastro-intestinal perforation - hypertriglyceridaemia - hypothyroidism - infusion related reactions - nephrolithiasis

**Frequency not known** Thrombocytopenia
Tocilizumab for the treatment of rheumatoid arthritis (February 2012—updated February 2016) NICE TA247
Tocilizumab, in combination with methotrexate, is recommended as an option for the treatment of rheumatoid arthritis in adults if:
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the patient cannot receive rituximab because of contra-indications or intolerance, and
tocilizumab is used as described for TNF inhibitor treatments (specifically the recommendations on disease activity) in the NICE guidance (August 2010)
- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab
- and the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

Patients currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet these criteria should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

www.nice.org.uk/TA247

Ustekinumab

INDICATIONS AND DOSE
Severe plaque psoriasis that has not responded to at least 2 standard systemic treatments and photochemotherapy, or when these treatments cannot be used because of intolerance or contra-indications

BY SUBCUTANEOUS INJECTION
- Adult (body-weight up to 100 kg): Initially 45 mg, then 45 mg after 4 weeks, then 45 mg every 12 weeks, discontinue if no response within 16 weeks
- Adult (body-weight 100 kg and above): Initially 45–90 mg, then 45–90 mg after 4 weeks, then 45–90 mg every 12 weeks, discontinue if no response within 16 weeks

Active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs

BY SUBCUTANEOUS INJECTION
- Adult (body-weight up to 100 kg): Initially 45 mg, then 45 mg after 4 weeks, then 45 mg every 12 weeks, review treatment if no response within 28 weeks
- Adult (body-weight 100 kg and above): Initially 45–90 mg, then 45–90 mg after 4 weeks, then 45–90 mg every 12 weeks, review treatment if no response within 28 weeks

CONTRA-INDICATIONS
Active infection

CAUTIONS
Development of malignancy - elderly - history of malignancy - predisposition to infection - start appropriate treatment if widespread erythema and skin exfoliation develop, and stop ustekinumab treatment if exfoliative dermatitis suspected
CAUTIONS, FURTHER INFORMATION

- **Tuberculosis** Active tuberculosis should be treated with standard treatment for at least 2 months before starting ustekinumab. Patients who have previously received adequate treatment for tuberculosis can start ustekinumab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting ustekinumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with ustekinumab.

  - **INTERACTIONS** → Appendix 1 (ustekinumab).

- **SIDE-EFFECTS**
  - **Common or very common** Arthralgia, diarrhoea, dizziness, headache, infections (sometimes severe), injection-site reactions, malaise, myalgia, nausea, oropharyngeal pain, pruritus
  - **Uncommon** Depression, facial palsy, hypersensitivity reactions (possibly delayed onset), nasal congestion, pustular psoriasis
  - **Rare** Exfoliative dermatitis

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment and for 15 weeks after stopping treatment.

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **PRE-TREATMENT SCREENING**
  - Tuberculosis Patients should be evaluated for tuberculous before treatment.

- **MONITORING REQUIREMENTS**
  - Monitor for non-melanoma skin cancer, especially in patients with a history of PUVA treatment or prolonged immunosuppressant therapy, or those over 60 years of age.
  - Monitor for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis.

- **PATIENT AND CARER ADVICE**
  - Exfoliative dermatitis Patients should be advised to seek prompt medical attention if symptoms suggestive of exfoliative dermatitis or erythrodermic psoriasis (such as increased redness and shedding of skin over a larger area of the body) develop.
  - Tuberculosis Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)**
    - **Ustekinumab for plaque psoriasis in adults** (September 2009) NICE TA180
      - Ustekinumab is recommended for the treatment of severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and to photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Ustekinumab should be withdrawn if the response is not adequate after 16 weeks.
      - For patients weighing over 100 kg, the manufacturer should provide the 90-mg dose of ustekinumab at the same price as the 45-mg dose.
      - www.nice.org.uk/TA180
    - **Ustekinumab for treating active psoriatic arthritis** (June 2015) NICE TA340
      - Ustekinumab is an option, alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults only when:
        - treatment with tumour necrosis factor (TNF) alpha inhibitors is contra-indicated but would otherwise be considered (as described in the NICE guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (August 2010) and golimumab for the treatment of psoriatic arthritis (April 2011)) or
        - the patient has had treatment with 1 or more TNF-alpha inhibitors.
      - Ustekinumab is recommended only if the manufacturer provides the 90 mg dose of ustekinumab for patients who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.
      - Ustekinumab treatment should be stopped if the patient’s psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks.
      - Patients currently receiving ustekinumab whose disease does not meet the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.
      - www.nice.org.uk/TA340

  - **Scottish Medicines Consortium (SMC) Decisions**
    - The Scottish Medicines Consortium has advised (February 2014) that ustekinumab (Stelara®) is accepted for restricted use within NHS Scotland either alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults who have responded inadequately to previous therapy with a non-biological disease-modifying anti-rheumatic drug, and failed on, or are unsuitable for, treatment with a TNF inhibitor.

  - **MEDIcular forms**
    - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - CAUTIONARY AND ADVISORY LABELS 10
      - **Stelara** (Janssen-Cilag Ltd)
        - Ustekinumab 90 mg per 1 ml
        - Stelara 90mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection
          - £2,147.00
        - Stelara 45mg/0.5ml solution for injection vials | 1 vial
          - £2,147.00
        - Stelara 45mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection
          - £2,147.00

- **IMMUNOSUPPRESSANTS**

  - **Abatacept**
    - **INDICATIONS AND DOSE**
      - Moderate to severe active rheumatoid arthritis (in combination with methotrexate) in patients unresponsive to other disease-modifying antirheumatic drugs (including methotrexate or a tumour necrosis factor (TNF) inhibitor)
        - **INITIALLY BY INTRAVENOUS INFUSION**
          - Adult (body-weight up to 60 kg): 500 mg every 2 weeks for 3 doses (loading dose), then (by intravenous infusion) 500 mg every 4 weeks, alternatively (by subcutaneous injection) 125 mg once weekly, first subcutaneous dose to be given within 1 day of the intravenous loading dose; patients who are unable to receive an infusion may initiate subcutaneous abatacept without receiving an intravenous loading dose
        - Adult (body-weight 60-100 kg): 750 mg every 2 weeks for 3 doses (loading dose), then (by intravenous infusion) 750 mg every 4 weeks, alternatively (by subcutaneous injection) 125 mg once weekly, first subcutaneous dose to be given within 1 day of the intravenous loading dose; patients who are unable to receive an infusion may initiate subcutaneous abatacept without receiving an intravenous loading dose
Adult (body-weight 101 kg and above): 1 g every 2 weeks for 3 doses (loading dose), then (by intravenous infusion) 1 g every 4 weeks, alternatively (by subcutaneous injection) 125 mg once weekly, first subcutaneous dose to be given within 1 day of the intravenous loading dose; patients who are unable to receive an infusion may initiate subcutaneous abatacept without receiving an intravenous loading dose

- CONTRA-INDICATIONS
  - Severe infection

- CAUTIONS
  - Do not initiate until active infections are controlled. Elderly (increased risk of side-effects) predisposition to infection (screen for latent tuberculosis and viral hepatitis). Progressive multifocal leucoencephalopathy (discontinue treatment if neurological symptoms present)

- INTERACTIONS
  - Appendix 1 (abatacept).

- SIDE-EFFECTS
  - Common or very common: Abdominal pain, conjunctivitis, cough, diarrhoea, dizziness, dyspepsia, fatigue, flushing, headache, hypertension, infection, leucopenia, nausea, pain in extremities, paraesthesia, stomatitis, vomiting
  - Uncommon: Psoriasis, alopecia, anxiety, arthralgia, basal and squamous cell carcinoma, bradycardia, bronchospasm, bruising, depression, dry eye, dry skin, dyspnoea, gastritis, hyperhidrosis, hypotension, menstrual disturbances, palpitation, skin papilloma, sleep disorder, tachycardia, thrombocytopenia, visual disturbance, weight gain
  - Frequency not known: Lung cancer, lymphoma

- CONCEPTION AND CONTRACEPTION
  - Effective contraception required during treatment and for 14 weeks after last dose.

- PREGNANCY
  - Manufacturer advises avoid unless essential.

- BREAST FEEDING
  - Present in milk in animal studies—manufacturer advises avoid breast-feeding during treatment and for 14 weeks after last dose.

- DIRECTIONS FOR ADMINISTRATION
  - For intravenous infusion, given intermittently in Sodium chloride 0.9%; reconstitute each vial with 10 mL water for injections using the silicone-free syringe provided; dilute requisite dose in Sodium Chloride 0.9% to 100 mL (using the same silicone-free syringe); give over 30 minutes through a low protein-binding filter (pore size 0.2–1.2 micron).

- NATIONAL FUNDING/ACCESS DECISIONS

  - NICE technology appraisals (TAs)
    - Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195
      - Abatacept, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other disease-modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor (TNF) inhibitor, and who cannot use rituximab because of contra-indications or intolerance. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months. www.nice.org.uk/TA195
    - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375
      - Abatacept, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if all the following criteria are met:
        - Disease is severe, that is, a disease activity score (DAS28) greater than 5.1,
        - Disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs),
        - the manufacturers provide abatacept as agreed in the patient access schemes.
      - Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.
      - Patients currently receiving abatacept whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA375

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  - Powder for solution for infusion
    - ELECTROLYTES: May contain Sodium
      - Orenzia (Bristol-Myers Squibb Pharmaceuticals Ltd)
      - Abatacept 250 mg (Orenzia 250mg powder for concentrate for solution for infusion vials | 1 vial £302.40 (Hospital only)

- IMMUNOSUPPRESSANTS

  - TUMOR NECROSIS FACTOR ALPHA (TNF-α) INHIBITORS

Adalimumab

- INDICATIONS AND DOSE
  - Severe plaque psoriasis either refractory to at least 2 standard systemic treatments or photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications
  - By subcutaneous injection
    - Adult: Initially 80 mg, then 40 mg every 2 weeks, to be started 1 week after initial dose, discontinue treatment if no response within 16 weeks
  - Moderate to severe active rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate) when response to other disease-modifying drugs (including methotrexate) has been inadequate
  - Severe, active, and progressive rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate) not previously treated with methotrexate
  - By subcutaneous injection
    - Adult: 40 mg every 2 weeks, then increased if necessary to 40 mg once weekly, dose to be increased only in patients receiving adalimumab alone, review treatment if no response within 12 weeks
  - Active and progressive psoriatic arthritis that has not responded adequately to other disease-modifying antirheumatic drugs
  - Severe active ankylosing spondylitis that has not responded adequately to other disease-modifying antirheumatic drugs
  - Severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of, NSAIDs
  - By subcutaneous injection
    - Adult: 40 mg every 2 weeks, discontinue treatment if no response within 12 weeks

Severe active Crohn’s disease

- By subcutaneous injection
  - Adult: Initially 80 mg, then 40 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose continued
Severe active Crohn’s disease (accelerated regimen)

- By subcutaneous injection
- Adult: Initially 160 mg, dose can alternatively be given as divided injections over 2 days, then 80 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose

Severe active ulcerative colitis

- By subcutaneous injection
- Adult: Initially 160 mg, dose can alternatively be given as divided injections over 2 days, then 80 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 8 weeks of initial dose

Active moderate to severe hidradenitis suppurativa (acne inversa) in patients with an inadequate response to conventional systemic therapy

- By subcutaneous injection
- Adult: Initially 160 mg, given as either four 40 mg injections in one day or as two 40 mg injections per day for 2 consecutive days, followed by 80 mg after 2 weeks, given as two 40 mg injections in one day, then 40 mg after 2 weeks; maintenance 40 mg once weekly, review treatment if no response within 12 weeks; if treatment interrupted—consult product literature.

**CONTRA-INDICATIONS**
- Moderate or severe heart failure
- Severe infection

**CAUTIONS**
- Demyelinating disorders (risk of exacerbation)
- Development of malignancy—do not initiate until active infections are controlled (discontinue if new serious infection develops)
- Hepatitis B virus—monitor for active infection
- History of malignancy
- Mild heart failure
- Predisposition to infection

**CAUTIONS, FURTHER INFORMATION**
- Tuberculosis
  - Active tuberculosis should be treated with standard treatment for at least 2 months before starting adalimumab. Patients who have previously received adequate treatment for tuberculosis can start adalimumab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with adalimumab.

**INTERACTIONS**
- Appendix 1 (adalimumab).

**SIDE-EFFECTS**
- Common or very common
  - Anxiety
  - Benign tumours
  - Chest pain
  - Cough
  - Dehydration
  - Dermatitis
  - Dizziness
  - Dyspepsia
  - Dyspnoea
  - Electrolyte disturbances
  - Eye disorders
  - Flushing
  - Gastrointestinal haemorrhage
  - Haematuria
  - Hyperlipidaemia
  - Hypertension
  - Hyperuricaemia
  - Impaired healing
  - Mood changes
  - Musculoskeletal pain
  - Oedema
  - Onycholysis
  - Paraesthesia
  - Rash
  - Renal impairment
  - Skin cancer
  - Sleep disturbances
  - Tachycardia
  - Vomiting

- Uncommon
  - Aortic aneurysm
  - Arrhythmias
  - Cholecytisit
  - Cholelithiasis
  - Dysphagia
  - Erectile dysfunction
  - Hearing loss
  - Hepatic steatosis
  - Interstitial lung disease
  - Leukaemia
  - Lymphoma
  - Malignancy
  - Neuropathy
  - Nocturia
  - Pancreatitis
  - Pneumonitis
  - Rhombdyomysitis
  - Solid tumours
  - Sinusitis
  - Tremor
  - Vascular occlusion

- Rare
  - Autoimmune hepatitis
  - Demyelinating disorders
  - Myocardial infarction

- Frequency not known
  - Abdominal pain
  - Anaemia
  - Antibody formation
  - Aplastic anaemia
  - Blood disorders
  - Cutaneous vasculitis
  - Depression
  - Fever
  - Headache
  - Hypersensitivity reactions
  - Injection-site reactions
  - Leucopenia
  - Lupus erythematosus-like syndrome
  - Nausea
  - New onset psoriasis
  - Pancytopenia
  - Pleural effusion
  - Pruritus
  - Pulmonary embolism
  - sarcoidosis
  - Stevens-Johnson syndrome
  - Thrombocytopenia
  - Worsening heart failure
  - Worsening of symptoms of dermatomyositis
  - Worsening psoriasis

**SIDE-EFFECTS, FURTHER INFORMATION**

Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises effective contraception required during treatment and for at least 5 months after last dose.

**PREGNANCY**
- Avoid.

**BREAST FEEDING**
- Avoid; manufacturer advises avoid for at least 5 months after last dose.

**PRE-TREATMENT SCREENING**
- Tuberculosis
  - Patients should be evaluated for tuberculosis before treatment.

**MONITORING REQUIREMENTS**
- Monitor for infection before, during, and for 4 months after treatment.
- Monitor for non-melanoma skin cancer before and during treatment, especially in patients with a history of PUVA treatment for psoriasis or extensive immunosuppressant therapy.

**PATIENT AND CARER ADVICE**
- An alert card should be provided.

**NATIONAL FUNDING/ACCESS DECISIONS**
- NICE technology appraisals (TAs)
  - Adalimumab for plaque psoriasis in adults (June 2008)
    - NICE TA146
      - Adalimumab is recommended for the treatment of severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Adalimumab should be withdrawn if the response is not adequate after 16 weeks.
      - www.nice.org.uk/TA146
  - Infliximab and adalimumab for Crohn’s disease (May 2010)
    - NICE TA187
      - Adalimumab is recommended for the treatment of severe active Crohn’s disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications. Adalimumab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter. Treatment should be continued beyond 12 months only if there is evidence of active disease—in these cases the need for treatment should be reviewed at least annually. If the disease relapses after stopping treatment, adalimumab can be restarted.
      - www.nice.org.uk/TA187
† Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329

Adalimumab is an option for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies.

The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen.

Adalimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

www.nice.org.uk/TA329

† Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010) NICE TA199

Adalimumab is recommended for the treatment of active and progressive psoriatic arthritis in adults who have peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and who have not responded adequately to at least 2 standard disease-modifying antirheumatic drugs (used alone or in combination).

Adalimumab should be discontinued if there is an inadequate response at 12 weeks.

www.nice.org.uk/TA199

† Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195

Adalimumab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other DMARDs including at least 1 TNF inhibitor, and who cannot use rituximab because of contra-indications or intolerance. In patients who cannot use methotrexate because of intolerance or contra-indications, adalimumab can be given as monotherapy. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months.

www.nice.org.uk/TA195

† Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Adalimumab, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and,
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs).

Adalimumab can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving adalimumab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA375

† TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthropathy (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

Adalimumab, certolizumab pegol and etanercept are also recommended as options for treating severe non-radiographic axial spondyloarthropathy in patients whose disease has responded inadequately to, or who are intolerant of, NSAIDs.

The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/TA383

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium issued similar advice for plaque psoriasis to NICE TA146 in May 2008.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS 10

† Humira (AbbVie Ltd)

Adalimumab 50 mg per 1 ml Humira 40mg/0.8ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £704.28

Humira 40mg/0.8ml solution for injection pre-filled pen | 2 pre-filled disposable injection £704.28

Humira 40mg/0.8ml solution for injection vials | 2 vial £704.28

Adalimumab 100 mg per 1 ml Humira 40mg/0.4ml solution for injection pre-filled pen | 2 pre-filled disposable injection £704.28

Humira 40mg/0.4ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £704.28

● INDICATIONS AND DOSE

Moderate to severe active rheumatoid arthritis when response to disease-modifying antirheumatic drugs (including methotrexate) has been inadequate (as monotherapy or in combination with methotrexate) | Severe, active and progressive rheumatoid arthritis in patients not previously treated with methotrexate or other disease-modifying antirheumatic drugs (in combination with methotrexate) | Active psoriatic arthritis when response to disease-modifying antirheumatic drugs has been inadequate (as monotherapy or in combination with methotrexate)

† BY SUBCUTANEOUS INJECTION

Adult: Loading dose 400 mg every 2 weeks for 3 doses, then maintenance 200 mg every 2 weeks, once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered, review treatment if no response within 12 weeks

Certolizumab pegol

31-May-2016

10 Musculoskeletal system
Contraindications

Moderate to severe heart failure

Severe active infection

Demyelinating CNS disorders (risk of exacerbation) do not initiate until active infections are controlled (discontinue if new serious infection develops and until infection controlled).

Hepatitis B virus (monitor for active infection).

History or development of malignancy.

Mild to moderate heart failure.

Pre-existing serious skin, soft tissue or bone infection.

Photosensitivity

Periodic paralytic attacks.

Pterygia.

Rheumatic heart disease.

Systemic lupus erythematosus.

Secondary Sjögren’s syndrome.

Severe, unstable angina.

Disorders of hepatic metabolism.

Gastrointestinal disorders.

Sepsis.

Tuberculosis

Active tuberculosis should be treated with caution.

Further information

National funding/access decisions

NICE technology appraisals (TAs)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if all the following criteria are met:

- Disease is severe, that is, a disease activity score (DAS28) greater than 5.1.
- Disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs),
- The manufacturers provide certolizumab pegol as agreed in the patient access schemes.

Certolizumab pegol can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.

continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving certolizumab pegol whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA375

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to or who are intolerant of, non-steroidal anti-inflammatory drugs.

Adalimumab, certolizumab pegol and etanercept are also recommended as options for treating severe non-radiographic axial spondyloarthritis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

The response to treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment.
with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response. www.nice.org.uk/TA383

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2014) that certolizumab pegol is accepted for restricted use within NHS Scotland, in combination with methotrexate, for the treatment of active psoriatic arthritis in patients whose disease has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
CAUTIONARY AND ADVISORY LABELS 10
- Cimzia (UCB Pharma Ltd)
  Certolizumab pegol 200 mg per 1 ml Cimzia 200mg/1ml solution for injection pre-filled pen | 2 pre-filled disposable injection POM £715.00 Cimzia 200mg/1ml solution for injection pre-filled syringes | 2 syringes POM £715.00

Etanercept
04-May-2016

INDICATIONS AND DOSE
Moderate to severe active rheumatoid arthritis (alone or in combination with methotrexate) when the response to other disease-modifying antirheumatic drugs is inadequate
Severe, active, and progressive rheumatoid arthritis not previously treated with methotrexate
Active and progressive psoriatic arthritis inadequately responsive to other disease-modifying antirheumatic drugs
Severe ankylosing spondylitis inadequately responsive to conventional therapy

CONTRA-INDICATIONS Active infection

CAUTIONS Development of malignancy - diabetes mellitus - heart failure (risk of exacerbation) - hepatitis B virus— monitor for active infection - hepatitis C infection (monitor for worsening infection) - history of blood disorders - history of malignancy - history or increased risk of demyelinating disorders - predisposition to infection (avoid if predisposition to sepsicaemia) - significant exposure to herpes zoster virus—interrupt treatment and consider varicella—zoster immunoglobulin

CAUTIONS, FURTHER INFORMATION
- Tuberculosis Active tuberculosis should be treated with standard treatment for at least 2 months before starting etanercept. Patients who have previously received adequate treatment for tuberculosis can start etanercept but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In patients at high risk of tuberculosis who cannot be assessed by tuberculosis skin test, chemoprophylaxis can be given concurrently with etanercept.

INTERACTIONS Appendix 1 (etanercept).

SIDE-EFFECTS
- Uncommon Interstitial lung disease - new onset or worsening psoriasis - rash - skin cancer - uveitis
- Rare Demyelinating disorders - lymphoma - seizures - Stevens-Johnson syndrome - vasculitis
- Very rare Toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION
Associated with infections, sometimes severe, including tuberculosis, sepsicaemia, and hepatitis B reactivation.

CONCEPTION AND CONTRAINDICATIONS Effective contraception required during treatment and for 3 weeks after last dose.

PREGNANCY Avoid—limited information available.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Use with caution in moderate to severe alcoholic hepatitis.

PRE-TREATMENT SCREENING
Tuberculosis Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS Monitor for skin cancer before and during treatment, particularly in those at risk (including patients with psoriasis or a history of PUVA treatment).

PRESCRIBING AND DISPENSING INFORMATION
Etanercept is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

PATIENT AND CARER ADVICE
An alert card should be provided.

Blood disorders Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Tuberculosis Patients and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Etanercept and efalizumab for plaque psoriasis (July 2006)

NICE TA103
Etanercept is recommended for severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and to photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Etanercept should be withdrawn if the response is not adequate after 12 weeks. www.nice.org.uk/TA103

- Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195
Etanercept, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other DMARDs including at
least 1 TNF inhibitor, and who cannot use rituximab because of contra-indications or intolerance. In patients who cannot use methotrexate because of intolerance or contra-indications, etanercept can be given as monotherapy. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months. www.nice.org.uk/TA195

- Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010) NICE TA199

Etanercept is recommended for the treatment of active and progressive psoriatic arthritis in adults who have peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and who have not responded adequately to at least 2 standard disease-modifying antirheumatic drugs (used alone or in combination).

Etanercept should be discontinued if there is an inadequate response at 12 weeks. www.nice.org.uk/TA199

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016)

NICE TA375

Etanercept, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs)

Etanercept can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving etanercept whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA375

- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016)

NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

Adalimumab, certolizumab pegol and etanercept are also recommended as options for treating severe non-radiographic axial spondyloarthritis in patients whose disease has responded inadequately to, or who are intolerant of, NSAIDs.

The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response. www.nice.org.uk/TA383

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium issued similar advice to NICE TA103 on the use of etanercept for severe plaque psoriasis in adults (August 2009) and children over 6 years old (April 2012).

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
CAUTIONARY AND ADVISORY LABELS 10

- Benepali (Biogen Idec Ltd) ▼

Etanercept 50 mg per 1 ml Benepali 50mg/1ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £65.00

Benepali 50mg/1ml solution for injection pre-filled pen | 4 pre-filled disposable injection £65.00

- Enbrel (Pfizer Ltd)

Etanercept 50 mg per 1 ml Enbrel 50mg/1ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £71.00

Enbrel 25mg/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £357.50

- Enbrel MyClic (Pfizer Ltd)

Etanercept 50 mg per 1 ml Enbrel 50mg/1ml solution for injection pre-filled MyClic pen | 4 pre-filled disposable injection £71.00

Powder and solvent for solution for injection
CAUTIONARY AND ADVISORY LABELS 10

EXCIPIENTS: May contain Benzyl alcohol

- Enbrel (Pfizer Ltd)

Etanercept 25 mg Enbrel 25mg powder and solvent for solution for injection vials | 4 vial £357.50

Golimumab

31-May-2016

- INDICATIONS AND DOSE

Treatment of severe ulcerative colitis in patients whose condition has not responded adequately to conventional therapy, or who are intolerant of it

- BY SUBCUTANEOUS INJECTION

- Adult (body-weight up to 80 kg): Initially 200 mg, then 100 mg after 2 weeks; maintenance 50 mg every 4 weeks, review treatment if no response after 4 doses

- Adult (body-weight 80 kg and above): Initially 200 mg, then 100 mg after 2 weeks; maintenance 100 mg every 4 weeks, review treatment if no response after 4 doses

Treatment of moderate to severe active rheumatoid arthritis (in combination with methotrexate) when response to disease-modifying antirheumatic drug (DMARD) therapy (including methotrexate) has been inadequate | Treatment of severe, active, and progressive rheumatoid arthritis (in combination with methotrexate) in patients not previously treated with methotrexate | Treatment of active and progressive psoriatic arthritis as monotherapy or in combination with methotrexate when response to DMARD therapy has been inadequate | Treatment of severe active ankylosing spondylitis when there is inadequate response to conventional treatment

- BY SUBCUTANEOUS INJECTION

- Adult (body-weight up to 100 kg): 50 mg once a month, on the same date each month, review treatment if no response after 3–4 doses

- Adult (body-weight 100 kg and above): Initially 50 mg once a month for 3–4 doses, on the same date each month, dose may be increased if inadequate response, increased to 100 mg once a month, review treatment if inadequate response to this higher dose after 3–4 doses

- CONTRA-INDICATIONS

Moderate or severe heart failure - severe active infection

- CAUTIONS

Active infection (do not initiate until active infections are controlled; discontinue if new serious infection develops until infection controlled), demyelinating disorders (risk of exacerbation), hepatitis B virus—monitor for active infection, history or development of malignancy, mild heart failure (discontinue if symptoms develop or worsen), predisposition to infection - risk factors for dysplasia or carcinoma of the colon—screen for dysplasia regularly
PATIENT AND CARER ADVICE

MONITORING REQUIREMENTS

HEPATIC IMPAIRMENT

BREAST FEEDING

PREGNANCY

SIDE-EFFECTS

INTERACTIONS → Appendix 1 (golimumab).

NATIONAL FUNDING/ACCESS DECISIONS

SIDE-EFFECTS, FURTHER INFORMATION

CONCEPTION AND CONTRACEPTION

SLEEP-INDUCTION REMEDIES

PRE-TREATMENT SCREENING

PATIENT AND CARER ADVICE

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Common or very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood disorders</td>
<td>Asthenia, dizziness, dyspepsia, hypertension</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Abdominal pain, anaemia, antibody formation, aplastic anaemia, blood disorders, depression, fever, headache, symptoms, reaction, leucopenia, lupus erythematosus, syndrome, nausea, pancytopenia, pruritus, thrombocytopenia, worsening heart failure</td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>Frequency not known</td>
</tr>
<tr>
<td>Rare</td>
<td>Associated with infections, sometimes severe, including tuberculosis, sepsicaemia, and hepatitis B reactivation</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Manoeuvre advises adequate contraception during treatment and for at least 6 months after last dose</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Use only if essential</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Manufacturer advises avoidance during and for at least 6 months after treatment—present in milk in animal studies</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>For doses requiring multiple injections, each injection should be administered at a different site</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>An alert card should be provided</td>
</tr>
</tbody>
</table>

Blood disorders

Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

NATIONAL FUNDING/ACCESS DECISIONS

Golimumab for the treatment of psoriatic arthritis (April 2011) NICE TA220

Golimumab is an option for the treatment of active and progressive psoriatic arthritis in adults only if:

- golimumab is used as described in the NICE guidance (August 2010) for other tumour necrosis factor (TNF) inhibitors, and
- the manufacturer provides the 100-mg dose of golimumab at the same price as the 50-mg dose.

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329

Golimumab is an option for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies.

Golimumab is recommended only if the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen.

Golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Golimumab, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if all the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1,
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs),
- the manufacturer provides golimumab as agreed in the patient access schemes.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving treatment with golimumab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are
intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

The response to treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF) -alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/TA383

Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs (June 2011—updated February 2016) NICE TA225

Golimumab, in combination with methotrexate, is an option for the treatment of rheumatoid arthritis in patients who have had an inadequate response to DMARDs, including a TNF inhibitor, if golimumab is used as described in the NICE technology appraisal guidance 195 (August 2010) for other TNF inhibitors, and the manufacturer provides the 100-mg dose of golimumab at the same price as the 50-mg dose.

www.nice.org.uk/TA225

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (June 2012) that golimumab (Simponi®) is accepted for restricted use within NHS Scotland at a dose of 50 mg, alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adults whose disease has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS

Simponi (Merck Sharp & Dohme Ltd)

Golimumab 100 mg per 1 ml Simponi 50mg/0.5ml solution for injection pre-filled disposable devices | 1 pre-filled disposable injection £762.97

Simponi 100mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection £1,525.94

Simponi 50mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £762.97

Infliximab

INDICATIONS AND DOSE

Severe active Crohn’s disease

▶ BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, then 5 mg/kg after 4 weeks, if condition has responded, then maintenance 5 mg/kg every 8 weeks

Fistulating Crohn’s disease

▶ BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, if condition has responded consult product literature for guidance on further doses

Severe active ulcerative colitis

▶ BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks, discontinue if no response 14 weeks after initial dose

Rheumatoid arthritis (in combination with methotrexate)

▶ BY INTRAVENOUS INFUSION

Adult: Initially 3 mg/kg, then 3 mg/kg after 2 weeks, followed by 2 mg/kg after 4 weeks, then 3 mg/kg every 8 weeks, dose to be increased only if response is inadequate after 12 weeks of initial treatment; increased in steps of 1.5 mg/kg every 8 weeks, increased if necessary up to 7.5 mg/kg every 8 weeks, alternatively increased if necessary to 3 mg/kg every 4 weeks, discontinue if no response by 12 weeks of initial infusion or after dose adjustment

Ankylosing spondylitis

▶ BY INTRAVENOUS INFUSION

Adult: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 6–8 weeks, discontinue if no response by 6 weeks of initial infusion

Psoriatic arthritis (in combination with methotrexate)

▶ BY INTRAVENOUS INFUSION

Adult: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks

Plaque psoriasis

▶ BY INTRAVENOUS INFUSION

Adult: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks, discontinue if no response within 14 weeks of initial infusion

IMPORTANT SAFETY INFORMATION

Adequate resuscitation facilities must be available when infliximab is used.

CONTRA-INDICATIONS

Moderate or severe heart failure • severe infections

CAUTIONS

Demyelinating disorders (risk of exacerbation) • dermatomyositis • development of malignancy • hepatitis B virus—monitor for active infection • history of colon carcinoma (in inflammatory bowel disease) • history of dysplasia (in inflammatory bowel disease) • history of malignancy • history of prolonged immunosuppressant or PUVA treatment in patients with psoriasis • mild heart failure (discontinue if symptoms develop or worsen) • predisposition to infection (discontinue if new serious infection develops) • risk of delayed hypersensitivity reactions if drug-free interval exceeds 16 weeks (re-administration after interval exceeding 16 weeks not recommended)

CAUTIONS, FURTHER INFORMATION

Tuberculosis Manufacturer advises to evaluate patients for active and latent tuberculosis before treatment. Active tuberculosis should be treated with standard treatment for at least 2 months before starting infliximab. If latent tuberculosis is diagnosed, treatment should be started before commencing treatment with infliximab. Patients who have previously received adequate treatment for tuberculosis can start infliximab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting infliximab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with infliximab. Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis develop (e.g. persistent cough, weight loss and fever).

Hypersensitivity reactions Hypersensitivity reactions (including fever, chest pain, hypotension, hypertension, dyspnoea, transient visual loss, pruritus, urticaria, serum sickness—like reactions, angioedema, anaphylaxis) reported during or within 1–2 hours after infusion (risk greatest during first or second infusion or in patients who discontinue other immunosuppressants). Manufacturer advises prophylactic antipyretics, antihistamines, or hydrocortisone may be administered.
INTERACTIONS  Appendix 1 (infliximab).

SIDE-EFFECTS

- Common or very common  Alopecia, arthralgia, constipation, diarrhoea, dizziness, dry skin, dyspepsia, ecchymosis, epistaxis, flushing, gastro-intestinal haemorrhage, gastro-oesophageal reflux, hyperhydryosis, hypertension, hypoaesthesia, hypotension, myalgia, new onset or worsening psoriasis, palpitation, paraesthesia, rash, sleep disturbances, tachycardia

- Uncommon  Abnormal skin pigmentation, agitation, amnesia, arthrythmia, bradycardia, bullous eruption, chelitis, cholecystitis, confusion, eye disorders, heart failure, hepatitis, hyperkeratosis, impaired healing, intestinal perforation, nervousness, neuropathy, pancreatitis, peripheral ischaemia, pleurisy, pulmonary oedema, rosacea, seborrhoea, seizures, syncope, vaginitis

- Rare  Demyelinating disorders, interstitial lung disease, leukaemia, lymphoma, melanoma, pericardial effusion, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasospasm

- Frequency not known  Abdominal pain, anaemia, antibody formation, aplastic anaemia, blood disorders, depression, fever, headache, hepatic failure, hepatosplenic T-cell lymphoma (more likely in inflammatory bowel disease), hypersensitivity reactions, injection-site reactions, leucopenia, lupus erythematosus-like syndrome, Merkel cell carcinoma, nausea, pancytopenia, pruritus, thrombocytopenia, worsening heart failure, worsening symptoms of dermatomyositis

SIDE-EFFECTS, FURTHER INFORMATION

Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

CONCEPTION AND CONTRAINDICATIONS

Manufacturer advises adequate contraception during and for at least 6 months after last dose.

PREGNANCY

Use only if essential.

BREAST FEEDING

Amount probably too small to be harmful.

PRE-TREATMENT SCREENING

Tuberculosis  Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS

- Monitor for infection before, during, and for 6 months after treatment.
- All patients should be observed carefully for 1–2 hours after infusion and resuscitation equipment should be available for immediate use (risk of hypersensitivity reactions).
- Monitor for symptoms of delayed hypersensitivity if re-administered after a prolonged period.
- Manufacturer advises periodic skin examination for non-melanoma skin cancer, particularly in patients with risk factors.

DIRECTIONS FOR ADMINISTRATION  For intravenous infusion (Remicade®), give intermittently in Sodium chloride 0.9%; reconstitute each 100-mg vial with 10 mL water for injections using a 21-gauge or smaller needle; gently swirl vial without shaking to dissolve; allow to stand for 5 minutes; dilute requisite dose with infusion fluid to a final volume of 250 mL and give through a low protein-binding filter (1.2 micron or less) over at least 2 hours (adults over 18 years who have tolerated 3 initial 2-hour infusions may be given subsequent infusions of up to 6 mg/kg over at least 1 hour); start infusion within 3 hours of reconstitution.

PRESCRIBING AND DISPENSING INFORMATION

Infliximab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

PATIENT AND CARER ADVICE

An alert card should be provided.

Tuberculosis  Patients and carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

Blood disorders  Patients and carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Hypersensitivity reactions  Patients and carers should be advised to keep Alert card with them at all times and seek medical advice if symptoms of delayed hypersensitivity develop.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Infliximab for plaque psoriasis in adults (January 2008)  NICE TA134
  Infliximab is recommended for the treatment of very severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) or to phototherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Infliximab should be withdrawn if the response is not adequate after 10 weeks.
  www.nice.org.uk/TA134

- Infliximab for acute exacerbations of ulcerative colitis (December 2008)  NICE TA163
  Infliximab is recommended as an option for the treatment of acute exacerbations of severe ulcerative colitis when treatment with ciclosporin is contra-indicated or inappropriate.
  www.nice.org.uk/TA163

- Infliximab and adalimumab for Crohn’s disease (May 2010)  NICE TA187
  Infliximab is recommended for the treatment of severe active Crohn’s disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications; infliximab can also be used in a similar way in children over 6 years of age. In adults over 18 years of age, infliximab is recommended for the treatment of fistulating Crohn’s disease that has not responded to conventional therapy (including antibacterials, drainage, and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications.
  Infliximab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter. Treatment should be continued beyond 12 months only if there is evidence of active disease—in these cases the need for treatment should be reviewed at least annually. If the disease relapses after stopping treatment, infliximab can be restarted.
  www.nice.org.uk/TA187

- Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010)  NICE TA195
  Infliximab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other DMARDs including at least 1 TNF inhibitor, and who cannot use rituximab because of contra-indications or intolerance. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months.
  www.nice.org.uk/TA195

- Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010)  NICE TA199
  Infliximab is recommended for the treatment of active and progressive psoriatic arthritis in adults who have peripheral arthritis with at least 3 tender joints and at least
3 swollen joints, and who have not responded adequately to at least 2 standard disease-modifying antirheumatic drugs (used alone or in combination).

Infliximab should be discontinued if there is an inadequate response at 12 weeks.

www.nice.org.uk/TA199

- Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329

Infliximab is an option for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies.

The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen.

Infliximab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

www.nice.org.uk/TA329

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Infliximab, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs).

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving infliximab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA375

- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs). Infliximab is recommended only if treatment is started with the least expensive infliximab product.

Patients currently receiving infliximab should continue treatment with the same infliximab product until they and their clinician considers it appropriate to stop.

The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/TA383

- Infliximab is recommended only if treatment is started with the least expensive infliximab product.

Patients currently receiving infliximab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/TA383

**PHOSPHODIESTERASE TYPE-4 INHIBITORS**

**Apremilast**

- **DRUG ACTION** Apremilast inhibits the activity of phosphodiesterase type-4 (PDE4) which results in suppression of pro-inflammatory mediator synthesis and promotes anti-inflammatory mediators.

- **INDICATIONS AND DOSE**

  Active psoriatic arthritis (in combination with disease-modifying antirheumatic drugs or alone) in patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy | Moderate to severe chronic plaque psoriasis that has not responded to standard systemic treatments or photochemotherapy, or when these treatments cannot be used because of intolerance or contra-indications

  - **BY MOUTH**
    - Adult: Initially 10 mg daily on day 1, then 10 mg twice daily on day 2, then 10 mg in the morning and 20 mg in the evening on day 3, then 20 mg twice daily on day 4, then 20 mg in the morning and 30 mg in the evening on day 5, then maintenance 30 mg twice daily, doses should be taken approximately 12 hours apart; review treatment if no response within 24 weeks of initiation

  - **SIDE-EFFECTS**

  - Common or very common

    - Back pain
    - Bronchitis
    - Cough
    - Decreased appetite
    - Diarrhoea
    - Dyspepsia
    - Fatigue
    - Gastroesophageal reflux disease
    - Headache
    - Insomnia
    - Migraine
    - Nasopharyngitis
    - Nausea
    - Tension headache
    - Upper abdominal pain
    - Upper respiratory tract infections
    - Vomiting

  - Uncommon

    - Rash

  - **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment and ensure effective contraception during treatment.

  - **PREGNANCY** Avoid—teratogenic in animal studies.

  - **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

  - **RENAL IMPAIRMENT** Reduce dose if eGFR less than 30 mL/minute/1.73 m²; consult product literature for initial dose titration.

  - **MONITORING REQUIREMENTS** Monitor body-weight regularly.

- **CAUTIONS** Low body-weight—consider discontinuation if weight loss is unexplained or clinically significant

- **INTERACTIONS** Appendix 1 (apremilast).

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**

    - NICE TA375

      - Infliximab 100 mg (Flixabi Biogen Idec Ltd)
      - Infliximab 100 mg (Remsima Napp Pharmaceuticals Ltd)
      - Infliximab 100 mg (Remicade Merck Sharp & Dohme Ltd)

    - **CAUTIONARY AND ADVISORY LABELS**

      - Infliximab

        - Biopharmaceuticals

        - Irritable bowel syndrome

        - Malignancy

        - Pancreatitis

        - Pneumonia

        - Progressive multifocal leukoencephalopathy

        - Varicella zoster virus

- **SIDE-EFFECTS**

  - Common or very common

    - Back pain
    - Bronchitis
    - Cough
    - Decreased appetite
    - Diarrhoea
    - Dyspepsia
    - Fatigue
    - Gastroesophageal reflux disease
    - Headache
    - Insomnia
    - Migraine
    - Nasopharyngitis
    - Nausea
    - Tension headache
    - Upper abdominal pain
    - Upper respiratory tract infections
    - Vomiting

  - Uncommon

    - Rash

  - **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment and ensure effective contraception during treatment.

  - **PREGNANCY** Avoid—teratogenic in animal studies.

  - **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

  - **RENAL IMPAIRMENT** Reduce dose if eGFR less than 30 mL/minute/1.73 m²; consult product literature for initial dose titration.

  - **MONITORING REQUIREMENTS** Monitor body-weight regularly.
Acute attacks of gout are usually treated with high doses of corticosteroid. A corticosteroid by intramuscular injection can be effective in podagra.

Canakinumab p. 772, a recombinant monoclonal antibody, can be used for the symptomatic treatment of frequent gouty arthritis attacks (at least 3 in the previous 12 months). It is licensed for use in patients whose condition has not responded adequately to treatment with NSAIDs or colchicine, or who are intolerant of them.

### Long-term control of gout

Frequent recurrence of acute attacks of gout, the presence of tophi, or signs of chronic gouty arthritis may call for the initiation of long-term (‘interval’) treatment. For long-term control of gout the formation of uric acid from purines may be reduced with the xanthine-oxidase inhibitors allopurinol or febuxostat alternatively the uricosuric drug sulfinpyrazone p. 980 may be used to increase the excretion of uric acid in the urine. Treatment should be continued indefinitely to prevent further attacks of gout by correcting the hyperuricaemia. These drugs should never be started during an acute attack; they are usually started 1–2 weeks after the attack has settled. The initiation of treatment may precipitate an acute attack, and therefore an anti-inflammatory analgesic or colchicine should be used as a prophylactic and continued for at least one month after the hyperuricaemia has been corrected. However, if an acute attack develops during treatment, then the treatment should continue at the same dosage and the acute attack treated in its own right.

Allopurinol is widely used and is especially useful in patients with renal impairment or urate stones when uricosuric drugs cannot be used; it is not indicated for the treatment of asymptomatic hyperuricaemia. It can cause rashes.

Febuxostat is licensed for the treatment of chronic hyperuricaemia where urate deposition has already occurred; it is not indicated for patients in whom the rate of urate formation is greatly increased, such as in malignant disease or in Lesch–Nyhan syndrome.

Sulfinpyrazone can be used instead of allopurinol or in conjunction with it in cases that are resistant to treatment. Benzbromarone (available from ‘special-order’ manufacturers or specialist importing companies) is a uricosuric drug that can be used in patients with mild renal impairment.

Crystallisation of urate in the urine can occur with the uricosuric drugs and it is important to ensure an adequate urine output especially in the first few weeks of treatment. As an additional precaution the urine may be rendered alkaline.

Aspirin and other salicylates antagonise the uricosuric drugs; they do not antagonise allopurinol but are nevertheless not indicated in gout.

### Other drugs used for Hyperuricaemia and gout

- Ketoprofen with omeprazole, p. 1003
- Naproxen with esomeprazole, p. 1007
- Naproxen with misoprostol, p. 1007

### ALKALOIDS

#### Colchicine

- **INDICATIONS AND DOSE**
  - **Acute gout**
    - **BY MOUTH**
    - Adult: 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course, do not repeat course within 3 days

## Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

### Tablet

**CAUTIONARY AND ADVISORY LABELS 25**

- **Otezla** (Celgene Ltd)
  - Apemilast 10 mg: Otezla 10 mg tablets | 4 tablet **POM** no price available
  - Apemilast 20 mg: Otezla 20 mg tablets | 4 tablet **POM** no price available
  - Apemilast 30 mg: Otezla 30 mg tablets | 19 tablet **POM** no price available | 56 tablet **POM** £550.00

## 2 Hyperuricaemia and gout

### Gout

#### Overview

It is important to distinguish drugs used for the treatment of acute attacks of gout from those used in the long-term control of the disease. The latter exacerbate and prolong the acute manifestations if started during an attack. The management of gout in adolescents requires specialist supervision.

### Acute attacks of gout

Acute attacks of gout are usually treated with high doses of NSAIDs such as diclofenac sodium p. 993, diclofenac potassium p. 992, etoricoxib p. 996, indometacin p. 1001, ketoprofen p. 1002, naproxen p. 1006 or sulindac p. 1009. Colchicine below is an alternative in patients in whom NSAIDs are contra-indicated. Aspirin p. 114 is not indicated in gout. Allopurinol p. 980, febuxostat p. 981, and uricosurics are not effective in treating an acute attack and may prolong it indefinitely if started during the acute episode.

The use of colchicine is limited by the development of toxicity at higher doses, but it is of value in patients with heart failure since, unlike NSAIDs, it does not induce fluid retention; moreover, it can be given to patients receiving anticoagulants.

Oral or parenteral corticosteroids are an effective alternative in those who cannot tolerate NSAIDs or who are resistant to other treatments. Intra-articular injection of a
Short-term prophylaxis during initial therapy with allopurinol and uricosuric drugs

- **BY MOUTH**
- Adult: 500 micrograms twice daily

**Prophylaxis of familial Mediterranean fever (recurring polyserositis)**

- **BY MOUTH**
- Adult: 0.5–2 mg once daily

- **UNLICENSED USE** BNF doses may differ from those in the product literature. Use of colchicine for prophylaxis of familial Mediterranean fever (recurring polyserositis) is an unlicensed indication.

- **CONTRA-INDICATIONS** Blood disorders

- **CAUTIONS** Cardiac disease · elderly · gastro-intestinal disease

- **INTERACTIONS** → Appendix 1 (colchicine).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · nausea · vomiting
  - **Rare** Alopecia · blood disorders with prolonged treatment · inhibition of spermatogenesis · myopathy · peripheral neuritis
  - **Frequency not known** Excessive doses may cause profuse diarrhoea · gastrointestinal haemorrhage · hepatic damage · rash · renal damage
  - **PREGNANCY** Avoid—teratogenicity in animal studies.
  - **BREAST FEEDING** Present in milk but no adverse effects reported. Manufacturers advise caution.
  - **HEPATIC IMPAIRMENT** Use with caution.
  - **RENAL IMPAIRMENT** Reduce dose or increase dosage interval if eGFR 10–50 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Colchicine (Non-proprietary) Colchicine 500 microgram Colchicine 500microgram tablets | 100 tablet (Pack) £42.56 DT price = £15.82

**URICOSURICS**

**Sulfinpyrazone** (Sulphinpyrazone)

- **INDICATIONS AND DOSE**
  - **Gout prophylaxis** | **Hyperuricaemia**
    - **BY MOUTH**
      - Adult: Initially 100–200 mg daily, dose to be taken with food (or milk); increased to 600–800 mg daily over 2–3 weeks, 800 mg daily is rarely given; continue until serum uric acid concentration normal then reduce dose for maintenance (maintenance dose may be as low as 200 mg daily)

- **CONTRA-INDICATIONS** Acute gout attack · acute porphyrias p. 950 · history of blood disorders · peptic ulceration

- **CAUTIONS** Cardiac disease (may cause salt and water retention) · ensure adequate fluid intake (about 2–3 litres daily) and render urine alkaline during initial treatment

- **INTERACTIONS** → Appendix 1 (sulfinpyrazone).

- **SIDE-EFFECTS**
  - **Common or very common** Gastro-intestinal disorders · rashes (withdraw therapy; if rash mild re-introduce cautiously but discontinue promptly if recurrence)
  - **Rare** Alopecia · aplastic anaemia · arthralgia · blood disorders · drowsiness · eosinophilia resembling Stevens-Johnson syndrome · hepatic damage · jaundice · myopathy · peripheral neuritis

- **ALLERGY AND CROSS-SENSITIVITY** Avoid in hypersensitivity to aspirin, salicylates, NSAIDs.

- **PREGNANCY** Manufacturer advises caution—no information available.

- **BREAST FEEDING** No information available.

- **HEPATIC IMPAIRMENT** Avoid in severe impairment.

- **RENAL IMPAIRMENT** Reduce dose. Avoid in severe impairment.

- **MONITORING REQUIREMENTS** Regular blood counts before treatment and at regular intervals during treatment.

- **MEDICINAL FORMS**
  - Available in unlicensed preparations.

**XANTHINE OXIDASE INHIBITORS**

**Allopurinol**

- **INDICATIONS AND DOSE**
  - **Prophylaxis of gout of and of uric acid and calcium oxalate renal stones** | **Prophylaxis of hyperuricaemia associated with cancer chemotherapy**
    - **BY MOUTH**
      - Adult: Initially 100 mg daily, for maintenance adjust dose according to plasma or urinary uric acid concentration, dose to be taken preferably after food

  **Prophylaxis of gout and of uric acid and calcium oxalate renal stones (usual maintenance in mild conditions)** | **Prophylaxis of hyperuricaemia associated with cancer chemotherapy (usual maintenance in mild conditions)**
    - **BY MOUTH**
      - Adult: 100–200 mg daily, dose to be taken preferably after food

  **Prophylaxis of gout and of uric acid and calcium oxalate renal stones (usual maintenance in moderately severe conditions)** | **Prophylaxis of hyperuricaemia associated with cancer chemotherapy (usual maintenance in moderately severe conditions)**
    - **BY MOUTH**
      - Adult: 300–600 mg daily in divided doses (max. per dose 300 mg), dose to be taken preferably after food

  **Prophylaxis of gout and of uric acid and calcium oxalate renal stones (usual maintenance in severe conditions)** | **Prophylaxis of hyperuricaemia associated with cancer chemotherapy (usual maintenance in severe conditions)**
    - **BY MOUTH**
      - Adult: 700–900 mg daily in divided doses (max. per dose 300 mg), dose to be taken preferably after food

- **CONTRA-INDICATIONS** Not a treatment for acute gout but continue if attack develops when already receiving allopurinol, and treat attack separately

- **CAUTIONS** Ensure adequate fluid intake (2–3 litres/day) · for hyperuricaemia associated with cancer therapy, allopurinol treatment should be started before cancer therapy

**CAUTIONS, FURTHER INFORMATION**

Administer prophylactic NSAID (not aspirin or salicylates) or colchicine until at least 1 month after hyperuricaemia corrected (usually for first 3 months) to avoid precipitating an acute attack.

- **INTERACTIONS** → Appendix 1 (allopurinol).

- **SIDE-EFFECTS**
  - **Common or very common** Gastro-intestinal disorders · rashes (withdraw therapy; if rash mild re-introduce cautiously but discontinue promptly if recurrence)
  - **Rare** Alopecia · aplastic anaemia · arthralgia · blood disorders · drowsiness · eosinophilia resembling Stevens-Johnson syndrome · hepatic damage · jaundice · myopathy · peripheral neuritis

- Very rare - Seizures
- PREGNANCY - Toxicity not reported. Manufacturer advises use only if no safer alternative and disease carries risk for mother or child.
- BREAST FEEDING - Present in milk — not known to be harmful.
- HEPATIC IMPAIRMENT - Reduce dose.
- RENAL IMPAIRMENT - Max. 100 mg daily, increased only if response inadequate; in severe impairment, reduce daily dose below 100 mg, or increase dose interval; if facilities available, adjust dose to maintain plasma-oxipurinol concentration below 100 micromol/litre.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, and mouthwash.

**Tablet**

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### Febuxostat

#### INDICATIONS AND DOSE

**Treatment of chronic hyperuricaemia in gout**

- **BY MOUTH**
- Adult: Initially 80 mg once daily, if after 2–4 weeks of initial dose, serum uric acid greater than 6 mg/100 mL then increase dose; increased if necessary to 120 mg once daily

**Prophylaxis and treatment of acute hyperuricaemia with initial chemotherapy for haematologic malignancies**

- **BY MOUTH**
- Adult: 120 mg once daily, to be started 2 days before start of cytotoxic therapy and continued for 7–9 days, according to chemotherapy duration

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: SERIOUS HYPERSENSITIVITY REACTIONS (JUNE 2012)**

There have been rare but serious reports of hypersensitivity reactions, including Stevens-Johnson syndrome and acute anaphylactic shock with febuxostat. Patients should be advised of the signs and symptoms of severe hypersensitivity; febuxostat must be stopped immediately if these occur (early withdrawal is associated with a better prognosis), and must not be restarted in patients who have ever developed a hypersensitivity reaction to febuxostat. Most cases occur during the first month of treatment; a prior history of hypersensitivity to allopurinol and/or renal disease may indicate potential hypersensitivity to febuxostat.

**CONTRA-INDICATIONS** - Not a treatment for acute gout but continue if attack develops when already receiving febuxostat, and treat attack separately

**CAUTIONS** - Congestive heart failure - ischaemic heart disease - thyroid disorders - transplant recipients

**CAUTIONS, FURTHER INFORMATION**

Administer prophylactic NSAIDs (not aspirin or salicylates) or colchicine for at least 6 months after starting febuxostat to avoid precipitating an acute attack.

**INTERACTIONS** - Appendix 1 (febuxostat).

**SIDE-EFFECTS**

- **Common or very common** - Abnormal liver function tests - gastro-intestinal disturbances - headache - oedema - rash
- **Rare** - Asthenia - blurred vision - hepatitis - jaundice - mouth ulceration - nervousness - pancreatitis - pancytopenia - rhabdomyolysis - thirst - thrombocytopenia - tinnitus - tubulointerstitial nephritis
- **PREGNANCY** - Manufacturer advises avoid — limited information available.
- **BREAST FEEDING** - Manufacturer advises avoid — present in milk in animal studies.
- **HEPATIC IMPAIRMENT** - Max. 80 mg daily in mild impairment. No dose information available in moderate or severe impairment.
- **RENAL IMPAIRMENT** - Use with caution if eGFR less than 30 mL/minute/1.73 m² — no information available.
- **PRE-TREATMENT SCREENING** - Monitor liver function tests before treatment as indicated.
- **MONITORING REQUIREMENTS** - Monitor liver function tests periodically during treatment as indicated.
- **NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Febuxostat for the management of hyperuricaemia in patients with gout (December 2008) NICE TAI64

Febuxostat is recommended as an option for the management of chronic hyperuricaemia in gout only for patients who are intolerant of allopurinol or for whom allopurinol is contra-indicated.

For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant discontinuation, or to prevent full dose escalation for optimal effectiveness.

www.nice.org.uk/TAI64

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium issued similar advice to NICE guidance: Febuxostat for the management of hyperuricaemia in patients with gout (December 2008), in August 2010.

The Scottish Medicines Consortium has advised (June 2016) that febuxostat (Adenuric®) is accepted for restricted use within NHS Scotland for the prevention and treatment of hyperuricaemia in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of tumour lysis syndrome, only when allopurinol is not tolerated or contra-indicated.
3 Neuromuscular disorders

Neuromuscular disorders

Drugs that enhance neuromuscular transmission

Anticholinesterases are used as first-line treatment in ocular myasthenia gravis and as an adjunct to immunosuppressant therapy for generalised myasthenia gravis.

Corticosteroids are used when anticholinesterases do not control symptoms completely. A second-line immunosuppressant such as azathioprine p. 765 is frequently used to reduce the dose of corticosteroid.

Plasmapheresis or infusion of intravenous immunoglobulin [unlicensed indication] may induce temporary remission in severe relapses, particularly where bulbar or respiratory function is compromised or before thymectomy.

Anticholinesterases

Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis. Excessive dosage of these drugs can impair neuromuscular transmission and precipitate cholinergic crises by causing a depolarising block. This may be difficult to distinguish from a worsening myasthenic state.

Muscarinic side-effects of anticholinesterases include increased sweating, increased salivary and gastric secretions, increased gastrointestinal and uterine motility, and bradycardia. These parasympathomimetic effects are antagonised by atropine sulfate p. 1179.

Neostigmine p. 983 produces a therapeutic effect for up to 4 hours. Its pronounced muscarinic action is a disadvantage, and simultaneous administration of an antimuscarinic drug such as atropine sulfate or propantheline bromide p. 81 may be required to prevent colic, excessive salivation, or diarrhoea. In severe disease neostigmine can be given every 2 hours. The maximum that most patients can tolerate is 180 mg daily.

Pyridostigmine bromide p. 984 is less powerful and slower in action than neostigmine but it has a longer duration of action. It is preferable to neostigmine because of its smoother action and the need for less frequent dosage. It is particularly preferred in patients whose muscles are weak on waking. It has a comparatively mild gastrointestinal effect but an antimuscarinic drug may still be required.

Neostigmine is also used to reverse the actions of the non-depolarising neuromuscular blocking drugs.

Immunosuppressant therapy

Corticosteroids are established as treatment for myasthenia gravis; although they are commonly given on alternate days there is little evidence of benefit over daily administration. Corticosteroid treatment is usually initiated under in-patient supervision and all patients should receive osteoporosis prophylaxis.

In generalised myasthenia gravis prednisolone p. 622 is given. About 10% of patients experience a transient but very serious worsening of symptoms in the first 2–3 weeks, especially if the corticosteroid is started at a high dose. Smaller doses of corticosteroid are usually required in ocular myasthenia. Once clinical remission has occurred (usually after 2–6 months), the dose of prednisolone should be reduced slowly to the minimum effective dose.

In generalised myasthenia gravis azathioprine is usually started at the same time as the corticosteroid and it allows a lower maintenance dose of the corticosteroid to be used. Ciclosporin p. 766, methotrexate p. 817, or mycophenolate mofetil p. 773 can be used in patients unresponsive or intolerant to other treatments [unlicensed indications].

Acetycholine-release enhancers

Amifampridine p. 984 is licensed for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS), a rare disorder of neuromuscular transmission.

Fampridine p. 775 is licensed for the improvement of walking in patients with multiple sclerosis who have a walking disability.

Skeletal muscle relaxants

The drugs described are used for the relief of chronic muscle spasm or spasticity associated with multiple sclerosis or other neurological damage; they are not indicated for spasm associated with minor injuries. Baclofen, diazepam, and tizanidine act principally on the central nervous system. Dantrolene has a peripheral site of action; cannabis extract has both a central and a peripheral action. Skeletal muscle relaxants differ in action from the muscle relaxants used in anaesthesia, which block transmission at the neuromuscular junction.

The underlying cause of spasticity should be treated and any aggravating factors (e.g. pressure sores, infection) remedied. Skeletal muscle relaxants are effective in most forms of spasticity except the rare alpha variety. The major disadvantage of treatment with these drugs is that reduction in muscle tone can cause a loss of splinting action of the spastic leg and trunk muscles and sometimes lead to an increase in disability.

Baclofen p. 985 inhibits transmission at spinal level and also depresses the central nervous system. The dose should be increased slowly to avoid the major side-effects of sedation and muscular hypotonia (other adverse events are uncommon). A cannabis extract p. 985 containing dronabinol (delta-9-tetrahydrocannabinol) and cannabidiol is licensed as an adjunct treatment for moderate to severe spasticity associated with multiple sclerosis in patients who have not responded adequately to other skeletal muscle relaxants. The dose should be titrated over 2 weeks; response to treatment should be reviewed after 4 weeks and treatment stopped if an adequate response is not achieved.

Dantrolene sodium p. 1191 acts directly on skeletal muscle and produces fewer central adverse effects making it a drug of choice. The dose should be increased slowly.

Diazepam p. 321 can also be used. Sedation and occasionally extensor hypotonus are disadvantages. Other benzodiazepines also have muscle-relaxant properties. Muscle-relaxant doses of benzodiazepines are similar to anxiolytic doses.

Tizanidine p. 986 is an alpha2-adrenoceptor agonist indicated for spasticity associated with multiple sclerosis or spinal cord injury.

Other muscle relaxants

The clinical efficacy of methocarbamol p. 986 and meprobamate p. 324 as muscle relaxants is not well established, although they have been included in compound analgesic preparations.
3.1 Myasthenia gravis and Lambert-Eaton myasthenic syndrome

### ANTICHOLINESTERASES

#### Anticholinesterases

- **DRUG ACTION** They prolong the action of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase.
- **CONTRA-INDICATIONS** Intestinal obstruction - urinary obstruction
- **CAUTIONS** Arrhythmias - asthma (extreme caution) - atropine or other antidote to muscarinic effects may be necessary (particularly when neostigmine is given by injection) but not given routinely because it may mask signs of overdosage - bradycardia - epilepsy - hyperthyroidism - hypotension - parkinsonism - peptic ulceration - recent myocardial infarction - vagotonia
- **INTERACTIONS** → Appendix 1 (parasympathomimetics).
- **SIDE-EFFECTS** Abdominal cramps (more marked with higher doses) - diarrhoea - increased salivation - nausea - vomiting

**Overdose**

Signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defaecation, involuntary micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** Amount probably too small to be harmful.

### Neostigmine

**(Neostigmine methylsulfate)**

- **INDICATIONS AND DOSE**

  **Treatment of myasthenia gravis**
  - **BY MOUTH**
    - Adult: Initially 15–30 mg, dose repeated at suitable intervals throughout the day, total daily dose 75–300 mg, the maximum that most patients can tolerate is 180 mg daily
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Adult: 1–2.5 mg, dose repeated at suitable intervals throughout the day (usual total daily dose 5–20 mg)

  **Reversal of non-depolarising (competitive) neuromuscular blockade**
  - **BY INTRAVENOUS INJECTION**
    - Adult: 2.5 mg (max. per dose 5 mg), repeated if necessary after or with glycopyrronium or atropine, to be given over 1 minute

- **CAUTIONS**
  - With intravenous use Glycopyrronium or atropine should also be given when reversing neuromuscular blockade

- **INTERACTIONS** → Appendix 1 (parasympathomimetics).

- **RENAL IMPAIRMENT** May need dose reduction.
Pyridostigmine bromide

**DRUG ACTION** Pyridostigmine bromide has weaker muscarinic action than neostigmine.

**INDICATIONS AND DOSE**
- **Myasthenia gravis**
  - **INITIALLY BY MOUTH**
  - Adult: 30–120 mg, doses to be given at suitable intervals throughout day; usual dose 0.3–1.2 g daily in divided doses, it is advisable to exceed a total daily dose of 450 mg in order to avoid acetylcholine receptor down-regulation; patients requiring doses exceeding 450 mg daily will usually require input from a specialised neuromuscular service. Immunosuppressant therapy is usually considered if the dose of pyridostigmine exceeds 360 mg daily.

**RENAI IMPAIRMENT** Reduce dose; excreted by kidney.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**
- Neostigmine (Non-proprietary)
  - Neostigmine bromide 15 mg Neostigmine 15mg tablets | 140 tablet (£) £99.60

**Solution for injection**
- Neostigmine (Non-proprietary)
  - Neostigmine metilsulfate 2.5 mg per 1 ml Neostigmine 2.5mg/1ml solution for injection ampoules | 10 ampoule (£) £4.95–£5.45

**CHOLINERGIC RECEPTOR STIMULATING DRUGS**

**Amifampridine**

**INDICATIONS AND DOSE**
- **Symptomatic treatment of Lambert-Eaton myasthenic syndrome (specialist use only)**
  - **BY MOUTH**
  - Adult: Initially 15 mg daily in 3 divided doses, then increased in steps of 5 mg every 4–5 days, increased to up to 60 mg daily in 3–4 divided doses (max. per dose 20 mg); maximum 60 mg per day

**CONTRA-INDICATIONS** Congenital QT syndromes · epilepsy · uncontrolled asthma

**CAUTIONS** Non-paraneoplastic form of Lambert- Eaton myasthenic syndrome

**INTERACTIONS** Caution if concomitant use of drugs that lower convulsive threshold.
Avoid concomitant use of drugs that prolong QT interval.
Avoid concomitant use of drugs with a narrow therapeutic index.

**SIDE-EFFECTS** Anxiety · arrhythmias · blurred vision · bronchial hypersecretion · chorea · convulsions · cough · dizziness · drowsiness · exacerbation or precipitation of asthma · gastro-intestinal disorders · headache · myoclonia · palpitations · paraesthesia · Raynaud’s syndrome · sleep disturbances · weakness

**CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment in men and women.

**PREGNANCY** Manufacturer advises avoid.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** In mild impairment reduce initial dose to 10 mg daily in divided doses, increased in steps of 5 mg every 7 days. In moderate or severe impairment reduce initial dose to 5 mg daily in divided doses, increased in steps of 5 mg every 7 days. Use with caution.

**RENAL IMPAIRMENT** In mild impairment reduce initial dose to 10 mg daily in divided doses, increased in steps of 5 mg every 7 days. In moderate or severe impairment reduce initial dose to 5 mg daily in divided doses, increased in steps of 5 mg every 7 days. Use with caution.

**MONITORING REQUIREMENTS** Clinical and ECG monitoring required at treatment initiation and yearly thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2012) that amifampridine phosphate (Firdapse) is not recommended for use within NHS Scotland for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 3, 21
  - Firdapse (BioMarin Europe Ltd) ▼
  - Amifampridine (as Amifampridine phosphate) 10 mg Firdapse 10mg tablets | 100 tablet (£) £1,815.00

3.2 Nocturnal leg cramps

**Nocturnal leg cramps**

**Quinine salts**
Quinine salts p. 573, such as quinine sulfate are effective in reducing the frequency of nocturnal leg cramps by about 25% in ambulatory patients; however, because of potential toxicity, quinine is not recommended for routine treatment and should not be used unless cramps cause regular disruption to sleep.
Quinine should only be considered when cramps are very painful or frequent; when other treatable causes of cramp have been excluded; and when non-pharmacological treatments have not worked (e.g. passive stretching exercises). It may take up to 4 weeks for improvement to become apparent; if there is benefit, quinine treatment can be continued. Treatment should be interrupted at intervals of approximately 3 months to assess the need for further quinine treatment. In patients taking quinine long term, a trial discontinuation may be considered. Quinine is toxic in overdosage and accidental fatalities have occurred.

3.3 Spasticity

Other drugs used for Spasticity Dantrolene sodium, p. 1191
- Diazepam, p. 321
CANNABINOIDS

Cannabis extract

● INDICATIONS AND DOSE
Adjunct in moderate to severe spasticity in multiple sclerosis (specialist use only)
  ▶ BY BUCCAL ADMINISTRATION
  ▶ Adult: (consult product literature)

● CONTRA-INDICATIONS  Family history of psychosis · history of other severe psychiatric disorder · personal history of psychosis

● CAUTIONS  History of epilepsy · significant cardiovascular disease

● INTERACTIONS  → Appendix 1 (cannabis extract).

● SIDE-EFFECTS
  ▶ Common or very common  Amnesia · blurred vision · constipation · depression · diarrhoea · disorientation · dissociation · dizziness · drowsiness · dry mouth · dysarthria · impaired attention · increased or decreased appetite · malaise · mood disturbance · mouth ulcers · nausea · oral pain · taste disturbance · vertigo · vomiting
  ▶ Uncommon  Abdominal pain · delusions · hallucinations · hypertension · oremucosal discolouration · palpitation · paranoia · pharyngitis · stomatitis · suicidal thoughts · syncope · tachycardia · tooth discoloration

  ▶ Frequency not known  Anxiety · seizures

● CONCEPTION AND CONTRACEPTION  Manufacturer recommends effective contraception during and for 3 months after treatment in men and women.

● PREGNANCY  Manufacturer advises use only if potential benefit outweighs risks.

● BREAST FEEDING  Avoid—present in milk.

● HEPATIC IMPAIRMENT  Manufacturer advises more frequent monitoring in significant hepatic impairment—possible risk of prolonged or enhanced effect.

● RENAL IMPAIRMENT  Manufacturer advises more frequent monitoring in significant renal impairment—possible risk of prolonged or enhanced effect.

● MONITORING REQUIREMENTS  Monitor oral mucosa—interrupt treatment if lesions or persistent soreness.

● PATIENT AND CARER ADVICE
  Driving and skilled tasks
  For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including cannabis, see Drugs and driving under Guidance on prescribing p. 1.

● MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Spray
  EXCIPIENTS: May contain Propylene glycol
  ▶ Sativex (Bayer Plc)
  Cannabidiol 2.5 mg per 1 dose, Dronabinol 2.7 mg per 1 dose Sativex oromucosal spray | 270 dose £375.00 (£34.3)

MUSCLE RELAXANTS  CENTRALLY ACTING

Baclofen

● INDICATIONS AND DOSE
  Pain of muscle spasm in palliative care
  ▶ BY MOUTH
  ▶ Adult: 5–10 mg 3 times a day
  Hiccups due to gastric distension (in palliative care)
  ▶ BY MOUTH
  ▶ Adult: 5 mg twice daily

  Adults: 5 mg (max. 40 mg) 24 times a day, initially titrated to a satisfactory response over 1–2 weeks, with dosage increments of 5 mg 4 times a day.

  Adults: Test intrathecal dose 300 micrograms (max. 1000 micrograms) 4 times a day, initially titrated to a satisfactory response over 1–2 weeks, with dosage increments of 100 micrograms 4 times a day.

  Adults: 300 micrograms, to be given over 5 minutes via catheter or lumbar puncture, then increased in steps of 300 micrograms (max. per dose 1200 micrograms), not given more often than every 24 hours to determine appropriate dose, then dose—titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1.4 mg daily for spasticity of cerebral origin) retaining some spasticity to avoid sensation of paralysis

  ▶ CONTRA-INDICATIONS  History of peptic ulcer · history of epilepsy · (serious) respiratory tract disease or (serious) respiratory problems · hyperhidrosis · malnutrition · previous spinal surgery · history of multiple sclerosis or traumatic partial section of spinal cord

  ▶ CAUTIONS
  ▶ With oral use  Avoid oral route in active peptic ulceration

  ▶ GENERAL CAUTIONS
  Cerebrovascular disease · diabetes · elderly · epilepsy · history of peptic ulcer · hypertonic bladder sphincter · Parkinson’s disease · psychiatric illness · respiratory impairment

  ▶ SPECIFIC CAUTIONS
  ▶ With intrathecal use  Coagulation disorders · malnutrition (increased risk of post-surgical complications) · previous spinal fusion procedure

  ▶ INTERACTIONS  → Appendix 1 (muscle relaxants).

  ▶ SIDE-EFFECTS
  ▶ Common or very common  Agitation · anxiety · ataxia · cardiovascular depression · confusion · depression · dizziness · drowsiness · dry mouth · euphoria · gastrointestinal disturbances · hallucinations · headache · hyperhidrosis · hypotension · insomnia · myalgia · nightmares · rash · respiratory depression · sedation · seizure · tremor · urinary disturbances · visual disorders

  ▶ Rare  Abdominal pain · changes in hepatic function · dysarthria · erectile dysfunction · paraesthesia · taste disturbances

  ▶ Very rare  Hypothermia

  ▶ PREGNANCY  Manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies).

  ▶ BREAST FEEDING  Present in milk—amount probably too small to be harmful.

  ▶ HEPATIC IMPAIRMENT  With oral use  Manufacturer advises use with caution.

Chronic severe spasticity resulting from disorders such as multiple sclerosis or traumatic partial section of spinal cord
  ▶ BY MOUTH
  ▶ Adult: Initially 5 mg 3 times a day, gradually increased; maintenance up to 60 mg daily in divided doses, review treatment if no benefit within 6 weeks of achieving maximum dose; maximum 100 mg per day

Severe chronic spasticity unresponsive to oral antispastic drugs (or where side-effects of oral therapy unacceptable) or as alternative to ablative neurosurgical procedures (specialist use only)
  ▶ BY INTRATHECAL INJECTION
  ▶ Adult: Test dose 25–50 micrograms, to be given over at least 1 minute via catheter or lumbar puncture, then increased in steps of 25 micrograms (max. per dose 100 micrograms), not given more often than every 24 hours to determine appropriate dose, then dose—titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1.4 mg daily for spasticity of cerebral origin) retaining some spasticity to avoid sensation of paralysis

IMPORTANT SAFETY INFORMATION
Consult product literature for details on test dose and titration—important to monitor patients closely in appropriately equipped and staffed environment during screening and immediately after pump implantation. Resuscitation equipment must be available for immediate use. Treatment with continuous pump— administered intrathecal baclofen should be initiated within 3 months of a satisfactory response to intrathecal baclofen testing.

CONTRA-INDICATIONS
  ▶ With intrathecal use  Local infection · systemic infection

  ▶ With oral use  Avoid oral route in active peptic ulceration

CAUTIONS

GENERAL CAUTIONS
Cerebrovascular disease · diabetes · elderly · epilepsy · history of peptic ulcer · hypertonic bladder sphincter · Parkinson’s disease · psychiatric illness · respiratory impairment

SPECIFIC CAUTIONS
  ▶ With intrathecal use  Coagulation disorders · malnutrition (increased risk of post-surgical complications) · previous spinal fusion procedure

INTERACTIONS  → Appendix 1 (muscle relaxants).

SIDE-EFFECTS
  ▶ Common or very common  Agitation · anxiety · ataxia · cardiovascular depression · confusion · depression · dizziness · drowsiness · dry mouth · euphoria · gastrointestinal disturbances · hallucinations · headache · hyperhidrosis · hypotension · insomnia · myalgia · nightmares · rash · respiratory depression · sedation · seizure · tremor · urinary disturbances · visual disorders

  ▶ Rare  Abdominal pain · changes in hepatic function · dysarthria · erectile dysfunction · paraesthesia · taste disturbances

  ▶ Very rare  Hypothermia

PREGNANCY  Manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING  Present in milk—amount probably too small to be harmful.

HEPATIC IMPAIRMENT  With oral use  Manufacturer advises use with caution.
Musculoskeletal system

986 Neuromuscular disorders

RENAL IMPAIRMENT
With oral use Risk of toxicity—use smaller doses (e.g. 5 mg daily by mouth) and if necessary increase dosage interval; if eGFR less than 15 mL/minute/1.73 m² manufacturer advises use by mouth only if potential benefit outweighs risk. Excreted by the kidney.

TREATMENT CESSATION
Avoid abrupt withdrawal (risk of hyperactive state, may exacerbate spasticity, and precipitate autonomic dysfunction including hyperthermia, psychiatric reactions and convulsions; to minimise risk, discontinue by gradual dose reduction over at least 1–2 weeks (longer if symptoms occur)).

PRESCRIBING AND DISPENSING INFORMATION
Flavours of oral liquid formulations may include raspberry.

Palliative care
For further information on the use of baclofen in palliative care, see www.palliativecare.com/formulary/en/baclofen.html

PATIENT AND CARER ADVICE
Driving and skilled tasks
Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection.

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Oral solution

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Solution for injection

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<tr>
<td>Baclofen 50 microgram per 1 ml</td>
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Solution for infusion

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Methocarbamol

INDICATIONS AND DOSE
Short-term symptomatic relief of muscle spasm
BY MOUTH
Adult: 1.5 g 4 times a day; reduced to 750 mg 3 times a day if required
Elderly: Up to 750 mg 4 times a day, dose may be sufficient

CONTRA-INDICATIONS
Brain damage • coma • epilepsy • myasthenia gravis • pre-coma

INTERACTIONS
Appendix 1 (muscle relaxants).

SIDE-EFFECTS
Amnesia • anaphylaxis • angioedema • anxiety • blurred vision • bradycardia • cholestatic jaundice • confusion • dizziness • drowsiness • dyspepsia • fever • headache • hypersensitivity reactions • hypotension • leucopenia • nasal congestion • nausea • pruritus • rash • restlessness • seizures • tremor • urticaria • vomiting

PREGNANCY
Manufacturer advises avoid unless potential benefit outweighs risk.

BREAST FEEDING
Present in milk in animal studies—manufacturer advises caution.

RENAL IMPAIRMENT
Manufacturer advises caution; half-life may be prolonged.

PATIENT AND CARER ADVICE
Driving and skilled tasks
Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

LESS SUITABLE FOR PRESCRIBING
Less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension.

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<td>Methocarbamol 750 mg Methocarbamol 750mg tablets</td>
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<td>Robaxin (Almirall Ltd)</td>
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<td>Methocarbamol 750 mg</td>
<td>Robaxin 750 tablets</td>
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Tizanidine

INDICATIONS AND DOSE
Spasticity associated with multiple sclerosis or spinal cord injury or disease
BY MOUTH
Adult: Initially 2 mg daily, then increased in steps of 2 mg daily in divided doses, increased at intervals of at least 3–4 days and adjust according to response; usual dose up to 24 mg daily in 3–4 divided doses; maximum 36 mg per day

CAUTIONS
Elderly

INTERACTIONS
Appendix 1 (muscle relaxants). Caution with concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS
Common or very common Altered liver enzymes
(discourage if persistently raised—consult product literature) • dizziness • drowsiness • dry mouth • fatigue • gastro-intestinal disturbance • hypotension • nausea
Uncommon Bradycardia
Pain and inflammation in musculoskeletal disorders

Non-steroidal anti-inflammatory drugs

Therapeutic effects

In single doses non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol p. 414, but paracetamol is preferred, particularly in the elderly.

In regular full dosage NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. Therefore, although paracetamol often gives adequate pain control in osteoarthritis, NSAIDs are more appropriate than paracetamol or the opioid analgesics in the osteoarthritis, NSAIDs are more appropriate than paracetamol often gives adequate pain control in inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other non-selective NSAIDs but its anti-inflammatory properties are weaker. It is unsuitable for conditions where inflammation is prominent, such as acute gout. Diclofenac p. 997 is as effective as naproxen, and flurbiprofen p. 998 may be slightly more effective. Both are associated with slightly more gastro-intestinal side-effects than ibuprofen.

Ketoprofen p. 1002 has anti-inflammatory properties similar to ibuprofen and has more side-effects. Diclofenac p. 997 is similar in activity and tolerance to naproxen.

Ketoprofen p. 1002 is comparable in efficacy to naproxen; it is licensed for symptomatic relief of osteoarthritis and rheumatoid arthritis.

Indometacin p. 1001 has an action equal to or superior to that of naproxen, but with a high incidence of side-effects including headache, dizziness, and gastro-intestinal disturbances. Mefenamic acid p. 1004 has minor anti-inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinuation of treatment. Meloxicam p. 1004 is licensed for the short-term relief of pain in osteoarthritis and for long-term treatment of rheumatoid arthritis and ankylosing spondylitis. Nabumetone p. 1005 is comparable in effect to naproxen. Phenylbutazone is licensed for ankylosing spondylitis, but is not recommended because it is associated with serious side-effects, in particular haematological reactions; it should be used only by a specialist in severe cases where other treatments have been found unsuitable.

Piroxicam p. 1007 is as effective as naproxen and has a long duration of action which permits once-daily administration. However, it has more gastro-intestinal side-effects than most other NSAIDs, and is associated with more frequent serious skin reactions. Sulindac p. 1009 is similar in tolerance to naproxen. Tenoxicam p. 1009 is similar in activity and tolerance to naproxen. Its long duration of action allows once-daily administration. Tolfenamic acid p. 440 is licensed for the treatment of migraine.

Ketorolac trometamol p. 1186 and the selective inhibitor of cyclo-oxygenase-2, parecoxib p. 1187, are licensed for the short-term management of postoperative pain. The selective inhibitors of cyclo-oxygenase-2, etoricoxib p. 996 and celecoxib p. 990, are as effective as non-selective
NSAIDs such as diclofenac sodium and naproxen. Although selective inhibitors can cause serious gastro-intestinal events, available evidence appears to indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin.

Celecoxib and etoricoxib are licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; etoricoxib is also licensed for the relief of pain from acute gout.

Aspirin p. 114 has been used in high doses to treat rheumatoid arthritis, but other NSAIDs are now preferred.

Dental and orofacial pain
Most mild to moderate dental pain and inflammation is effectively relieved by NSAIDs. Those used for dental pain include ibuprofen, diclofenac sodium, and diclofenac potassium p. 992.

Asthma
Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.

NSAIDs and cardiovascular events
All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term.

Cyclo-oxygenase-2 selective inhibitors, diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic events. Although there are limited data regarding the thrombotic effects of aceclofenac, treatment advice has been updated in line with diclofenac, based on aceclofenac’s structural similarity to diclofenac and its metabolism to diclofenac. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib. Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.

The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.

NSAIDs and gastro-intestinal events
All NSAIDs are associated with serious gastro-intestinal toxicity; the risk is higher in the elderly. Evidence on the relative safety of non-selective NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam p. 1007, ketoprofen p. 1002, and ketorolac trometamol p. 1186 are associated with the highest risk; indomethacin, p. 1004, diclofenac, and naproxen p. 1006 are associated with intermediate risk, and ibuprofen p. 999 with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk). Selective inhibitors of cyclo-oxygenase-2 are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Recommendations are that NSAIDs associated with a low risk e.g. ibuprofen are generally preferred, to start at the lowest recommended dose and not to use more than one oral NSAID at a time.

The combination of a NSAID and low-dose aspirin can increase the risk of gastro-intestinal side-effects; this combination should be used only if absolutely necessary and the patient should be monitored closely.

While it is preferable to avoid NSAIDs in patients with active or previous gastro-intestinal ulceration or bleeding, and to withdraw them if gastro-intestinal lesions develop, nevertheless patients with serious rheumatic diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness.

Patients at risk of gastro-intestinal ulceration (including the elderly), who need NSAID treatment should receive gastroprotective treatment.

Systemic as well as local effects of NSAIDs contribute to gastro-intestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia.

**ANALGESICS** NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

### Aceclofenac

- **INDICATIONS AND DOSE**
  - Pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis
    - **BY MOUTH**
      - Adult: 100 mg twice daily

- **CONTRA-INDICATIONS**
  - Active gastro-intestinal bleeding
  - Active gastro-intestinal ulceration
  - Cerebrovascular disease
  - History of gastro-intestinal bleeding related to previous NSAID therapy
  - History of gastro-intestinal perforation related to previous NSAID therapy
  - History of recurrent gastro-intestinal haemorrhage
  - Two or more distinct episodes
  - History of recurrent gastro-intestinal ulceration
  - Ischaemic heart disease
  - Mild heart failure
  - Peripheral arterial disease
  - Severe heart failure

- **CAUTIONS**
  - Allergic disorders
  - Avoid in acute porphyrias
  - p. 930 Cardiac impairment (NSAIDs may impair renal function)
  - Coagulation defects
  - Connective-tissue disorders
  - Crohn’s disease (may be exacerbated)
  - Elderly
  - Risk of serious side-effects and fatalities
  - History of cardiac failure
  - Hypertension
  - Left ventricular dysfunction
  - Oedema
  - Risk factors for cardiovascular events
  - Ulcerative colitis (may be exacerbated)

- **INTERACTIONS**
  - Appendix 1 (NSAIDs).

- **SIDE-EFFECTS**
  - Rare
    - Alveolitis
    - Aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible)
    - Hepatic damage
    - Interstitial fibrosis associated with NSAIDs can lead to renal failure
    - Pancreatitis
    - Papillary necrosis associated with NSAIDs can lead to renal failure
    - Pulmonary eosinophilia
    - Stevens-Johnson syndrome
    - Toxic epidermal necrolysis
    - Visual disturbances

  - **Frequency not known**
    - Angioedema
    - Blood disorders
    - Bronchospasm
    - Colitis (induction of or exacerbation of)
    - Crohn’s disease (induction of or exacerbation of)
    - Depression
    - Diarrhoea
    - Dizziness
    - Drowsiness
    - Fluid retention (rarely precipitating congestive heart failure)
    - Gastro-intestinal bleeding
    - Gastro-intestinal discomfort
    - Gastro-intestinal disturbances
    - Gastro-intestinal ulceration
    - Haematuria
    - Headache
    - Hearing disturbances
    - Hypersensitivity reactions
    - Insomnia
    - Nausea
    - Nervousness
    - Photosensitivity
    - Raised blood pressure
    - Rash
    - Renal failure (especially in patients with pre-existing renal impairment)
    - Tinnitus
    - Vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

- Serious side-effects
  - For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
Acemetacin

**INDICATIONS AND DOSE**

- **Pain and inflammation in rheumatic disease**
- **Postoperative analgesia**

  - **By mouth**
  - Adult: 120 mg daily in divided doses, then increased if necessary to 180 mg daily in divided doses, dose to be taken with food

- **CONTRA-INDICATIONS**
  - Active gastro-intestinal bleeding
  - History of gastro-intestinal ulceration
  - History of gastrointestinal perforation related to previous NSAID therapy
  - History of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)
  - History of recurrent gastro-intestinal ulceration (two or more distinct episodes)
  - Severe heart failure

- **CAUTIONS**
  - Allergic disorders
  - Cardiac impairment (NSAIDs may impair renal function)
  - Cerebrovascular disease
  - Coagulation defects
  - Connective-tissue disorders
  - Crohn’s disease (may be exacerbated)
  - Elderly (risk of serious side-effects and fatalities)
  - Epilepsy
  - Heart failure
  - Ischaemic heart disease
  - Parkinsonism
  - Peripheral arterial disease
  - Psychiatric disturbances
  - Risk factors for cardiovascular events
  - Ulcerative colitis (may be exacerbated)
  - Uncontrolled hypertension

**INTERACTIONS**

- Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- **Rare**
  - Alveolitis
  - Aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible)
  - Blood disorders
  - Confusion
  - Convulsions
  - Hepatic damage
  - Hyperglycaemia
  - Interstitial fibrosis associated with NSAIDs can lead to renal failure
  - Intestinal strictures
  - Pancreatitis
  - Papillary necrosis associated with NSAIDs can lead to renal failure
  - Peripheral neuropathy
  - Psychiatric disturbances
  - Pulmonary eosinophilia
  - Stevens-Johnson syndrome
  - Syncope
  - Thrombocytopenia
  - Toxic epidermal necrolysis
  - Visual disturbances

- **Frequency not known**
  - Angioedema
  - Blood disorders
  - Bronchospasm
  - Collitis (induction of or exacerbation of)
  - Crohn’s disease (induction of or exacerbation of)
  - Depression
  - Diarrhoea
  - Dizziness
  - Drowsiness
  - Fluid retention (rarely precipitating congestive heart failure)
  - Gastro-intestinal bleeding
  - Gastro-intestinal discomfort
  - Gastro-intestinal disturbances
  - Gastro-intestinal ulceration
  - Haematuria
  - Headache
  - Hearing disturbances
  - Hyperkalaemia
  - Hypersensitivity reactions
  - Insomnia
  - Nausea
  - Nervousness
  - Photosensitisation
  - Raised blood pressure
  - Rash
  - Renal failure (especially in patients with pre-existing renal impairment)
  - Tinnitus
  - Vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

- Serious side-effects
  - For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- **ALLERGY AND CROSS-SENSITIVITY**
  - Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION**
  - Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY**
  - Most manufacturers advise avoiding the use of NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs the risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and its duration may be increased.

- **BREAST FEEDING**
  - Use with caution during breast-feeding. Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT**
  - Initially 100 mg daily. Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT**
  - The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution; avoid in moderate to severe impairment. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**DRUG ACTION**

Glycolic acid ester of indometacin.
### Celecoxib

**INDICATIONS AND DOSE**

Pain and inflammation in osteoarthritis

- **BY MOUTH**
  - Adult: 200 mg daily in 1–2 divided doses, then increased if necessary up to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose

Pain and inflammation in rheumatoid arthritis

- **BY MOUTH**
  - Adult: 100 mg twice daily, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose

Ankylosing spondylitis

- **BY MOUTH**
  - Adult: 200 mg daily in 1–2 divided doses, then increased if necessary up to 400 mg daily in 1–2 divided doses, discontinue if no improvement after 2 weeks on maximum dose

**CONTRA-INDICATIONS**

Active gastro-intestinal bleeding, active gastro-intestinal ulceration, cerebrovascular disease, inflammatory bowel disease, ischaemic heart disease, mild to severe heart failure, peripheral arterial disease

**CAUTIONS**

Allergic disorders, cardiac impairment (NSAIDs may impair renal function), coagulation defects, connective-tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), history of cardiac failure, hypertension, left ventricular dysfunction, oedema, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated)

**INTERACTIONS**

Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- Common or very common: Dyspnoea, influenza-like symptoms
- Uncommon: Cerebral infarction, fatigue, muscle cramps, palpitation, paraesthesia, stomatitis
- Rare: Alopecia, alveolitis, aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible), hepatic damage, interstitial fibrosis associated with NSAIDs can lead to renal failure, pancreatitis, papillary necrosis associated with NSAIDs can lead to renal failure, pulmonary eosinophilia, Stevens-Johnson syndrome, taste disturbance, toxic epidermal necrolysis, visual disturbances
- Very rare: Seizures
- Frequency not known: Angioedema, blood disorders, bronchospasm, chest pain, colitis (induction of or exacerbation of), Crohn’s disease (induction of or exacerbation of), depression, diarrhoea, dizziness, drowsiness, fluid retention (rarely precipitating congestive heart failure), gastro-intestinal bleeding, gastro-intestinal discomfort, gastro-intestinal disturbances, gastro-intestinal ulceration, haematuria, headache, hearing disturbances, hypersensitivity reactions, insomnia, nausea, nervousness, photosensitivity, raised blood pressure, rashes, renal failure (especially in patients with pre-existing renal impairment), tinnitus, vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

- Serious side-effects: For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
- **ALLERGY AND CROSS-SENSITIVITY**
  - Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
  - Contra-indicated in patients with sulfonamide sensitivity.

**CONCEPTION AND CONTRACEPTION**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

Avoid (teratogenic in animal studies).

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Halve initial dose in moderate impairment. Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**

The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. Avoid if eGFR less than 30 mL/minute/1.73 m². In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MONITORING REQUIREMENTS**

Monitor blood pressure before and during treatment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Celecoxib (Non-proprietary)
  - Celecoxib 100 mg
    - Capsule (Pfizer Ltd) £21.55 0T price = £2.25
  - Celecoxib 200 mg
    - Capsule (Pfizer Ltd) £21.55 0T price = £1.98
- Celebrex (Pfizer Ltd)
  - Celecoxib 100 mg
    - Capsule (Pfizer Ltd) £21.55 0T price = £2.25
  - Celecoxib 200 mg
    - Capsule (Pfizer Ltd) £21.55 0T price = £1.98

### Dexibuprofen

**INDICATIONS AND DOSE**

- **BY MOUTH**
  - Adult: 600–900 mg daily in up to 3 divided doses; increased if necessary up to 1.2 g daily (max. per dose 400 mg)

**Mild to moderate pain and inflammation in dysmenorrhoea**

- **BY MOUTH**
  - Adult: 600–900 mg daily in up to 3 divided doses (max. per dose 300 mg); maximum 900 mg per day

**CONTRA-INDICATIONS**

Active gastro-intestinal bleeding, active gastro-intestinal ulceration, history of gastro-intestinal bleeding related to previous NSAID therapy, history of gastro-intestinal perforation related to previous NSAID therapy, history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes), history of recurrent gastro-intestinal ulceration (two or more distinct episodes), severe heart failure

**CAUTIONS**

Allergic disorders, cardiac impairment (NSAIDs may impair renal function), cerebrovascular disease, coagulation defects, connective-tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), heart failure, ischaemic heart disease, peripheral arterial disease, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated), uncontrolled hypertension
Dexketoprofen

- **INDICATIONS AND DOSE**

  Short-term treatment of mild to moderate pain including dysmenorrhea
  - **BY MOUTH**
    - Adult: 12.5 mg every 4–6 hours, alternatively 25 mg every 8 hours; maximum 75 mg per day
    - Elderly: 12.5 mg every 4–6 hours, alternatively 25 mg every 8 hours, initial max. 50 mg; maximum 75 mg daily

- **CONTRA-INDICATIONS**

  Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

- **CAUTIONS**

  Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

  **INTERACTIONS** → Appendix 1 (NSAIDs).

- **SIDE-EFFECTS**

  Rare Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

  **SIDE-EFFECTS, FURTHER INFORMATION**

  Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- **ALLERGY AND CROSS-SENSITIVITY**

  Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION**

  Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY**

  Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING**

  Use with caution during breast-feeding. Present in milk—but risk to infant minimal.

- **HEPATIC IMPAIRMENT**

  Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT**

  Reduce initial dose. The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. Avoid if eGFR less than 30 mL/minute/1.73 m². In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  CAUTIONARY AND ADVISORY LABELS 21

  Seractil (Thornton & Ross Ltd)

  - **Dexibuprofen 400 mg** Seractil 400mg tablets | 60 tablet [POM]
    - £8.47 DT price = £8.47

  Manufacturer advises avoid—no information available.
**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 22**
- Keral (A. Menarini Farmaceutica Internazionale SRL)
  - Dexketoprofen (as Dexketoprofen trometamol) 25 mg Keral 25 mg tablets | 20 tablet | £3.67 | 50 tablet | £9.18 DT price = £9.18

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**Diclofenac potassium**

**INDICATIONS AND DOSE**

**Pain and inflammation in rheumatic disease and other musculoskeletal disorders**
- **BY MOUTH**
  - Child 14-17 years: 75–100 mg daily in 2–3 divided doses
  - Adult: 75–150 mg daily in 2–3 divided doses

**Acute gout**
- **BY MOUTH**
  - Adult: 75–150 mg daily in 2–3 divided doses

**Postoperative pain**
- **BY MOUTH**
  - Child 9–13 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day
  - Child 14–17 years: 75–100 mg daily in 2–3 divided doses
  - Adult: 75–150 mg daily in 2–3 divided doses

**Migraine**
- **BY MOUTH**
  - Adult: 50 mg, to be given at onset of migraine, then 50 mg after 2 hours if required, then 50 mg after 4–6 hours; maximum 200 mg per day

**Fever in ear, nose, or throat infection**
- **BY MOUTH**
  - Child 9–17 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day

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**Unlicensed Use**

Voltarol® Rapid not licensed for use in children under 14 years or in fever.

**Contra-Indications**

Active gastro-intestinal bleeding · active gastro-intestinal ulceration · cerebrovascular disease · history of gastro-intestinal bleeding related to previous NSAID therapy · history of gastro-intestinal perforation related to previous NSAID therapy · history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) · history of recurrent gastro-intestinal ulceration (two or more distinct episodes) · ischaemic heart disease · mild to severe heart failure · peripheral arterial disease

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**Caution**

Allergic disorders · cardiac impairment (NSAIDs may impair renal function) · coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · elderly (risk of serious side-effects and fatalities) · history of cardiac failure · hypertension · left ventricular dysfunction · oedema · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated)

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**Contraindications**

Reduce initial dose to 50 mg daily. The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. Avoid in moderate to severe impairment. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

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**INTERACTIONS**

Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- **Rare** Alveolitis · aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · hepatic damage · interstitial fibrosis associated with NSAIDs can lead to renal failure · pancreatitis · papillary necrosis associated with NSAIDs can lead to renal failure · pulmonary eosinophilia · Stevens–Johnson syndrome · toxic epidermal necrolysis · visual disturbances

- **Frequency not known** Angioedema · blood disorders · bronchospasm · colitis (induction of or exacerbation of) · Crohn’s disease (induction of or exacerbation of · depression · diarrhoea · dizziness · drowsiness · fluid retention (rarely precipitating congestive heart failure) · gastro-intestinal bleeding · gastro-intestinal discomfort · gastro-intestinal disturbances · gastro-intestinal ulceration · haematuria · headache · hearing disturbances · hypersensitivity reactions · insomnia · nausea · nervousness · photosensitivity · raised blood pressure · rashes · renal failure (especially in patients with pre-existing renal impairment) · tinnitus · vertigo

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**Allergy and Cross-Sensitivity**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

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**Conception and Contraception**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**Pregnancy**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**Breast Feeding**

Use with caution during breast-feeding. Amount in milk too small to be harmful.

**Hepatic Impairment**

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**Renal Impairment**

Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**Patient and Carer Advice**

Medicines for Children leaflet: Diclofenac for pain and inflammation www.medicinesforchildren.org.uk/diclofenac-for-pain-and-inflammation

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21**
- **Diclofenac potassium (Non-proprietary)**
  - Diclofenac potassium 25 mg Diclofenac potassium 25 mg tablets | 28 tablet | £3.87
  - Diclofenac potassium 50 mg Diclofenac potassium 50 mg tablets | 28 tablet | £7.41
- **Voltarol Rapid** (Novartis Pharmaceuticals UK Ltd)
  - Diclofenac potassium 50 mg Voltarol Rapid 50 mg tablets | 30 tablet | £7.94 DT price = £7.94
Diclofenac sodium

**INDICATIONS AND DOSE**

**Pain and inflammation in musculoskeletal disorders**

- **Acute gout**
  - Adult: 75–150 mg daily in 2–3 divided doses
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 75–150 mg daily in 2–3 divided doses

- **Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis**
  - Adult: 75–150 mg daily in 2–3 divided doses
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Postoperative pain**
  - Adult: 75–150 mg daily in 2–3 divided doses
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

**DICLOMAX RETARD®**

- **Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
  - Adult: 1 capsule once daily
  - **BY MOUTH**

**DICLOMAX SR®**

- **Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
  - Adult: 1 capsule 1–2 times a day, alternatively 2 capsules once daily
  - **BY MOUTH**

**DYLOJECT®**

- **Acute exacerbations of pain and postoperative pain**
  - **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg once daily for maximum 2 days, to be administered into the gluteal muscle

**Acute exacerbations of pain and postoperative pain (severe cases)**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg twice daily for maximum 2 days, to be administered into the gluteal muscle

**Ureteric colic**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg, then 75 mg after 30 minutes if required

**Acute postoperative pain (in supervised settings)**

- **BY INTRAVENOUS INJECTION**
  - Adult: 75 mg every 4–6 hours if required for maximum 2 days; maximum 150 mg per day

**Prevention of postoperative pain**

- **BY INTRAVENOUS INJECTION**
  - Adult: 25–50 mg, to be given after surgery; further doses given after 4–6 hours if necessary; maximum 150 mg in 24 hours for 2 days

**MOTIFENE®**

- **Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
  - Adult: 1 capsule 1–2 times a day

**VOLTAROL® 75MG SR TABLETS**

- **Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
  - Adult: 1 tablet 1–2 times a day

**VOLTAROL® EMULGEL**

- **Relief of pain in musculoskeletal conditions | Adjunctive treatment in knee or hand osteoarthritis**
  - **TO THE SKIN**
  - Adult: Apply 3–4 times a day, therapy should be reviewed after 14 days (or after 28 days for osteoarthritis)

**VOLTAROL® RETARD**

- **Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
  - Adult: 75 mg 1–2 times a day for maximum 2 days, twice daily administration in severe cases, to be injected into the gluteal muscle

**Acute exacerbations of pain**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg 1–2 times a day for maximum 2 days, twice daily administration in severe cases, to be injected into the gluteal muscle

**Ureteric colic**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg, then 75 mg after 30 minutes if required

**Acute postoperative pain (in hospital setting)**

- **BY INTRAVENOUS INFUSION**
  - Adult: 75 mg, then 75 mg after 4–6 hours if required for maximum 2 days; maximum 150 mg per day

**Prevention of postoperative pain (in hospital setting)**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 25–50 mg, to be given after surgery over 15–60 minutes, then 5 mg/hour for maximum 2 days; maximum 150 mg per day

**CONTRA-INDICATIONS**

- With intravenous use: Dehydration | history of asthma | history of confirmed or suspected cerebrovascular bleeding | history of haemorrhagic diathesis | hypovolaemia | operations with high risk of haemorrhage

- With systemic use: Active gastro-intestinal bleeding | active gastro-intestinal ulceration | avoid suppositories in proctitis | cerebrovascular disease | history of gastro-intestinal bleeding related to previous NSAID therapy | history of gastro-intestinal perforation related to previous NSAID therapy | history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) | history of recurrent gastro-intestinal ulceration (two or more distinct episodes) | ischaemic heart disease | mild to severe heart failure | peripheral arterial disease

**CAUTIONS**

- With systemic use: Allergic disorders | cardiac impairment (NSAIDs may impair renal function) | coagulation defects | connective-tissue disorders | Crohn’s disease (may be exacerbated) | elderly (risk of serious side-effects and fatalities) | history of cardiac failure | hypertension | left ventricular dysfunction | oedema | risk factors for cardiovascular events | ulcerative colitis (may be exacerbated)

- With topical use: Avoid contact with eyes | avoid contact with inflamed or broken skin | avoid contact with mucous membranes | not for use with occlusive dressings | topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)
INTERACTIONS  Appendix 1 (NSAIDs). Interactions do not generally apply to topical NSAIDs.

- With intravenous use Contra-indicated in concomitant NSAID use. Contra-indicated in concomitant anticoagulant use (including low-dose heparins).

SIDE-EFFECTS

- Rare

  - With systemic use Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

  - Frequency not known

  - With intramuscular use or intravenous use Injection site reactions

  - With rectal use Suppositories may cause rectal irritation


  - With topical use Paraeesthesia - photosensitivity - rash (discontinue use if develops)

SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

  - With topical use Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

- With systemic use Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY

- With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

  - With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

BREAST FEEDING

- With systemic use Use with caution during breast-feeding. Amount in milk too small to be harmful.

  - With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

HEPATIC IMPAIRMENT

- With systemic use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

RENAI IMPAIRMENT

- With systemic use Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

  - With intravenous use Avoid intravenous use if serum creatinine greater than 160 micromol/litre. Contra-indicated in moderate or severe renal impairment.

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Voltarol®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%. Dilute 75 mg with 100–500 mL infusion fluid (previously buffered with 0.5 mL sodium bicarbonate 8.4% solution or with 1 mL sodium bicarbonate 4.2% solution). For intermittent infusion give 25–50 mg over 15–60 minutes or 75 mg over 30–120 minutes. For continuous infusion give at a rate of 5 mg/hour.

  - With topical use For topical preparations, apply with gentle massage only.

PRESCRIBING AND DISPENSING INFORMATION

- With oral use Voltarol® dispersible tablets are more suitable for short-term use in acute conditions for which treatment required for no more than 3 months (no information on use beyond 3 months).

PATIENT AND CARER ADVICE For topical preparations, patients and their carers should be advised to wash hands immediately after use. Photosensitivity For topical preparations, patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

EXCEPTIONS TO LEGAL CATEGORY Various pack sizes of gel preparations may be available on sale to the public.

PROFESSION SPECIFIC INFORMATION

Dental practitioners' formulary Diclofenac Sodium Tablets may be prescribed.

NATIONAL FUNDING/ACCESS DECISIONS

DYLOJECT®

Scottish Medicines Consortium (SMC) Decisions The Scottish Medicines Consortium (SMC) has advised (February 2008) that Dyloject® is accepted for restricted use within NHS Scotland for the treatment or prevention of postoperative pain by intravenous injection in supervised healthcare settings.

MEDITICL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: dispersible tablet, oral suspension, oral solution

Gastro-resistant tablet CAUTIONARY AND ADVISORY LABELS 5, 25

- Diclofenac sodium (Non-proprietary)
  - Diclofenac sodium 25 mg Diclofenac sodium 25 mg gastro-resistant tablets | 28 tablet Par P2.25–8.99 DT price = £2.47 | 84 tablet Par P26.97
  - Diclofenac sodium 50 mg Diclofenac sodium 50 mg gastro-resistant tablets | 28 tablet Par P £4.97 DT price = £3.29 | 84 tablet Par P £15.00 | 100 tablet Par P no price available
  - Dicloflex (Dexcel-Pharma Ltd, Almus Pharmaceuticals Ltd)
  - Diclofenac sodium 25 mg Dicloflex 25 mg gastro-resistant tablets | 84 tablet Par P P4.42
  - Diclofenac sodium 50 mg Dicloflex 50 mg gastro-resistant tablets | 28 tablet Par P £2.75 DT price = £2.25 (Hospital only) | 84 tablet Par P £8.05–8.65
  - Fenactol (Discovery Pharmaceuticals)
  - Diclofenac sodium 50 mg Fenactol 50 mg gastro-resistant tablets | 100 tablet Par P P3.90
  - Voltarol (Novartis Pharmaceuticals UK Ltd)
  - Diclofenac sodium 25 mg Voltarol 25 mg gastro-resistant tablets | 84 tablet Par P P2.94

- Fenactol (Discovery Pharmaceuticals)
Gel
EXCIPIENTS: May contain Benzyl alcohol, fragrances, propylene glycol

Voltarol Emulgel (Novartis Consumer Health UK Ltd)
Diclofenac diethylammonium 11.6 mg per 1 gram Voltarol 1.16% Emulgel P | 30 gram £3.23 | 50 gram £4.71 | 100 gram £7.71 DT price = £5.63
 Voltarol 1.16% Emulgel | 100 gram £5.63 DT price = £5.63
Diclofenac diethylammonium 23.2 mg per 1 gram Voltarol 12 Hour Emulgel P 2.32% gel | 30 gram £4.19 DT price = £4.19 | 50 gram £5.99 DT price = £5.99 | 100 gram £10.79 DT price = £10.79

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS 21 (does not apply to Motifene® 75 mg), 25
EXCIPIENTS: May contain Propylene glycol

Diclofenac Retard (Galen Ltd)
Diclofenac sodium 100 mg Diclofenac Retard 100mg capsules | 28 capsule £6.97 DT price = £6.97

Diclofenac SR (Galen Ltd)
Diclofenac sodium 75 mg Diclofenac SR 75mg capsules | 56 capsule £9.69 DT price = £9.69

Motifene (Daichi Sankyo UK Ltd)
Diclofenac sodium 75 mg Motifene 75mg modified-release capsules | 56 capsule £8.00 DT price = £8.00

Solution for injection
EXCIPIENTS: May contain Benzyl alcohol, propylene glycol

Voltarol (Novartis Pharmaceuticals UK Ltd)
Diclofenac sodium 25 mg per 1 ml Voltarol 75mg/3ml solution for injection ampoules | 10 ampoule £9.91 DT price = £9.91

Suppository
Diclofenac sodium (Non-proprietary)
Diclofenac sodium 100 mg Diclofenac 100mg suppositories | 10 suppository £4.05 DT price = £3.64

Econa (AMCo)
Diclofenac sodium 100 mg Econa 100mg suppositories | 10 suppository £3.04 DT price = £3.64

Voltarol (Novartis Pharmaceuticals UK Ltd)
Diclofenac sodium 12.5 mg Voltarol 12.5mg suppositories | 10 suppository £8.00 DT price = £8.00

Diclofenac sodium 25 mg Voltarol 25mg suppositories | 10 suppository £1.24 DT price = £1.24

Diclofenac sodium 50 mg Voltarol 50mg suppositories | 10 suppository £2.04 DT price = £2.04

Diclofenac sodium 100 mg Voltarol 100mg suppositories | 10 suppository £3.64 DT price = £3.64

Diclofenac sodium with misoprostol

The properties listed below are those particular to the combination only. For the properties of the components please consider, diclofenac sodium p. 993, misoprostol p. 73.

INDICATIONS AND DOSE

ARHTROTEC® 50/200
Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
▶ Adult: 1 tablet 2–3 times a day, take with food

ARHTROTEC® 75/200
Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
▶ BY MOUTH
▶ Adult: 1 tablet twice daily, take with food

MISOFEN® 50/200
Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
▶ BY MOUTH
▶ Adult: 1 tablet 2–3 times a day, take with food

MISOFEN® 75/200
Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
▶ BY MOUTH
▶ Adult: 1 tablet twice daily, take with food

UNLICENSED USE The BNF recommends a higher starting dose of misoprostol for prophylaxis against NSAID-induced gastroduodenal ulceration than that provided by the combination preparations of diclofenac and misoprostol.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Gastro-resistant tablet
CAUTIONARY AND ADVISORY LABELS 21, 25

Arthrotec (Pfizer Ltd)
Diclofenac sodium 75 mg, Misoprostol 200 microgram Arthrotec 75 gastro-resistant tablets | 60 tablet £15.83 DT price = £15.83
Diclofenac sodium 50 mg, Misoprostol 200 microgram Arthrotec 50 gastro-resistant tablets | 60 tablet £11.98 DT price = £11.98

Misofen (Morningside Healthcare Ltd)
Diclofenac sodium 75 mg, Misoprostol 200 microgram Misofen 75mg/200microgram gastro-resistant tablets | 60 tablet £15.83 DT price = £15.83
Diclofenac sodium 50 mg, Misoprostol 200 microgram Misofen 50mg/200microgram gastro-resistant tablets | 60 tablet £11.98 DT price = £11.98

ETODOLAC

INDICATIONS AND DOSE
Pain and inflammation in rheumatoid arthritis and osteoarthritis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: 300–600 mg daily in 1–2 divided doses
▶ BY MOUTH USING MODIFIED-RELEASE MEDICINES
▶ Adult: 600 mg daily

CONTRA-INDICATIONS Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

CAUTIONS Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - colangitis - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

INTERACTIONS → Appendix 1 (NSAIDs).

SIDE-EFFECTS
▶ Rare Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
▶ Frequency not known Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - confusion - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - dysphagia - dysuria - fatigue - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal
bleeding · gastro-intestinal discomfort · gastro-intestinal disturbances · gastro-intestinal ulceration · haematuria · headache · hearing disturbances · hypersensitivity reactions · insomnia · nausea · nervousness · palpitation · paraesthesia · photosensitivity · pruritus · pyrexia · raised blood pressure · rashes · renal failure (especially in patients with pre-existing renal impairment) · stomatitis · tinnitus · tremor · urinary frequency · vasculitis · vertigo

SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
- PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
- BREAST FEEDING Use with caution during breast-feeding. Manufacturer advises avoid.
- HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastrointestinal bleeding and fluid retention. Avoid in severe liver disease.
- RENAL IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

- Etodolac (Non-proprietary)
  - Etodolac 600 mg: Etodolac 600mg modified-release tablets | 30 tablet POM £14.60 DT price = £15.50
  - Etodolac XL: Etodolac XL 600mg tablets | 30 tablet POM £14.60 DT price = £15.50
- Lodine SR (Almriall Ltd)
  - Lodine 600 mg: Lodine SR 600mg tablets | 30 tablet POM £15.50 DT price = £15.50
- Eccoxolac (Taro Pharmaceuticals (UK) Ltd)
  - Eccoxolac 300 mg: Eccoxolac 300mg capsules | 60 capsule POM £8.14 DT price = £8.14

Capsule

- Eccoxolac (Meda Pharmaceuticals Ltd)
  - Eccoxolac 300 mg: Eccoxolac 300mg capsules | 60 capsule POM

Etoricoxib

INDICATIONS AND DOSE

Pain and inflammation in osteoarthritis

- BY MOUTH
  - Child 16-17 years: 30 mg once daily, increased if necessary to 60 mg once daily
  - Adult: 30 mg once daily, increased if necessary to 60 mg once daily

Pain and inflammation in rheumatoid arthritis | Ankylosing spondylitis

- BY MOUTH
  - Child 16-17 years: 60 mg once daily, increased if necessary to 90 mg once daily

- CONTRA-INDICATIONS Active gastro-intestinal bleeding · active gastro-intestinal ulceration · cerebrovascular disease · inflammatory bowel disease · ischaemic heart disease · mild to severe heart failure · peripheral arterial disease · uncontrolled hypertension (persistently above 140/90 mmHg)

- CAUTIONS Allergic disorders · cardiac impairment (NSAIDs may impair renal function) · coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · dehydration · elderly (risk of serious side-effects and fatalities) · history of cardiac failure · hypertension · left ventricular dysfunction · oedema · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated)

- INTERACTIONS → Appendix 1 (NSAIDs).

SIDE-EFFECTS, FURTHER INFORMATION

- Very rare Confusion · hallucinations
- Frequency not known Angioedema · blood disorders · bronchospasm · colitis (induction of or exacerbation of) · Crohn’s disease (induction of or exacerbation of) · depression · diarrhoea · dizziness · dry mouth · dyspnoea · electrolyte disturbance · epistaxis · flushing · mental acuity impaired · mouth ulcer · myalgia · paraesthesia · taste disturbance · transient ischaemic attack · weight change
- Rare Alveolitis · asptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · hepatic damage · interstitial fibrosis associated with NSAIDs can lead to renal failure · pancreatitis · papillary necrosis associated with NSAIDs can lead to renal failure · pulmonary eosinophilia · Stevens-Johnson syndrome · toxic epidermal necrolysis · visual disturbances
- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
- PREGNANCY Manufacturer advises avoid (teratogenic in animal studies). Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
Pregnancy

Allergy and cross-sensitivity

Serious side-effects

Side-effects

Interactions

Cautions

Drug action

Indications and dose

Medicinal forms

Felbinac

Drug action

Indications and dose

Medicinal forms

Pain and inflammation in musculoskeletal disorders

Breast feeding

Hepatic impairment

Renal impairment

Monitoring requirements

Indications and dose

CONTRA-INDICATIONS

For topical preparations, apply with gentle massage only. Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Foam

Cautions

Avoid contact with eyes • avoid contact with inflamed or broken skin • avoid contact with mucous membranes • not for use with occlusive dressings • topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported). • Interactions → Appendix 1 (NSAIDs). Interactions do not generally apply to topical NSAIDs. • Side-effects Photosensitivity • rash (discontinue use if develops)

Side-effects, further information

Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported). • Serious side-effects • For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

Allergy and cross-sensitivity

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

Pregnancy

Patient packs for topical preparations carry a warning to avoid during pregnancy.

Patient packs for topical preparations carry a warning to avoid during breast-feeding.

Deterioration in renal function has also been reported after topical use.

For topical preparations, apply with gentle massage only.

For topical preparations patients and carers should be advised to wash hands immediately after use.

Aspirin or any other NSAID. • haemorrhage (two or more distinct episodes) • recurrent gastro-intestinal ulceration (two or more distinct episodes) • peripheral arterial disease • aseptic meningitis (patients with connective-tissue disorders). • interstitial lung disease (induction of or exacerbation of) • colitis (induction of or exacerbation of) • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances

Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

Avoid if estimated glomerular filtration rate less than 30 ml/minute/1.73 m².

Avoid if eGFR less than 30 ml/minute/1.73 m².

Avoid contact with eyes

Adult: Apply 2–4 times a day, therapy should be reviewed after 14 days; maximum 25 g per day

Adult: 300–600 mg 3–4 times a day; maximum 3 g per day

Topical preparations, apply with gentle massage only.

Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

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Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.
ulceration · haematuria · headache · hearing disturbances · hypersensitivity reactions · insomnia · nasopharyngitis · nausea · nervousness · photosensitivity · raised blood pressure · rashes · renal failure (especially in patients with pre-existing renal impairment) · tinnitus · upper respiratory-tract infection · vertigo

SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- BREAST FEEDING Use with caution during breast-feeding. Amount too small to be harmful.

- HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- RENAL IMPAIRMENT Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

- Flennopron (Tyrpharm Ltd)
  - Fenoprofen (as Fenoprofen calcium) 300 mg
  - Fenoprofen 300 tablets

| 100 tablet (PSM) | £9.45 |

Flurbiprofen

INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Migraine | Postoperative analgesia | Mild to moderate pain

- BY MOUTH
  - Child 12–17 years: 150–200 mg daily in 2–4 divided doses, then increased to 300 mg daily, dose to be increased only in acute conditions
  - Adult: 150–200 mg daily in 2–4 divided doses, then increased to 300 mg daily, dose to be increased only in acute conditions

Dysmenorrhoea

- BY MOUTH
  - Child 12–17 years: Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 300 mg per day
  - Adult: Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 300 mg per day

CONTRA-INDICATIONS Active gastro-intestinal bleeding · active gastro-intestinal ulceration · history of gastro-intestinal bleeding related to previous NSAID therapy · history of gastro-intestinal perforation related to previous NSAID therapy · history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) · history of recurrent gastro-intestinal ulceration (two or more distinct episodes) · severe heart failure

- CAUTIONS Allergic disorders · cardiac impairment (NSAIDs may impair renal function) · cerebrovascular disease · coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · elderly (risk of serious side-effects and fatalities) · heart failure · ischaemic heart disease · peripheral arterial disease · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated) · uncontrolled hypertension

INTERACTIONS Appendix 1 (NSAIDs).

SIDE-EFFECTS

- Common or very common
  - Stomatitis

- Uncommon
  - Confusion · fatigue · hallucinations · paraesthesia

- Rare
  - Alveolitis · aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · hepatic damage · interstitial fibrosis associated with NSAIDs can lead to renal failure · pancreatitis · papillary necrosis associated with NSAIDs can lead to renal failure · pulmonary eosinophilia · Stevens-Johnson syndrome · toxic epidermal necrolysis · visual disturbances

- Frequency not known
  - Angioedema · blood disorders · bronchospasm · colitis (induction of or exacerbation of) · Crohn’s disease (induction of or exacerbation of) · depression · diarrhoea · dizziness · drowsiness · fluid retention (rarely precipitating congestive heart failure) · gastro-intestinal bleeding · gastro-intestinal discomfort · gastro-intestinal disturbances · gastro-intestinal ulceration · haematuria · headache · hearing disturbances · hypersensitivity reactions · insomina · nausea · nervousness · photosensitivity · raised blood pressure · rashes · renal failure (especially in patients with pre-existing renal impairment) · tinnitus · vertigo

SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- BREAST FEEDING Use with caution during breast-feeding. Amount too small to be harmful.

- HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- RENAL IMPAIRMENT Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- RENAL IMPAIRMENT Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. Avoid in severe impairment. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

Deterioration in renal function has also been reported after topical use.
Ibuprofen

### INDICATIONS AND DOSE

#### Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Mild to moderate pain including dysmenorrhoea | Postoperative analgesia | Migraine | Dental pain

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 300–400 mg 3–4 times a day; increased if necessary up to 600 mg 4 times a day; maintenance 200–400 mg 3 times a day, may be adequate
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 1.6 g once daily, dose to be taken in the early evening, increased if necessary to 2.4 g daily in 2 divided doses, dose to be increased only in severe cases

#### Mild to moderate pain | Pain and inflammation of soft-tissue injuries | Pyrexia with discomfort

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 3–5 months: 50 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
  - Child 6–11 months: 50 mg 3–4 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
  - Child 1–3 years: 100 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
  - Child 4–6 years: 150 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
  - Child 7–9 years: 200 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
  - Child 10–11 years: 300 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
  - Child 12–17 years: Initially 300–400 mg 3–4 times a day; increased if necessary up to 600 mg 4 times a day; maintenance 200–400 mg 3 times a day, may be adequate

#### Pain and inflammation

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 12–17 years: 1.6 g once daily, dose preferably taken in the early evening, increased to 2.4 g daily in 2 divided doses, dose to be increased only in severe cases

#### Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 3 months–17 years: 30–40 mg/kg daily in 3–4 divided doses; maximum 2.4 g per day

#### Pain and inflammation in systemic juvenile idiopathic arthritis

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 3 months–17 years: Up to 60 mg/kg daily in 4–6 divided doses; maximum 2.4 g per day

### Post-immunisation pyrexia in infants (on doctor’s advice only)

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 2–3 months: 50 mg for 1 dose, followed by 50 mg after 6 hours if required

#### Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

- **TO THE SKIN**
  - Adult: Apply up to 3 times a day, ibuprofen gel 5% gel to be administered

### FENBID® FORTE

#### Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

- **TO THE SKIN**
  - Adult: Apply up to 4 times a day, therapy should be reviewed after 14 days

### IBUGEL® FORTE

#### Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

- **TO THE SKIN**
  - Adult: Apply up to 3 times a day

### UNLICENSED USE

- Not licensed for use in children under 3 months or body-weight under 5 kg. Maximum dose for systemic juvenile idiopathic arthritis is unlicensed.

### CONTRA-INDICATIONS

- With oral use Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

### CAUTIONS

- With oral use Allergic disorders (in adults) - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) (in adults) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- With topical use Avoid contact with eyes - avoid contact with inflamed or broken skin - avoid contact with mucous membranes - not for use with occlusive dressings - topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

### CAUTIONS, FURTHER INFORMATION

- High-dose ibuprofen A small increase in cardiovascular risk, similar to the risk associated with cyclo-oxygenase-2 inhibitors and diclofenac, has been reported with high-dose ibuprofen (>2.4 g daily); use should be avoided in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, congestive heart failure (New York Heart Association classification II–III), and uncontrolled hypertension.

### INTERACTIONS

- Appendix 1 (NSAIDs).

- Interactions do not generally apply to topical NSAIDs.

### SIDE-EFFECTS

- Rare

- With oral use Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure -
pulmonary eosinophilia • Stevens-Johnson syndrome •
poisonous to epidermal necrosis • visual disturbances

- Frequency not known
  - With oral use Angioedema • blood disorders • bronchospasm
  • colitis (induction of or exacerbation of) • Crohn’s disease
  (induction of or exacerbation of) • depression • diarrhoea •
  dizziness • drowsiness • fluid retention (rarely precipitating
  congestive heart failure) • gastro-intestinal bleeding •
  gastro-intestinal discomfort • gastro-intestinal
  disturbances • gastro-intestinal ulceration • haematura •
  headache • hearing disturbances • hypersensitivity
  reactions • insomnia • nausea • nervousness •
  photosensitivity • raised blood pressure • rashes • renal
  failure (especially in patients with pre-existing renal
  impairment) • tinnitus • vertigo

- With topical use Photosensitivity • rash (discontinue use if
  develops)

### SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects For information about cardiovascular
  and gastro-intestinal side-effects, and a possible
  exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- With topical use Topical application of large amounts can
  result in systemic effects, including hypersensitivity and
  asthma (renal disease has also been reported).

### Overdose

Overdosage with ibuprofen may cause nausea, vomiting,
epigastric pain, and tinnitus, but more serious toxicity is
very uncommon. Charcoal, activated p. 1211 followed by
symptomatic measures are indicated if more than
100 mg/kg has been ingested within the preceding hour.

For details on the management of poisoning, see
Emergency treatment of poisoning p. 1204.

- Allergy and cross-sensitivity Contra-indicated in
  patients with a history of hypersensitivity to aspirin or any
  other NSAID—which includes those in whom attacks of
  asthma, angioedema, urticaria or rhinitis have been
  precipitated by aspirin or any other NSAID.

- Conception and contraception Caution—long-term use of
  some NSAIDs is associated with reduced female
  fertility, which is reversible on stopping treatment.

- Pregnancy
  - With oral use Avoid unless the potential benefit outweighs
    the risk. Avoid during the third trimester (risk of closure of
    fetal ductus arteriosus in utero and possibly persistent
    pulmonary hypertension of the newborn); onset of labour
    may be delayed and duration may be increased.
  - With topical use Patient packs for topical preparations carry
    a warning to avoid during pregnancy.

- Breast feeding
  - With oral use Use with caution during breast-feeding.
    Amount too small to be harmful but some manufacturers
    advise avoid.
  - With topical use Patient packs for topical preparations carry
    a warning to avoid during breast-feeding.

- Hepatic impairment
  - With oral use Use with caution; there is an increased risk of
    gastro-intestinal bleeding and fluid retention. Avoid in
    severe liver disease.

- Renal impairment
  - With oral use Avoid if possible or use with caution. Avoid in
    severe impairment. The lowest effective dose should be
    used for the shortest possible duration. In renal
    impairment monitor renal function; sodium and water
    retention may occur and renal function may deteriorate,
    possibly leading to renal failure.
  - With topical use Deterioration in renal function has also
    been reported after topical use.

- Directions for administration For topical
  preparations, apply with gentle massage only.

### Prescribing and dispensing information

- Flavours of syrup may include orange.

### Patient and carer advice

- Medicines for Children leaflet: ibuprofen for pain and
  inflammation www.medicinesforchildren.org.uk/ibuprofen-for-
  pain-and-inflammation

- With topical use For topical preparations, patients and their
  carers should be advised to wash hands immediately after
  use.

- Photosensitivity For topical preparations, patients or their
  carers should be advised against excessive exposure to
  sunlight or area treated in order to avoid possibility of
  photosensitivity.

### Professional specific information

- Dental practitioners’ formulary
  Ibuprofen Oral Suspension Sugar-free may be prescribed.
  Ibuprofen Tablets may be prescribed.

### Exceptions to legal category

- Smaller pack sizes of gel
  preparations may be available on sale to the public.

- Oral preparations can be sold to the public in certain
  circumstances.

### Medicinal forms

There can be variation in the licensing of different medicines
containing the same drug. Forms available from special-order
manufacturers include: oral suspension

#### tablet

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen (Non-proprietary)</td>
<td></td>
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<tr>
<td>Ibuprofen 200 mg</td>
<td>Ibuprofen 200mg tablets</td>
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<tr>
<td>24 tablet (p)</td>
<td>0.97 DT price = £0.97</td>
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<tr>
<td>84 tablet (p)</td>
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<tr>
<td>Ibuprofen 200mg tablets film coated</td>
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<tr>
<td>Ibuprofen 200mg caplets</td>
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<tr>
<td>96 tablet (p) no price available</td>
<td>100 tablet (p) no price available</td>
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<tr>
<td>Ibuprofen 400 mg</td>
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<td>Ibuprofen 600mg tablets film coated</td>
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<tr>
<td>Brufen (BGP Products Ltd)</td>
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<td>Ibuprofen 400 mg</td>
<td>Brufen 400mg tablets</td>
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<td>Ibuprofen 600 mg</td>
<td>Brufen 600mg tablets</td>
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<td>Cuprofen (SSL International Pte)</td>
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<tr>
<td>Ibuprofen 2400 mg</td>
<td>Cuprofen Maximum Strength 400mg tablets</td>
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<td>48 tablet (p)</td>
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<td>Ibucalm (Asparg Pharmaceuticals Ltd)</td>
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<td>48 tablet (p) £2.44</td>
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<td>Nurofen (Reckitt Benckiser Healthcare (UK) Ltd)</td>
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<td>Ibuprofen 200 mg</td>
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<td>Ibuprofen (as ibuprofen lysine) 400 mg</td>
<td>Nurofen Maximum Strength Migraine Pain 684mg caplets</td>
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#### Modified-release tablet

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<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 25, 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brufen Retard (BGP Products Ltd)</td>
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<tr>
<td>Brufen 800 mg</td>
<td>Brufen Retard 800mg tablets</td>
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<tr>
<td>£7.74 DT price = £7.74</td>
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</table>
Capsule

- **Ibuprofen (Non-proprietary)**
  - Ibuprofen 200 mg: Ibuprofen 200mg capsules | 30 capsule [P] no price available DT price = £4.40 | 32 capsule [P] £0.79
  - Ibuprofen 400 mg: Ibuprofen 400mg capsules | 10 capsule [P] no price available | 20 capsule [P] no price available DT price = £5.49

Chewable capsule

- **Nurofen** (Reckitt Benckiser Healthcare (UK) Ltd)
  - Ibuprofen 100 mg: Nurofen for Children 100mg chewable capsules | 12 capsule [P] £3.23

Effervescent granules

- **CAUTIONARY AND ADVISORY LABELS**: May contain Sodium
  - **Brufen** (BGP Products Ltd)
    - Ibuprofen 600 mg: Brufen 600mg effervescent granules sachets | 20 sachet [P] £6.80 DT price = £6.80

Oral suspension

- **CAUTIONARY AND ADVISORY LABELS**: 13, 21
  - **Electrolytes**: May contain Sodium
  - **Brufen** (BGP Products Ltd)
    - Ibuprofen 20 mg per 1 ml: Brufen 100mg/5ml oral suspension sugar-free | 100 ml [P] £1.33 sugar-free | 150 ml [P] no price available sugar-free | 500 ml [P] £6.60 sugar-free
  - Ibuprofen 20 mg per 1 ml: Brufen 100mg/5ml oral suspension sugar-free | 200 ml [P] £3.42
  - **Calprofen** (McNeill Products Ltd)
    - Ibuprofen 20 mg per 1 ml: Calprofen 100mg/5ml oral suspension sugar-free | 100 ml [P] £1.67 DT price = £1.33 sugar-free
  - **Mandafen** (M & A Pharmachem Ltd)
    - Ibuprofen 20 mg per 1 ml: Mandafen for Children 100mg/5ml oral suspension sugar-free | 100 ml [P] £0.69 DT price = £1.33
  - **Nurofen** (Reckitt Benckiser Healthcare (UK Ltd)
    - Ibuprofen 20 mg per 1 ml: Nurofen for Children 100mg/5ml oral suspension orange sugar-free | 200 ml [P] £4.20
    - Nurofen for Children 100mg/5ml oral suspension strawberry sugar-free | 200 ml [P] £4.20
  - **Orbifen** (Orbis Consumer Products Ltd)
    - Ibuprofen 20 mg per 1 ml: Orbifen For Children 100mg/5ml oral suspension sugar-free | 100 ml [P] £1.167 DT price = £1.33 sugar-free
    - 150 ml [P] £2.71

Gel

- **EXCIPIENTS**: May contain Benzyl alcohol

- **Ibuprofen (Non-proprietary)**
  - Ibuprofen 50 mg per 1 gram: Ibuprofen 5% gel | 30 gram [P] £1.39 | 50 gram [P] £2.31 DT price = £2.31 | 100 gram [P] £4.62 DT price = £4.62
  - Ibuprofen 100 mg per 1 gram: Ibuprofen 10% gel | 30 gram [P] £1.48 | 50 gram [P] £3.32 | 100 gram [P] £5.03 DT price = £4.92

- **Fenbid** (AMCo)
  - Ibuprofen 50 mg per 1 gram: Fenbid 5% gel | 100 gram [P] £1.50 DT price = £1.50
  - Ibuprofen 100 mg per 1 gram: Fenbid Forte 10% gel | 100 gram [P] £2.00 DT price = £2.00

- **Ibuge** (Dermal Laboratories Ltd)
  - Ibuprofen 50 mg per 1 gram: Ibugel 5% gel | 100 gram [P] £4.87 DT price = £4.87
  - Ibuprofen 100 mg per 1 gram: Ibugel Forte 10% gel | 100 gram [P] £4.92 DT price = £4.92

- **Ibulieve** (Dendron Ltd)
  - Ibuprofen 50 mg per 1 gram: Ibulieve 5% gel | 30 gram [P] £2.64 | 50 gram [P] £3.70 DT price = £3.21 | 100 gram [P] £6.80 DT price = £6.80
  - Ibuprofen 100 mg per 1 gram: Ibulieve Maximum Strength 10% gel | 30 gram [P] £3.39 | 50 gram [P] £4.63

- **Phorpain** (AMCo)
  - Ibuprofen 50 mg per 1 gram: Phorpain 5% gel | 100 gram [P] £1.50 DT price = £1.50
  - Ibuprofen 100 mg per 1 gram: Phorpain Maximum Strength 10% gel | 50 gram [P] £4.00 | 100 gram [P] £4.00 DT price = £4.92

Indomethacin

**Indomethacin**

- **INDICATIONS AND DOSE**
  - **Pain and moderate to severe inflammation in rheumatic disease and other musculoskeletal disorders**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: 50–200 mg daily in divided doses
    - **BY RECTUM**
      - Adult: 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg
    - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
      - Adult: 75 mg 1–2 times a day

- **Acute gout**
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Adult: 150–200 mg daily in divided doses
  - **BY RECTUM**
    - Adult: 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Adult: 75 mg daily

- **Dysmenorrhoea**
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Adult: Up to 75 mg daily
  - **BY RECTUM**
    - Adult: 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Adult: 75 mg daily

- **CONTRA-INDICATIONS**
  - Active gastro-intestinal bleeding, active gastro-intestinal ulceration, history of gastro-intestinal bleeding related to previous NSAID therapy, history of gastro-intestinal perforation related to previous NSAID therapy, history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes), history of recurrent gastro-intestinal ulceration (two or more distinct episodes), severe heart failure

- **CAUTIONS**
  - Allergic disorders, avoid rectal administration in haemorrhoids, avoid rectal administration in proctitis, cardiac impairment (NSAIDs may impair renal function), cerebrovascular disease, coagulation defects, connective-tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), epilepsy, heart failure, ischaemic heart disease, parkinsonism, peripheral arterial disease, psychiatric disturbances, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated), uncontrolled hypertension

- **INTERACTIONS**
  - Appendix I (NSAIDs)

- **SIDE-EFFECTS**
  - Rare: Alveolitis, aseptic meningo, patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible, blood disorders, confusion, convulsions, hepatic damage, hyperglycaemia, interstitial fibrosis associated with NSAIDs can lead to renal failure, intestinal strictures, pancreatitis, papillary necrosis associated with NSAIDs can lead to renal failure, peripheral neuropathy, psychiatric disturbances, pulmonary eosinophilia, Stevens-Johnson syndrome, syncope, thrombocytopenia, toxic epidermal necrolysis, visual disturbances

- **Frequency not known**
  - Angioedema, blood disorders, bronchospasm, colitis (induction of or exacerbation of), Crohn’s disease (induction of or exacerbation of)
1002  Pain and inflammation in musculoskeletal disorders

**Musculoskeletal system**

**MEDICINAL FORMS**

- Indometacin (Non-proprietary)
  - Indometacin 100 mg  Indometacin 100 mg suppositories  | 10 suppository  
    Barnardos  £17.61 DT price = £17.61
  - Indocid  (Aspen Pharma Trading Ltd)  
    - Indometacin 100 mg  Indocid 100mg suppositories  | 10 suppository  
      Barnardos  £17.61 DT price = £17.61

**Ketoprofen**

- **INDICATIONS AND DOSE**
  - **Pain and mild inflammation in rheumatic disease**
    ▶  **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      Adult: 100–200 mg daily in 2–4 divided doses
    ▶  **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
      Adult: 100–200 mg once daily, dose to be taken with food
  - **BY RECTUM**
    Adult: 100 mg once daily, to be administered at bedtime, combined oral and rectal treatment, maximum total daily dose 200 mg

**Indications and dose**

**Pain in musculoskeletal disorders**

<table>
<thead>
<tr>
<th>Indometacin 100 mg</th>
<th>Indocid 100mg suppositories</th>
<th>10 suppository</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnardos</td>
<td>£17.61 DT price = £17.61</td>
<td></td>
</tr>
</tbody>
</table>

**SIDE-EFFECTS, FURTHER INFORMATION**

- **SPECIFIC SIDE-EFFECTS**
  - **Photosensitivity**
  - **General side-effects**
    - **Contra-indications**
    - **Interactions**
    - **Additional information**

**Suppository**

- **Indometacin (Non-proprietary)**
- **Indometacin 100 mg**  Indometacin 100 mg suppositories  | 10 suppository  
  - Barnardos  £17.61 DT price = £17.61

**PATIENT AND CARER ADVICE**

- With oral use  Nausea
- With rectal use  Suppositories may cause occasional bleeding  — suppositories may cause rectal irritation

**SIDE-EFFECTS**

- **Renal impairment**
  - Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**CONTRA-INDICATIONS**

- With systemic use  Active gastro-intestinal bleeding  · active gastro-intestinal ulceration  · history of gastro-intestinal bleeding  · history of gastro-intestinal perforation  · history of gastro-intestinal ulceration  · severe heart failure

**INTERACTIONS**

- With topical use  Avoid contact with eyes  — avoid contact with inflamed or broken skin  — avoid contact with mucous membranes  — not for use with occlusive dressings  — topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

- With topical use  Interactions do not generally apply to topical NSAIDs.

**SIDE-EFFECTS**

- **General side-effects**
  - Photosensitivity
- **Specific side-effects**
  - **Rare**
    - With systemic use  Arthritis  · aseptic meningitis (patients with connective-tissue disorders such as systemic lupus

**INDICATIONS AND DOSE**

**Pain and mild inflammation in rheumatic disease**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 100–200 mg daily in 2–4 divided doses

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 100–200 mg once daily, dose to be taken with food

**RELIEF OF PAIN IN MUSCULOSKELETAL DISORDERS**

**TREATMENT IN KNEE OR HAND OSTEARTHritis (adjunct)**

- **TO THE SKIN**
  - Adult: 2–4 times a day for up to 7 days, ketoprofen 2.5% gel to be administered; maximum 15 g per day

**POWERGEL®**

**RELIEF OF PAIN IN MUSCULOSKELETAL CONDITIONS**

**ADJUNCTIVE TREATMENT IN KNEE OR HAND OSTEARTHritis**

- **TO THE SKIN**
  - Adult: Apply 2–3 times a day for up to max. 10 days

**CONTRA-INDICATIONS**

- With systemic use  Active gastro-intestinal bleeding  · active gastro-intestinal ulceration  · history of gastro-intestinal bleeding  · history of gastro-intestinal perforation  · history of gastro-intestinal ulceration  · severe heart failure

**CAUTIONS**

- With systemic use  Allergic disorders  · cardiac impairment (NSAIDs may impair renal function)  · cerebrovascular disease  · coagulation defects  · connective-tissue disorders  · Crohn’s disease (may be exacerbated)  · elderly (risk of serious side-effects and fatalities)  · heart failure  · ischaemic heart disease  · peripheral arterial disease  · risk factors for cardiovascular events  · ulcerative colitis (may be exacerbated)  · uncontrolled hypertension

- With topical use  Avoid contact with eyes  — avoid contact with inflamed or broken skin  — avoid contact with mucous membranes  — not for use with occlusive dressings  — topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

- **INTERACTIONS**
  - Appendix 1 (NSAIDs).
  - With topical use  Interactions do not generally apply to topical NSAIDs.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

**Photosensitivity**

**SPECIFIC SIDE-EFFECTS**

- **Rare**
  - With systemic use  Arthritis  · aseptic meningitis (patients with connective-tissue disorders such as systemic lupus

**Driving and skilled tasks**

Dizziness may affect performance of skilled tasks (e.g. driving).

**Medication notes**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS**
  - 21
  - **Indometacin (Non-proprietary)**
    - Indometacin 25 mg  Indometacin 25mg capsules  | 28 capsule  
      Barnardos  £5.00 DT price = £1.06
    - Indometacin 50 mg  Indometacin 50mg capsules  | 28 capsule  
      Barnardos  £7.50 DT price = £1.37
  - **Modified-release capsule**
    - **CAUTIONARY AND ADVISORY LABELS**
      - 21, 25
      - **Indometacin (Non-proprietary)**
        - Indometacin 75 mg  Indometacin 75mg modified-release capsules  | 100 capsule  
          Barnardos  £8.65 DT price = £8.65
        - Berlind Retard  (Tillomed Laboratories Ltd)  
          Indometacin 75 mg  Berlind 75 Retard capsules  | 100 capsule  
          Barnardos  £8.65 DT price = £8.65

- **Driving and skilled tasks**
  - Dizziness may affect performance of skilled tasks (e.g. driving).
erythematous may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

- **Frequency not known**
  - With topical use Suppositories may cause rectal irritation
  - With systemic use Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn's disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo
  - With topical use Rash (discontinue use if develops)

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
  - With topical use Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION**
  - With systemic use Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY**
  - With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
  - With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

- **BREAST FEEDING**
  - With systemic use Use with caution during breast-feeding. Amount probably too small to be harmful but manufacturers advise avoid.
  - With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

- **HEPATIC IMPAIRMENT**
  - With systemic use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Should be avoided in severe liver disease.

- **RENAL IMPAIRMENT**
  - With systemic use Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.
  - With topical use Deterioration in renal function has also been reported after topical use.

- **DIRECTIONS FOR ADMINISTRATION** For topical preparations apply with gentle massage only.

- **PRESCRIBING AND DISPENSING INFORMATION** Caution—topical preparations not generally suitable for children.

- **Flavours of oral liquid formulations may include strawberry.**

- **PATIENT AND CARER ADVICE**
  - With topical use For topical preparations, patients and their carers should be advised to wash hands immediately after use.
  - Photosensitivity
  - With topical use Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity. Patients should be advised not to expose area treated to sunbeds or sunlight (even on a bright but cloudy day) during, and for two weeks after stopping treatment; treated areas should be protected with clothing.

- **EXCEPTIONS TO LEGAL CATEGORY** Smaller pack sizes of gel preparations may be available on sale to the public.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Modified-release capsule**
    - **CAUTIONARY AND ADVISORY LABELS** 21, 25
    - **Ketoprofen (Non-proprietary)**
      - Ketoprofen 200 mg Ketoprofen 200 mg modified-release capsules | 28 capsule POM £23.85 DT price = £23.85
      - Larafen CR (Engnen Pharma Ltd) Ketoprofen 200 mg Larafen CR 200 mg capsules | 28 capsule POM £19.08 DT price = £23.85
      - Oruvail (Sanofi) Ketoprofen 100 mg Oruvail 100 modified-release capsules | 56 capsule POM £23.93 DT price = £23.93
      - Ketoprofen 200 mg Oruvail 200 modified-release capsules | 28 capsule POM £23.85 DT price = £23.85
      - Tiloket CR (Tillomed Laboratories Ltd) Ketoprofen 100 mg Tiloket CR 100 mg capsules | 56 capsule POM £10.70 DT price = £23.93
      - Ketoprofen 200 mg Tiloket CR 200 mg capsules | 28 capsule POM £10.70 DT price = £23.85
      - Valket Retard (Tillomed Laboratories Ltd) Ketoprofen 200 mg Valket 200 Retard capsules | 28 capsule POM £10.70 DT price = £23.85

  - **Gel**
    - **EXCIPIENTS:** May contain Fragrances
      - **Ketoprofen (Non-proprietary)**
        - Ketoprofen 25 mg per 1 gram Ketoprofen 2.5% gel | 50 gram POM £1.80 DT price = £1.64 | 100 gram POM £3.36 DT price = £3.28
        - Oruvail (Sanofi) Ketoprofen 25 mg per 1 gram Oruvail 2.5% gel | 100 gram POM £6.84 DT price = £3.28
        - Powergel (A. Menarini Farmaceutica Internazionale SRL) Ketoprofen 25 mg per 1 gram Powergel 2.5% gel | 50 gram POM £3.06 DT price = £1.64 | 100 gram POM £5.89 DT price = £3.28
        - Tiloket (Tillomed Laboratories Ltd) Ketoprofen 25 mg per 1 gram Tiloket 2.5% gel | 50 gram POM £3.00 DT price = £1.64 | 100 gram POM £6.00 DT price = £3.28

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**Ketoprofen with omeprazole**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ketoprofen p. 1002, omeprazole p. 76.

- **INDICATIONS AND DOSE**
  - Patients requiring ketoprofen for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, who are at risk of NSAID associated duodenal or gastric ulcer or gastroduodenal erosions
    - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Adult: Initially 100/20 mg daily, increased if necessary to 200/20 mg daily, depending on severity of symptoms, dose expressed as x/y mg ketoprofen/omeprazole
Mefenamic acid

## INDICATIONS AND DOSE

**Pain and inflammation in rheumatoid arthritis and osteoarthritis** | Postoperative pain | Mild to moderate pain
---|---|---
**BY MOUTH**
- Adult: 500 mg 3 times a day
- Child 12-17 years: 500 mg 3 times a day
- Adult: 500 mg 3 times a day

**Acute pain including dysmenorrhoea** | Menorrhagia
---|---
**BY MOUTH**
- Child 12-17 years: 500 mg 3 times a day
- Adult: 500 mg 3 times a day

## CONTRA-INDICATIONS

- Active gastro-intestinal bleeding
- active gastro-intestinal ulceration
- history of gastro-intestinal bleeding related to previous NSAID therapy
- history of gastro-intestinal perforation related to previous NSAID therapy
- history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)
- history of recurrent gastro-intestinal ulceration (two or more distinct episodes)
- inflammatory bowel disease
- severe heart failure

## CAUTIONS

- Acute porphyrias p. 930 - allergic disorders
- cardiac impairment (NSAIDs may impair renal function)
- cerebrovascular disease - coagulation defects - connective-tissue disorders
- Crohn's disease (may be exacerbated)
- elderly (risk of serious side-effects and fatalities)
- epilepsy
- heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated)
- uncontrolled hypertension

## INTERACTIONS

See Appendix 1 (NSAIDs).

## SIDE-EFFECTS

- Common or very common
  - Diarrhoea (withdraw treatment)
  - rashes
- Uncommon
  - Fatigue
  - paraesthesia
- Rare
  - Alveolitis
  - aplastic anaemia
  - aseptic meningitis
  - allergic disorders
  - connective-tissue disorders
  - glucose intolerance
  - haemolytic anaemia
  - hepatic damage
  - hypotension
  - interstitial fibrosis
  - kidney failure
  - skin disorders
  - thrombocytopenia
  - visual disturbances

## ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—-which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

## CONCEPTION AND CONTRACEPTION

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

## PREGNANCY

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

## BREAST FEEDING

Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.

## HEPATIC IMPAIRMENT

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

## RENAL IMPAIRMENT

Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

## MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

### Tablet

- CAUTIONARY AND ADVISORY LABELS 21
- **Mefenamic acid (Non-proprietary)**
  - Mefenamic acid 500 mg | Mefenamic acid 500mg tablets | 28 tablet(PM) £18.00 DT price = £6.99 | 84 tablet(PM) £44.99
- **Ponstan** (Chemidex Pharma Ltd)
  - Mefenamic acid 500 mg | Ponstan Forte 500mg tablets | 100 tablet(PM) £15.72

### Capsule

- CAUTIONARY AND ADVISORY LABELS 21
- **Mefenamic acid (Non-proprietary)**
  - Mefenamic acid 250 mg | Mefenamic acid 250mg capsules | 100 capsule(PM) £15.00 DT price = £9.46
- **Ponstan** (Chemidex Pharma Ltd)
  - Mefenamic acid 250 mg | Ponstan 250mg capsules | 100 capsule(PM) £8.17 DT price = £9.46

Meloxicam

## INDICATIONS AND DOSE

**Exacerbation of osteoarthritis (short-term)**

- **BY MOUTH**
- Child 16-17 years: 7.5 mg once daily, then increased if necessary up to 15 mg once daily
- Adult: 7.5 mg once daily, then increased if necessary up to 15 mg once daily

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**PRESCRIBING AND DISPENSING INFORMATION**

Capsules enclose microgranules containing modified-release ketoprofen and gastro-resistant omeprazole.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Modified-release capsule**
  - CAUTIONARY AND ADVISORY LABELS 21, 25
  - EXCIPIENTS: May contain Propylene glycol
  - Axorid (Meda Pharmaceuticals Ltd)
    - Omeprazole 20 mg, Ketoprofen 100 mg | Axorid 100mg/20mg modified-release capsules | 30 capsule(PM) £13.80
    - Omeprazole 20 mg, Ketoprofen 200 mg | Axorid 200mg/20mg modified-release capsules | 30 capsule(PM) £13.80

**SIDE-EFFECTS, FURTHER INFORMATION**

- Serious side-effects
  - For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
  - **Overdose**
    - Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent, require treatment.
    - For details on the management of poisoning, see Emergency treatment of poisoning p. 1204, in particular, Convulsions.

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**

Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**

Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.
Pain and inflammation in rheumatic disease | Ankylosing spondylitis
▶ BY MOUTH
▶ Child 16-17 years: 15 mg once daily, then reduced to 7.5 mg once daily if required
▶ Adult: 15 mg once daily, then reduced to 7.5 mg once daily if required
▶ Elderly: 7.5 mg once daily

Relief of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in children intolerant to other NSAIDs
▶ BY MOUTH
▶ Child 12-17 years (body-weight up to 50 kg): 7.5 mg once daily
▶ Child 12-17 years (body-weight 50 kg and above): 15 mg once daily

● UNLICENSED USE Not licensed for use in children under 16 years.
● CONTRA-INDICATIONS Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure
● CAUTIONS Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension
● INTERACTIONS → Appendix 1 (NSAIDs).

● SIDE-EFFECTS
▶ Rare Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
▶ Frequency not known Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

SIDE-EFFECTS, FURTHER INFORMATION
Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
● ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
● CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

● PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
● BREAST FEEDING Use with caution during breast-feeding. Present in milk in animal studies—manufacturer advises avoid.
● HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.
● RENAL IMPAIRMENT Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure. In adults Avoid if eGFR less than 25 ml/minute/1.73 m².
   In children Avoid if estimated glomerular filtration rate less than 25 ml/minute/1.73 m².

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 21
▶ Meloxicam (Non-proprietary)
Meloxicam 7.5 mg Meloxicam 7.5mg tablets | 30 tablet Pos £4.00 DT price = £1.12
Meloxicam 15 mg Meloxicam 15mg tablets | 30 tablet Pos £4.00 DT price = £1.16
Orodispersible tablet
▶ Meloxicam (Non-proprietary)
Meloxicam 7.5 mg Meloxicam 75mg orodispersible tablets sugar free sugar-free | 30 tablet Pos £15.50
Meloxicam 15 mg Meloxicam 15mg orodispersible tablets sugar free sugar-free | 30 tablet Pos £15.50

Nabumetone
● INDICATIONS AND DOSE
Pain and inflammation in osteoarthritis and rheumatoid arthritis
▶ BY MOUTH
▶ Adult: 1 g once daily, dose to be taken at night
▶ Elderly: 0.5–1 g daily
Pain and inflammation in osteoarthritis and rheumatoid arthritis (severe and persistent symptoms)
▶ BY MOUTH
▶ Adult: 0.5–1 g, dose to be taken in the morning and 1 g, dose to be taken at night
▶ Elderly: 0.5–1 g daily

● CONTRA-INDICATIONS Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure
● CAUTIONS Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension
● INTERACTIONS → Appendix 1 (NSAIDs).
Musculoskeletal system

- **SIDE-EFFECTS**
  - Rare Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis
  - Frequency not known Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematura - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
  - **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
  - **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
  - **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
  - **BREAST FEEDING** Use with caution during breast-feeding. Manufacturer advises avoid.
  - **HEPATIC IMPAIRMENT** Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.
  - **RENAL IMPAIRMENT** Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 21
      - Nabumetone (Non-proprietary)
        - Nabumetone 500 mg Nabumetone 500mg tablets | 56 tablet £20.00 DT price = £7.88
        - Reflex (Meda Pharmaceuticals Ltd)
          - Nabumetone 500 mg Reflex 500mg tablets | 56 tablet £6.18 DT price = £7.88

### Naproxen

- **INDICATIONS AND DOSE**
  - **Pain and inflammation in rheumatic disease**
    - **BY MOUTH**
    - Adult: 0.5–1 g daily in 1–2 divided doses
  - **Acute gout**
    - **BY MOUTH**
    - Adult: Initially 750 mg, then 250 mg every 6–8 hours until attack has passed

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure
  - **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension
  - **INTERACTIONS** Appendix 1 (NSAIDs).
  - **SIDE-EFFECTS**
    - Rare Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
    - Frequency not known Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal ulceration - haematura - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**
  - Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
  - **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
  - **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
  - **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
  - **BREAST FEEDING** Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.
PRESCRIBING AND DISPENSING INFORMATION

The properties listed below are those particular to the combination only. For the properties of the components please consider, naproxen p. 1006, misoprostol p. 73.

### Naproxen with misoprostol

The properties listed below are those particular to the combination only. For the properties of the components please consider, naproxen p. 1006, misoprostol p. 73.

#### MEDICATIONS

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

<table>
<thead>
<tr>
<th>NAPROXEN WITH ESOMEPRAZOLE (NON-PROPRIETARY)</th>
<th>22, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 500 mg</td>
<td>Naproxen 500mg / Esomeprazole 20mg modified-release tablets</td>
</tr>
<tr>
<td>Vimovo (AstraZeneca UK Ltd)</td>
<td>Esomeprazole (as Esomeprazole magnesium trihydrate) 20 mg, Naproxen 500 mg</td>
</tr>
</tbody>
</table>

#### INDICATIONS AND DOSE

Patients requiring naproxen for rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis, with prophylaxis against NSAID-induced gastroduodenal ulceration

- **BY MOUTH**
  - Adult: 500 mg twice daily, naproxen and 200 micrograms twice daily, misoprostol, taken together with food

#### PRESCRIBING AND DISPENSING INFORMATION

The BNF recommends a higher starting dose of misoprostol for prophylaxis against NSAID-induced gastroduodenal ulceration than that provided by the misoprostol with naproxen combination pack.

#### MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>NAPROXEN (NON-PROPRIETARY)</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 250 mg</td>
<td>Naproxen 250mg tablets</td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>Naproxen 500mg tablets</td>
</tr>
<tr>
<td>Naprosyn (Atnahs Pharma UK Ltd)</td>
<td>Naproxen 250 mg</td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>Naprosyn 500mg tablets</td>
</tr>
</tbody>
</table>

**Effervescent tablet**

<table>
<thead>
<tr>
<th>STIRLSEN (Stirling Anglian Pharmaceuticals Ltd)</th>
<th>22, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 250 mg</td>
<td>Naproxen 250mg effervescent tablets sugar-free</td>
</tr>
</tbody>
</table>

**Gastro-resistant tablet**

<table>
<thead>
<tr>
<th>NAPROXEN (NON-PROPRIETARY)</th>
<th>5, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 250 mg</td>
<td>Naproxen 250mg gastro-resistant tablets</td>
</tr>
<tr>
<td>Naproxen 250 mg</td>
<td>Naproxen 250mg gastro-resistant tablets</td>
</tr>
<tr>
<td>Naprosyn (Atnahs Pharma UK Ltd)</td>
<td>Naproxen EC</td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>Naproxen 500mg gastro-resistant tablets</td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>Naproxen EC 500mg tablets</td>
</tr>
</tbody>
</table>

**Oral suspension**

<table>
<thead>
<tr>
<th>NAPROXEN (NON-PROPRIETARY)</th>
<th>22, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 25 mg/5ml</td>
<td>Naproxen 5mg/ml oral suspension sugar free-sugar-free</td>
</tr>
<tr>
<td>Naproxen 25 mg/5ml</td>
<td>Naproxen 5mg/ml oral suspension sugar free-sugar-free</td>
</tr>
</tbody>
</table>

### Piroxicam

**INDICATIONS AND DOSE**

Rheumatoid arthritis (initiated by a specialist) | Osteoarthritis (initiated by a specialist) | Ankylosing spondylitis (initiated by a specialist)

- **BY MOUTH**
  - Adult: Up to 20 mg once daily

**Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)**

- **TO THE SKIN**
  - Adult: Apply 3–4 times a day, 0.5% gel to be applied; review treatment after 4 weeks

#### IMPORTANT SAFETY INFORMATION

**CHMP ADVICE—PIROXICAM (JUNE 2007)**

- With systemic use

  The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastrointestinal side effects and serious skin reactions. The CHMP has advised that:

  - piroxicam should be initiated only by physicians experienced in treating inflammatory or degenerative rheumatic diseases
  - piroxicam should not be used as first-line treatment
  - in adults, use of piroxicam should be limited to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
  - piroxicam dose should not exceed 20 mg daily

### Naproxen with esomeprazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, naproxen p. 1006, esomeprazole p. 74.

#### INDICATIONS AND DOSE

Patients requiring naproxen for osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, who are at risk of NSAID-associated duodenal or gastric ulcer and when treatment with lower doses of naproxen or other NSAIDs ineffective

- **BY MOUTH**
  - Adult: 500/20 mg twice daily, dose expressed as x/y mg naproxen/esomeprazole

#### PRESCRIBING AND DISPENSING INFORMATION

Naproxen component is gastro-resistant.
• piroxicam should no longer be used for the treatment of acute painful and inflammatory conditions
• treatment should be reviewed 2 weeks after initiating piroxicam, and periodically thereafter
• concomitant administration of a gastro-protective agent should be considered.

Topical preparations containing piroxicam are not affected by these restrictions.

**CONTRA-INDICATIONS**
- With systemic use Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding - history of gastro-intestinal perforation - history of gastro-intestinal ulceration - inflammatory bowel disease - severe heart failure

**CAUTIONS**
- With systemic use Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension
- With topical use Avoid contact with eyes - avoid contact with inflamed or broken skin - avoid contact with mucous membranes - not for use with occlusive dressings - topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

**INTERACTIONS** ➔ Appendix 1 (NSAIDs).
- With topical use Interactions do not generally apply to topical NSAIDs.

**SIDE-EFFECTS**
- Rare
  - With systemic use Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
- Frequency not known
  - With topical use Photosensitivity - rash (discontinue use if develops)

**SIDE-EFFECTS, FURTHER INFORMATION**
- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.
- With topical use Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**
- With systemic use Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**
- With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
- With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

**BREAST FEEDING**
- With systemic use Use with caution during breast-feeding. Amount too small to be harmful.
- With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

**HEPATIC IMPAIRMENT**
- With systemic use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**
- With systemic use Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.
- With topical use Deterioration in renal function has also been reported after topical use.

**DIRECTIONS FOR ADMINISTRATION**
Piroxicam orodispersible tablets can be taken by placing on the tongue and allowing to dissolve or by swallowing. For topical preparations apply with gentle massage only.

**PATIENT AND CARER ADVICE**
- With topical use For topical preparations, patients and their carers should be advised to wash hands immediately after use.
- Photosensitivity For topical preparations, patients should be advised against excessive exposure to sunlight or treatment in order to avoid possibility of photosensitivity.

**LESS SUITABLE FOR PRESCRIBING**
- With oral use Piroxicam is less suitable for prescribing.

**MEDIcINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Orodispersible tablet**

**Cautionary and advisory labels** 10, 21

**Excipients:** May contain Aspartame

- **Feldene Melt** (Pfizer Ltd)
  - Piroxicam 20 mg Feldene Melt 20mg tablets sugar-free | 30 tablet [POM] £10.53 DT price = £10.53

**Capsule**

**Cautionary and advisory labels** 21

- **Piroxicam (Non-proprietary)**
  - Piroxicam 10 mg Piroxicam 10mg capsules | 56 capsule [POM] £16.82 DT price = £3.50
  - Piroxicam 20 mg Piroxicam 20mg capsules | 28 capsule [POM] £17.60 DT price = £2.82
- **Feldene** (Pfizer Ltd)
  - Piroxicam 10 mg Feldene 10mg capsules | 30 capsule [POM] £3.86
  - Piroxicam 20 mg Feldene 20 capsules | 30 capsule [POM] £7.71

**Gel**

**Excipients:** May contain Benzyl alcohol, propylene glycol

- **Piroxicam (Non-proprietary)**
  - Piroxicam 5 mg per 1 gram Piroxicam 0.5% gel | 60 gram [POM] £3.50 DT price = £2.77 | 100 gram [POM] £4.80 | 112 gram [POM] £7.25 DT price = £5.17
- **Feldene** (Pfizer Ltd)
  - Piroxicam 5 mg per 1 gram Feldene 0.5% gel | 60 gram [POM] £6.00 DT price = £2.77 | 112 gram [POM] £9.41 DT price = £5.17
Sulindac

**INDICATIONS AND DOSE**

Pain and inflammation in musculoskeletal disorders | Acute gout

- **BY MOUTH**
- **Adult:** 200 mg twice daily for maximum duration 7–10 days in peri-articular disorders, dose may be reduced according to response; acute gout should respond within 7 days; maximum 400 mg per day

**CONTRA-INDICATIONS**

- Active gastro-intestinal bleeding
- active gastro-intestinal ulceration
- history of gastro-intestinal bleeding related to previous NSAID therapy
- history of gastro-intestinal perforation related to previous NSAID therapy
- history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)
- history of recurrent gastro-intestinal ulceration (two or more distinct episodes)
- severe heart failure

**CAUTIONS**

- Allergic disorders
- cardiac impairment (NSAIDs may impair renal function)
- cerebrovascular disease
- coagulation defects
- connective-tissue disorders
- Crohn’s disease (may be exacerbated)
- elderly (risk of serious side-effects and fatalities)
- ensure adequate hydration
- heart failure
- history of renal stones
- ischaemic heart disease
- peripheral arterial disease
- risk factors for cardiovascular events
- ulcerative colitis (may be exacerbated)
- uncontrolled hypertension

**INTERACTIONS** → Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- Rare
  - Alveolitis
  - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible)
  - hepatic damage
  - interstitial fibrosis associated with NSAIDs can lead to renal failure
  - pancreatitis
  - papillary necrosis associated with NSAIDs can lead to renal failure
  - pulmonary eosinophilia
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis
  - visual disturbances

- Frequency not known
  - Angioedema
  - blood disorders
  - bronchospasm
  - cholestasis
  - colitis (induction of or exacerbation of)
  - Crohn’s disease (induction of or exacerbation of)
  - depression
  - diarrhoea
  - dizziness
  - drowsiness
  - fluid retention (rarely precipitating congestive heart failure)
  - gastro-intestinal bleeding
  - gastro-intestinal discomfort
  - gastro-intestinal disturbances
  - gastro-intestinal ulceration
  - haematuria
  - headache
  - hearing disturbances
  - hepatic failure
  - hepatitis
  - hypersensitivity reactions
  - insomnia
  - jaundice
  - nausea
  - nervousness
  - photosensitivity
  - raised blood pressure
  - rashes
  - renal failure (especially in patients with pre-existing renal impairment)
  - tinnitus
  - urine discoloration
  - vertigo

SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects: For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**

Use with caution during breast-feeding.

**HEPATIC IMPAIRMENT**

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**

Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21

- **Sulindac (Non-proprietary)**
  - Sulindac 100 mg Sulindac 100 mg tablets | 56 tablet £43.75
  - Sulindac 200 mg Sulindac 200 mg tablets | 56 tablet £56.25

DT price = £38.29

Tenoxicam

**INDICATIONS AND DOSE**

Pain and inflammation in musculoskeletal disorders

- **BY MOUTH**
- **Adult:** 20 mg once daily
- **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
- **Adult:** 20 mg once daily as initial treatment for 1–2 days if oral administration not possible

Pain and inflammation in acute musculoskeletal disorders

- **BY MOUTH**
- **Adult:** 20 mg once daily for 7 days; maximum duration of treatment 14 days (including treatment by intravenous or intramuscular injection)
- **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
- **Adult:** 20 mg once daily as initial treatment for 1–2 days if oral administration not possible

**CONTRA-INDICATIONS**

- Active gastro-intestinal bleeding
- active gastro-intestinal ulceration
- history of gastro-intestinal bleeding related to previous NSAID therapy
- history of gastro-intestinal perforation related to previous NSAID therapy
- history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)
- history of recurrent gastro-intestinal ulceration (two or more distinct episodes)
- severe heart failure

**CAUTIONS**

- Allergic disorders
- cardiac impairment (NSAIDs may impair renal function)
- cerebrovascular disease
- coagulation defects
- connective-tissue disorders
- Crohn’s disease (may be exacerbated)
- elderly (risk of serious side-effects and fatalities)
- heart failure
- ischaemic heart disease
- peripheral arterial disease
- risk factors for cardiovascular events
- ulcerative colitis (may be exacerbated)
- uncontrolled hypertension

**INTERACTIONS** → Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- Rare
  - Alveolitis
  - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible)
  - hepatic damage
  - interstitial fibrosis associated with NSAIDs can lead to renal failure
  - pancreatitis
  - papillary necrosis associated with NSAIDs can lead to renal failure
  - pulmonary eosinophilia
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis
  - visual disturbances

- Frequency not known
  - Angioedema
  - blood disorders
  - bronchospasm
  - cholestasis
  - colitis (induction of or exacerbation of)
  - Crohn’s disease (induction of or exacerbation of)
  - depression
  - diarrhoea
  - dizziness
  - drowsiness
  - fluid retention (rarely precipitating congestive heart failure)
  - gastro-intestinal bleeding
  - gastro-intestinal discomfort
  - gastro-intestinal disturbances
  - gastro-intestinal ulceration
  - haematuria
  - headache
  - hearing disturbances
  - hepatic failure
  - hepatitis
  - hypersensitivity reactions
  - insomnia
  - jaundice
  - nausea
  - nervousness
  - photosensitivity
  - raised blood pressure
  - rashes
  - renal failure (especially in patients with pre-existing renal impairment)
  - tinnitus
  - urine discoloration
  - vertigo

SIDE-EFFECTS, FURTHER INFORMATION

- Serious side-effects: For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
Pain and inflammation in musculoskeletal disorders

**MEDICINAL FORMS**
- Tenoxicam (Non-proprietary)

**SIDE-EFFECTS, FURTHER INFORMATION**
- Serious side-effects: For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

**ALLERGY AND CROSS-SENSITIVITY**
- Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**
- Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**
- Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**
- Use with caution during breast-feeding. Present in milk in animal studies.

**HEPATIC IMPAIRMENT**
- Use with caution; there is an increased risk of gastrointestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**
- Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tbody>
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<td>Tenoxicam (Non-proprietary)</td>
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<td>Tenoxicam 20 mg Tenoxicam 20mg tablets</td>
<td>28 tablet POk</td>
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<td>DT price</td>
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<td>Mobilfix (Meda Pharmaceuticals Ltd)</td>
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**Powder and solvent for solution for injection**

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<tbody>
<tr>
<td>Tenoxicam 20 mg Tenoxicam 20mg powder and solvent for solution for injection vials</td>
<td>1 vial POk</td>
</tr>
</tbody>
</table>

**Tiaprofenic acid**

**INDICATIONS AND DOSE**
- Pain and inflammation in rheumatic disease and other musculoskeletal disorders
  - By mouth
  - Adult: 300 mg twice daily

**SPECIAL ADVISORY INFORMATION**

**CSM ADVICE**
- Following reports of severe cystitis the CSM has recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and should be stopped if urinary symptoms develop.

- Patients should be advised to stop taking tiaprofenic acid and to report to their doctor promptly if they develop urinary-tract symptoms (such as increased frequency, nocturia, urgency, pain on urinating, or blood in urine).

**CONTRA-INDICATIONS**
- Active bladder disease (or symptoms) • active gastro-intestinal bleeding • active gastro-intestinal ulceration • active prostate disease (or symptoms) • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • history of recurrent urinary-tract disorders (if urinary symptoms develop immediately and perform urine tests and culture) • severe heart failure

**CAUTIONS**
- Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • heart failure • ischaemic heart disease • peripheral arterial disease • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated) • uncontrolled hypertension

**INTERACTIONS**
- Appendix 1 (NSAIDs).

**SIDE-EFFECTS**
- Rare
  - Alveolitis • aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • hepatic damage • interstitial fibrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances

- Frequency not known
  - Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**
- Serious side-effects: For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

**ALLERGY AND CROSS-SENSITIVITY**
- Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**
- Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**
- Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**
- Use with caution during breast-feeding. Amount too small to be harmful.

**HEPATIC IMPAIRMENT**
- Reduce dose in mild or moderate impairment. Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.
**RENAI IMPAIRMENT** Reduce dose in mild or moderate impairment. The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. Avoid in severe impairment. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDIINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
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<tr>
<th>CAUTIARY AND ADVISORY LABELS</th>
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<tr>
<td>Surgam (Sanofi)</td>
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<td>Tiaprofenic acid 300 mg</td>
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5 Soft tissue and joint disorders

5.1 Local inflammation of joints and soft tissue

Other drugs used for local inflammation of joints and soft tissue  
Betamethasone p. 618

**CORTICOSTERADS**

**Corticosteroids, inflammatory disorders**

Systemic corticosteroids

Short-term treatment with corticosteroids can help to rapidly improve symptoms of rheumatoid arthritis. Long-term treatment in rheumatoid arthritis should be considered only after evaluating the risks and all other treatment options have been considered. Corticosteroids can induce osteoporosis, and prophylaxis should be considered on long-term treatment.

In severe, possibly life-threatening, situations a high initial dose of corticosteroid is given to induce remission and the dose is then reduced gradually and discontinued altogether. Relapse may occur as the dose of corticosteroid is reduced, particularly if the reduction is too rapid. The tendency is therefore to increase the maintenance dose and consequently the patient becomes dependent on corticosteroids. For this reason pulse doses of corticosteroids (e.g. methylprednisolone p. 1012 up to 1 g intravenously on 3 consecutive days) are used to suppress highly active inflammatory disease while longer-term treatment with a disease-modifying drug is commenced.

Prednisolone p. 1012 may reduce the rate of joint destruction in moderate to severe *rheumatoid arthritis* of less than 2 years’ duration. The reduction in joint destruction must be distinguished from mere symptomatic improvement (which lasts only 6 to 12 months at this dose) and care should be taken to avoid increasing the dose above 7.5 mg daily. Evidence supports maintenance of this anti-erosive dose for 2–4 years only after which treatment should be tapered off to reduce long-term adverse effects.

A modified-release preparation of prednisone p. 623 is also available for the treatment of moderate to severe rheumatoid arthritis.

*Polymyalgia rheumatica* and *giant cell (temporal) arteritis* are always treated with corticosteroids. Relapse is common if therapy is stopped prematurely. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long-term low-dose corticosteroid treatment.

*Polyarteritis nodosa* and *polymyositis* are usually treated with corticosteroids.

*Systemic lupus erythematosus* is treated with corticosteroids when necessary using a similar dosage regimen to that for *polyarteritis nodosa* and *polymyositis*. Patients with pleurisy, pericarditis, or other systemic manifestations will respond to corticosteroids. It may then be possible to reduce the dosage; alternate-day treatment is sometimes adequate, and the drug may be gradually withdrawn. In some mild cases corticosteroid treatment may be stopped after a few months. Many mild cases of systemic lupus erythematosus do not require corticosteroid treatment. Alternative treatment with anti-inflammatory analgesics, and possibly chloroquine p. 569 or hydroxychloroquine sulfate p. 962, should be considered.

*Ankylosing spondylitis* should not be treated with long-term corticosteroids; rarely, pulse doses may be needed and may be useful in extremely active disease that does not respond to conventional treatment.

**Local corticosteroid injections**

Corticosteroids are injected locally for an anti-inflammatory effect. In inflammatory conditions of the joints, particularly in rheumatoid arthritis, they are given by *intra-articular injection* to relieve pain, increase mobility, and reduce deformity in one or a few joints; they can also provide symptomatic relief while waiting for DMARDs to take effect. Full aseptic precautions are essential; infected areas should be avoided. Occasionally an acute inflammatory reaction develops after an intra-articular or soft-tissue injection of a corticosteroid. This may be a reaction to the microcrystalline suspension of the corticosteroid used, but must be distinguished from sepsis introduced into the injection site.

Smaller amounts of corticosteroids may also be injected directly into soft tissues for the relief of inflammation in conditions such as *tennis or golfer’s elbow* or *compression neuropathies*. In *tendinitis*, injections should be made into the tendon sheath and not directly into the tendon (due to the absence of a true tendon sheath and a high risk of rupture, the Achilles tendon should not be injected).

Hydrocortisone acetate p. 1012 or one of the synthetic analogues is generally used for local injection. Intra-articular corticosteroid injections can cause flushing and may affect the hyaline cartilage. Each joint should not usually be treated more than 4 times in one year.

Corticosteroid injections are also injected into soft tissues for the treatment of skin lesions.

**Dexamethasone**

06-Jun-2016

**INDICATIONS AND DOSE**

**Local inflammation of joints**

° BY INTRA-ARTICULAR INJECTION

° Adult: 0.3–3.3 mg, where appropriate, dose may be repeated at intervals of 3–21 days according to response, dose given according to size—consult product literature

**Local inflammation of soft tissues**

° BY LOCAL INFILTRATION

° Adult: 1.7–5 mg, dose given according to size—consult product literature, where appropriate may be repeated at intervals of 3–21 days, use the 3.3 mg/mL injection preparation for this dose

**PREGNANCY** Dexamethasone readily crosses the placenta.

**PREScribing and dispensing information**

Dexamethasone 3.8 mg/mL. Injection has replaced Dexamethasone 4 mg/mL. Injection. All dosage recommendations for intravenous, intramuscular,
intra-articular use or local infiltration are given in units of dexamethasone base.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**CAUTIONARY AND ADVISORY LABELS 10**

- **Dexamethasone (Non-proprietary)**
  - Dexamethasone (as Dexamethasone sodium phosphate) 3.3 mg per 1 ml Dexamethasone 6.6mg/2ml solution for injection vials | 5 vial £24.00 DT price = £24.00
  - Dexamethasone 6.6mg/2ml solution for injection ampoules | 5 ampoule £11.00 DT price = £11.00
  - Dexamethasone 3.3mg/1ml solution for injection ampoules | 5 ampoule £12.00 | 10 ampoule £12.00
  - Dexamethasone (as Dexamethasone sodium phosphate) 3.8 mg per 1 ml Dexamethasone 3.8mg/1ml solution for injection vials | 10 vial £19.99 DT price = £19.99

**Hydrocortisone**

- **INDICATIONS AND DOSE**

  **HYDROCORTISONE**

  **Local inflammation of joints and soft-tissues**

  ▶ **BY INTRA-ARTICULAR INJECTION**

  - Adult: 5–50 mg, select dose according to size of patient and joint; where appropriate dose may be repeated at intervals of 21 days. Not more than 3 joints should be treated on any one day, for details consult product literature

  **Suspension for injection**

  ▶ **Hydrocortisone (AMCo)**

  Hydrocortisone acetate 25 mg per 1 ml Hydrocortisone 25mg/1ml suspension for injection ampoules | 10 ampoule £68.72 DT price = £68.72

**Methylprednisolone with lidocaine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, methylprednisolone above, lidocaine hydrochloride p. 97.

- **INDICATIONS AND DOSE**

  **Local inflammation of joints**

  ▶ **BY INTRA-ARTICULAR INJECTION**

  - Adult: 4–80 mg, dose adjusted according to size; where appropriate may be repeated at intervals of 7–35 days, for details consult product literature

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Depo-Medrone with Lidocaine (Pfizer Ltd)**

  Lidocaine hydrochloride 10 mg per 1 ml, MethyLPrednisolone acetate 40 mg per 1 ml Depo-Medrone with Lidocaine suspension for injection 2ml vials | 1 vial £7.06 DT price = £7.06 | 10 vial £70.13
  - Depo-Medrone with Lidocaine suspension for injection 1ml vials | 1 vial £3.94 DT price = £3.94 | 10 vial £38.88

**Prednisolone**

- **INDICATIONS AND DOSE**

  **DELTASTAB**

  **Local inflammation of joints**

  ▶ **BY INTRA-ARTICULAR INJECTION**

  - Adult: 5–25 mg, dose according to size; not more than 3 joints should be treated on any one day; where appropriate may be repeated when relapse occurs, for details consult product literature

  **PREGNANCY**

  As it crosses the placenta 88% of prednisolone is inactivated.

  **BREAST FEEDING**

  Prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Deltastab (AMCo)**

  Prednisolone acetate 25 mg per 1 ml Deltastab 25mg/1ml suspension for injection ampoules | 10 ampoule £68.72

**Triamcinolone acetonide**

- **INDICATIONS AND DOSE**

  **ADCOR TYL INTRA-ARTICULAR/INTRADERMAL**

  **Local inflammation of joints and soft tissues**

  ▶ **BY INTRA-ARTICULAR INJECTION**

  - Adult: 2.5–15 mg, adjusted according to size (for larger doses use Kenalog®). Where appropriate dose may be repeated when relapse occurs, for details consult product literature.

  ▶ **BY INTRADERMAL INJECTION**

  - Adult: 2–3 mg, max. 5 mg at any one site (total max. 30 mg). Where appropriate may be repeated at intervals of 1–2 weeks, for details consult product literature

  **KENALOG® VIALS**

  **Local inflammation of joints and soft tissues**

  ▶ **BY INTRA-ARTICULAR INJECTION**

  - Adult: 5–40 mg (max. per dose 80 mg), for further details consult product literature, select dose according
to size. For doses below 5 mg use Adcortyl® Intra-articular/Intradermal injection, where appropriate dose may be repeated when relapse occurs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

CAUTIONARY AND ADVISORY LABELS 10 EXCPIENTS: May contain Benzyl alcohol

- Adcortyl Intra-articular / Intradermal (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Triamcinolone acetonide 10 mg per 1 ml Adcortyl Intra-articular / Intradermal 50mg/5ml suspension for injection vials | 1 vial (Pom) £3.63
  - Adcortyl Intra-articular / Intradermal 10mg/1ml suspension for injection ampoules | 5 ampoules (Pom) £4.47 DT price = £4.47
- Kenalog (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Triamcinolone acetonide 40 mg per 1 ml Kenalog Intra-articular / Intramuscular 40mg/1ml suspension for injection vials | 5 vial (Pom) £7.45 DT price = £7.45

**Triamcinolone hexacetonide**

**INDICATIONS AND DOSE**

Local inflammation of joints and soft-tissues (for details, consult product literature)

- **BY INTRA-ARTICULAR INJECTION**
  - Adult: 2–20 mg, adjusted according to size of joint, no more than 2 joints should be treated on any one day, where appropriate, may be repeated at intervals of 3–4 weeks
- **BY PERI-ARTICULAR INJECTION**
  - Adult: 10–20 mg, adjusted according to size of joint, no more than 2 joints should be treated on any one day

**CONTRA-INDICATIONS** Consult product literature

**CAUTIONS** Consult product literature

**SIDE-EFFECTS** Consult product literature

**PRESCRIBING AND DISPENSING INFORMATION** Various strengths available from ‘special order’ manufacturers or specialist importing companies.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

EXCPIENTS: May contain Benzyl alcohol

- Triamcinolone hexacetonide (Non-proprietary)
  - Triamcinolone hexacetonide 20 mg per 1 ml Triamcinolone hexacetonide 20mg/1ml suspension for injection ampoules | 10 ampoule (Pom) £120.00

5.2 Soft tissue disorders

**Soft-tissue disorders**

**Extravasation**

Local guidelines for the management of extravasation should be followed where they exist or specialist advice sought.

Extravasation injury follows leakage of drugs or intravenous fluids from the veins or inadvertent administration into the subcutaneous or subdermal tissue. It must be dealt with promptly to prevent tissue necrosis.

Acidic or alkaline preparations and those with an osmolarity greater than that of plasma can cause extravasation injury; excipients including alcohol and polyethylene glycol have also been implicated. Cytotoxic drugs commonly cause extravasation injury. In addition, certain patients such as the very young and the elderly are at increased risk. Those receiving anticoagulants are more likely to lose blood into surrounding tissues if extravasation occurs, while those receiving sedatives or analgesics may not notice the early signs or symptoms of extravasation.

**Prevention of extravasation**

Precautions should be taken to avoid extravasation; ideally, drugs likely to cause extravasation injury should be given through a central line and patients receiving repeated doses of hazardous drugs peripherally should have the cannula resited at regular intervals. Attention should be paid to the manufacturers’ recommendations for administration.

Placing a glyceryl trinitrate patch p. 207 distal to the cannula may improve the patency of the vessel in patients with small veins or in those whose veins are prone to collapse.

Patients should be asked to report any pain or burning at the site of injection immediately.

**Management of extravasation**

If extravasation is suspected the infusion should be stopped immediately but the cannula should not be removed until after an attempt has been made to aspirate the area (through the cannula) in order to remove as much of the drug as possible. Aspiration is sometimes possible if the extravasation presents with a raised bleb or blister at the injection site and is surrounded by hardened tissue, but it is often unsuccessful if the tissue is soft or soggy.

**Corticosteroids** are usually given to treat inflammation, although there is little evidence to support their use in extravasation. Hydrocortisone p. 1012 or dexamethasone p. 1011 can be given either locally by subcutaneous injection or intravenously at a site distant from the injury.

**Antihistamines** and **analgesics** may be required for symptom relief.

The management of extravasation beyond these measures is not well standardised and calls for specialist advice. Treatment depends on the nature of the offending substance; one approach is to localise and neutralise the substance whereas another is to spread and dilute it.

The first method may be appropriate following extravasation of vesicant drugs and involves administration of an antidote (if available) and the application of cold compresses 3–4 times a day (consult specialist literature for details of specific antidotes). Spreading and diluting the offending substance involves infiltrating the area with physiological saline, applying warm compresses, elevating the affected limb, and administering hyaluronidase p. 1014. A saline flush-out technique (involving flushing the subcutaneous tissue with physiological saline) may be effective but requires specialist advice. Hyaluronidase should not be administered following extravasation of vesicant drugs (unless it is either specifically indicated or used in the saline flush-out technique). Dextrazoxane p. 837 is licensed for the treatment of anthracycline-induced extravasation.

**Enzymes**

**Collagenase**

Collagenase p. 1014 are proteolytic enzymes that are derived from the fermentation of Clostridium histolyticum and have the ability to break down collagen. A preparation containing a mixture of two collagenases is licensed for the treatment of Dupuytren’s contracture; the preparation should be injected into a palpable cord with a contracture of a metacarpophalangeal joint or proximal interphalangeal joint.

**Hyaluronidase**

Hyaluronidase is used to render the tissues more readily permeable to injected fluids, e.g. for introduction of fluids by subcutaneous infusion (termed hypodermoclysis).
Rubefacients, topical NSAIDs, capsaicin, and poulitics

Rubefacients act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method that itself produces irritation of the skin. Topical rubefacient preparations may contain nicotinate and salicylate compounds, essential oils, capsicum, and camphor. The evidence available does not support the use of topical rubefacients in acute or chronic musculoskeletal pain.

Topical NSAIDs
The use of a NSAID by mouth is effective for relieving musculoskeletal pain. Topical NSAIDs (e.g. felibac p. 997, ibuprofen p. 999, ketoprofen p. 1002, and piroxicam p. 1007 may provide some relief of pain in musculoskeletal conditions; they can be considered as an adjunctive treatment in knee or hand osteoarthritis.

Capsaicin
A preparation containing capsaicin 0.025% p. 446 can be considered as an adjunct in hand or knee osteoarthritis. It may need to be used for 1–2 weeks before pain is relieved.

A capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia after lesions have healed, and for the relief of painful diabetic neuropathy.

A self-adhesive patch containing capsaicin 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients.

ENZYMES

Collagenase

**INDICATIONS AND DOSE**

Dupuytren's contracture in patients with a palpable cord

- **BY INTRALESIONAL INJECTION**
  - Adult: 580 micrograms, then 580 micrograms every 4 weeks if required, inject into palpable cord, maximum 3 injections per cord, maximum 8 injections in total and only one cord may be treated at a time

**CONTRA-INDICATIONS**
Avoid injecting into other structures containing collagen (e.g. tendons, nerves, and blood vessels)—risk of tendon rupture or ligament damage

**CAUTIONS**
Coagulation disorders - use of anticoagulants

**SIDE-EFFECTS**

- **Common or very common** Arthralgia - burning sensation - ecchymosis - hyperhidrosis - hypoesthesia - injection site reactions - joint swelling - lymphadenopathy - myalgia - paraesthesia

- **Uncommon** Complex regional pain syndrome - crepitus - ligament injury - monoplegia - muscle spasm - muscle weakness - tendon rupture - tremor - wound dehiscence

**PREGNANCY**
Manufacturer advises avoid.

**BREAST FEEDING**
Systemic absorption by mother negligible.

**DIRECTIONS FOR ADMINISTRATION**
Reconstitution and injected volumes vary with site of injection—consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium (SMC) has advised (April 2012) that collagenase Clostridium histolyticum (Xiapex®) is accepted for restricted use within NHS Scotland as an alternative to limited fasciectomy, for the treatment of Dupuytren's contracture of moderate severity (as defined by the British Society for Surgery of the Hand) in patients with a palpable cord and up to two affected joints per hand, who are suitable for limited fasciectomy, but for whom percutaneous needle fasciectomy is not considered a suitable treatment option.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- **Xiapex (Swedish Orphan Biovitrum Ltd)**
  - Collagenase clostridium histolyticum 900 microgram
  - Xiapex 0.5mg powder and solvent for solution for injection vials | 1 vial [POM] £650.00

Hyaluronidase

**INDICATIONS AND DOSE**

Enhance permeation of subcutaneous or intramuscular injections

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 1500 units, to be dissolved directly into the solution to be injected (ensure compatibility)

Enhance permeation of local anaesthetics

- **BY LOCAL INFILTRATION**
  - Adult: 1500 units, to be mixed with the local anaesthetic solution

Enhance permeation of ophthalmic local anaesthetic

- **TO THE EYE**
  - Adult: 15 units/mL, to be mixed with the local anaesthetic solution

Hypodermolysis

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride and infiltrated into affected area as soon as possible after extravasation

Haematoma

- **BY LOCAL INFILTRATION**
  - Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride and infiltrated into affected area

**CONTRA-INDICATIONS**
Avoid sites where infection is present - avoid sites where malignancy is present - do not apply direct to cornea - not for anaesthesia in unexplained premature labour - not for intravenous administration - not to be used to enhance the absorption and dispersion of dopamine and/or alpha-adrenoceptor agonists - not to be used to reduce swelling of bites - not to be used to reduce swelling of stings

**CAUTIONS**
Elderly (control speed and total volume and avoid overhydration especially in renal impairment)

**SIDE-EFFECTS**

- **Common or very common** Oedema
- **Rare** Bleeding - bruising - infection - local irritation
- **Frequency not known** Anaphylaxis - severe allergy

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- Hyaluronidase (Non-proprietary)
  - Hyaluronidase 1500 unit
  - Hyaluronidase 1,500unit powder for solution for injection ampoules | 10 ampoule [POM] £136.55
Chapter 11
Eye

Administration of drugs to the eye

Drugs are most commonly administered to the eye by topical application as eye drops or eye ointments. When a higher drug concentration is required within the eye, a local injection may be necessary.

Eye-drop dispenser devices are available to aid the instillation of eye drops from plastic bottles and some are prescribable on the NHS (consult Drug Tariff—see Appliances and Reagents). Product-specific devices may be supplied by manufacturers—consult individual manufacturers for information. They are particularly useful for the elderly, visually impaired, arthritic, or otherwise physically limited patients.

Eye drops and eye ointments

Eye drops are generally instilled into the pocket formed by gently pulling down the lower eyelid and keeping the eye closed for as long as possible after application; one drop is all that is needed. Instillation of more than one drop should be discouraged because it may increase systemic side-effects. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eye-drop preparations are used at the same time of day, dilution and overflow may occur when one immediately follows the other. The patient should therefore leave an interval of at least 5 minutes between the two; the interval should be extended when eye drops with a prolonged contact time, such as gels and suspensions, are used. Eye ointment should be applied after drops.

Systemic effects may arise from absorption of drugs into the general circulation from conjunctival vessels or from the nasal mucosa after the excess preparation has drained down the tear ducts. The extent of systemic absorption following ocular administration is highly variable; nasal drainage of drugs is associated with eye drops much more often than with eye ointments. Pressure on the lacrimal punctum for at least a minute after applying eye drops reduces nasolacrimal drainage and therefore decreases systemic absorption from the nasal mucosa.

After using eye drops or eye ointments, patients should be warned not to drive or perform other skilled tasks until vision is clear.

Also see warnings relating to eye drops and contact lenses.

Eye lotions

These are solutions for the irrigation of the conjunctival sac. They act mechanically to flush out irritants or foreign bodies as a first-aid treatment. Sterile sodium chloride 0.9% p. 1026 solution is usually used. Clean water will suffice in an emergency.

Other preparations administered to the eye

Subconjunctival injection may be used to administer anti-infective drugs, mydriatics, or corticosteroids for conditions not responding to topical therapy; intracameral and intravitreal routes can also be used to administer certain drugs, for example antibacterials. These injections should only be used under specialist supervision.

Drugs such as antimicrobials and corticosteroids may be administered systemically to treat susceptible eye conditions.

Ophthalmic Specials

Certain eye drops, e.g. amphotericin, ceftazidime, cefuroxime, colistimethate sodium, desferrioxamine mesilate, dexamethasone, gentamicin, and vancomycin can be prepared aseptically from material supplied for injection.

The Royal College of Ophthalmologists and the UK Ophthalmic Pharmacy Group have produced the Ophthalmic Specials Guidance to help prescribers and pharmacists manage and restrict the use of unlicensed eye preparations. 'Specials' should only be prescribed in situations where a licensed product is not suitable for a patient’s needs. The Ophthalmic Specials Guidance can be accessed on the Royal College of Ophthalmologists website (www.rcophth.ac.uk).

The guidance will be reviewed every six months to ensure the most accurate and up-to-date information is available.

Preservatives and sensitisers

Information on preservatives and substances identified as skin sensitisers is provided under Excipients statements in preparation entries. Very rarely, cases of corneal calcification have been reported with the use of phosphate-containing eye drops in patients with significantly damaged corneas—consult product literature for further information.

Control of microbial contamination

Preparations for the eye should be sterile when issued. Care should be taken to avoid contamination of the contents during use.

Eye drops in multiple-application containers for domiciliary use should not be used for more than 4 weeks after first opening (unless otherwise stated by the manufacturer).

Multiple application eye drops for use in hospital wards are
normally discarded 1 week after first opening—local practice may vary. Individual containers should be provided for each patient. A separate container should be supplied for each eye only if there are special concerns about contamination. Containers used before an eye operation should be discarded at the time of the operation and fresh containers supplied postoperatively. A fresh supply should also be provided upon discharge from hospital; in specialist ophthalmology units, it may be acceptable to issue containers that have been dispensed to the patient on the day of discharge.

In out-patient departments single-application containers should be used; if multiple-application containers are used, they should be discarded after single patient use within one clinical session.

In eye surgery single-application containers should be used if possible; if a multiple-application container is used, it should be discarded after single use. Preparations used during intra-ocular procedures and others that may penetrate into the anterior chamber must be isotonic and without preservatives and buffered if necessary to a neutral pH. Specially formulated fluids should be used for intra-ocular surgery; intravenous infusion preparations are not usually suitable for this purpose (Hartmann’s solution may be used in some ocular surgery). For all surgical procedures, a previously unopened container is used for each patient.

Contact lenses

For cosmetic reasons many people prefer to wear contact lenses rather than spectacles; contact lenses are also sometimes required for medical indications. Visual defects are corrected by either rigid (‘hard’ or gas permeable) lenses or soft (hydrogel or silicone hydrogel—in adults only) lenses; soft lenses are the most popular type, because they are initially the most comfortable, but they may not give the best vision. Lenses should usually be worn for a specified number of hours each day and removed for sleeping. The risk of infectious and non-infectious keratitis is increased by extended continuous contact lens wear, which is not recommended, except when medically indicated.

Contact lenses require meticulous care. Poor compliance with directions for use, and with daily cleaning and disinfection, can result in complications including ulcerative keratitis or conjunctivitis. One-day disposable lenses, which are worn only once and therefore require no disinfection or cleaning, are becoming increasingly popular.

Acanthamoeba keratitis, a painful and sight-threatening condition, is associated with ineffective lens cleaning and disinfection, the use of contaminated lens cases, or tap water coming into contact with the lenses. The condition is especially associated with the use of soft lenses (including frequently replaced lenses) and should be treated by specialists.

Contact lenses and drug treatment

Special care is required in prescribing eye preparations for contact lens users. Some drugs and preservatives in eye preparations can accumulate in hydrogel lenses and may induce toxic and adverse reactions. Therefore, unless medically indicated, the lenses should be removed before instillation of the eye preparation and not worn during the period of treatment. Alternatively, unpreserved drops can be used. Eye drops may, however, be instilled while patients are wearing rigid corneal contact lenses. Ointment preparations should never be used in conjunction with contact lens wear; oily eye drops should also be avoided.

Many drugs given systemically can also have adverse effects on contact lens wear. These include oral contraceptives (particularly those with a higher oestrogen content), drugs which reduce blink rate (e.g. anxiolytics, hypnotics, antihistamines, and muscle relaxants), drugs which reduce lacrimation (e.g. antihistamines, antimuscarinics, phenothiazines and related drugs, some beta-blockers, diuretics, and tricyclic antidepressants), and drugs which increase lacrimation (including ephedrine hydrochloride p. 254 and hydralazine hydrochloride p. 171). Other drugs that may affect contact lens wear are isotretinoin p. 1122 (can cause conjunctival inflammation), aspirin p. 114 (salicylic acid appears in tears and can be absorbed by contact lenses—leading to irritation), and rifampicin p. 535 and sulfasalazine p. 39 (can discolour lenses).

1 Allergic and inflammatory eye conditions

Eye, allergy and inflammation

Corticosteroids

Corticosteroids administered locally to the eye or given by mouth are effective for treating anterior segment inflammation, including that which results from surgery. Topical corticosteroids are applied frequently for the first 24–48 hours; once inflammation is reduced, the frequency of application is reduced. They should normally only be used under expert supervision; three main dangers are associated with their use:

- a ‘red eye’, when the diagnosis is unconfirmed, may be due to herpes simplex virus, and a corticosteroid may aggravate the condition, leading to corneal ulceration, with possible damage to vision and even loss of the eye.
- Bacterial, fungal, and amoebic infections pose a similar hazard;
- a ‘steroid glaucoma’ can follow the use of corticosteroid eye preparations in susceptible individuals;
- a ‘steroid cataract’ can follow prolonged use.

Combination products containing a corticosteroid with an anti-infective drug are sometimes used after ocular surgery to reduce inflammation and prevent infection; use of combination products is otherwise rarely justified.

Systemic corticosteroids may be useful for ocular conditions. The risk of producing a ‘steroid cataract’ increases with the dose and duration of corticosteroid use.

Intravitreal corticosteroids

An intravitreal implant containing dexamethasone p. 1019 (Ozurdex®) is licensed for the treatment of adults with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion; it is also licensed for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

An intravitreal implant containing fluocinolone acetonide p. 1048 (Fluiven®) is licensed for the treatment of visual impairment associated with chronic diabetic macular oedema which is insufficiently responsive to available therapies. It should be administered by specialists experienced in the use of intravitreal injections.

Other anti-inflammatory preparations

Other preparations used for the topical treatment of inflammation and allergic conjunctivitis include antihistamines, lodoxamide p. 1018, and sodium cromoglicate p. 1018.

Eye drops containing antihistamines, such as antazoline (with xylometazoline hydrochloride p. 1057 as Otrivine–Antistin®), azelastine hydrochloride p. 1017, epinastine hydrochloride p. 1017, ketotifen p. 1017, and olopatadine p. 1018, can be used for allergic conjunctivitis.

Sodium cromoglicate (sodium cromoglycate) and nedocromil sodium p. 1018 eye drops can be useful for vernal
keratoconjunctivitis and other allergic forms of conjunctivitis. Lodocamide eye drops are used for allergic conjunctival conditions including seasonal allergic conjunctivitis. Diclofenac sodium eye drops p. 1034 and edemastine eye drops below are also licensed for seasonal allergic conjunctivitis. Non-steroidal anti-inflammatory eye drops are used for the prophylaxis and treatment of inflammation of the eye following surgery or laser treatment. Ciclosporin p. 1022 is licensed for severe keratitis in patients with dry eye disease, which has not improved despite treatment with tear substitutes.

### 1.1 Allergic conjunctivitis

#### Antihistamines

**Antazoline with xylometazoline**

- **INDICATIONS AND DOSE**
  - **Allergic conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply 2–3 times a day for maximum 7 days
    - Adult: Apply 2–3 times a day for maximum 7 days

- **CAUTIONS**
  - Angle-closure glaucoma, cardiovascular disease, diabetes mellitus, hypertension, hyperthyroidism, phaeochromocytoma, urinary retention

- **INTERACTIONS**
  - Appendix 1 (antihistamines and sympathomimetics). Absorption of antazoline and xylometazoline may result in the possibility of interaction with other drugs.

- **SIDE-EFFECTS**
  - Common or very common: Transient stinging
  - Frequency not known: Bitter taste, mild transient irritation

  **SIDE-EFFECTS, FURTHER INFORMATION**

  Absorption of antazoline and xylometazoline may result in systemic side-effects.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
    - **Otrivine Antistin** (Thea Pharmaceuticals Ltd)
      - Antazoline sulphate 5 mg per 1 ml, Xylometazoline hydrochloride 500 microgram per 1 ml Otrivine Antistin 0.5%/0.09% eye drops | 10 ml P | £3.35 DT price = £3.35

**Azelastine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 4-17 years: Apply twice daily, increased if necessary to 4 times a day
    - Adult: Apply twice daily, increased if necessary to 4 times a day
  - **Perennial conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply twice daily; increased if necessary to 4 times a day, maximum duration of treatment 6 weeks
    - Adult: Apply twice daily; increased if necessary to 4 times a day, maximum duration of treatment 6 weeks

- **SIDE-EFFECTS**
  - Frequency not known: Bitter taste, mild transient irritation

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
    - **Optilast** (Meda Pharmaceuticals Ltd)
      - Azelastine hydrochloride 500 microgram per 1 ml Optilast 0.05% eye drops | 8 ml P | £6.40 DT price = £6.40

**Emedastine**

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 3-17 years: Apply twice daily
    - Adult: Apply twice daily

- **SIDE-EFFECTS**
  - Blurred vision, corneal infiltrates (discontinue), corneal staining, dry eye, headache, irritation, keratitis, lacrimation, local oedema, photophobia, rhinitis, transient burning, transient stinging

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - EXCIPIENTS: May contain Benzalkonium chloride
    - **Emadine** (Alcon Laboratories (UK) Ltd)
      - Emedastine (as Emedastine difumarate) 500 microgram per 1 ml Emadine 0.5mg/ml eye drops | 5 ml P | £7.31 DT price = £7.31

**Epinastine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply twice daily for maximum 8 weeks
    - Adult: Apply twice daily for maximum 8 weeks

- **SIDE-EFFECTS**
  - Common or very common: Burning
  - Uncommon: Conjunctival hyperaemia, dry eye, eye pain, eye pruritus, headache, increased lacrimation, nasal irritation, rhinitis, taste disturbance, visual disturbance

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - EXCIPIENTS: May contain Benzalkonium chloride
    - **Relestat** (Allergan Ltd)
      - Epinastine hydrochloride 500 microgram per 1 ml Relestat 500 micrograms/ml eye drops | 5 ml P | £9.90 DT price = £9.90

**Ketotifen**

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 3-17 years: Apply twice daily
    - Adult: Apply twice daily

- **INTERACTIONS**
  - Interactions do not generally apply to antihistamines used for topical action.
Nedocromil sodium

- **INDICATIONS AND DOSE**
  - **Seasonal and perennial conjunctivitis**
    - **TO THE EYE**
    - Child 6-17 years: Apply twice daily, increased if necessary to 4 times a day, max. 12 weeks duration of treatment for seasonal allergic conjunctivitis
    - Adult: Apply twice daily, increased if necessary to 4 times a day, max. 12 weeks duration of treatment for seasonal allergic conjunctivitis
  - **Seasonal keratoconjunctivitis**
    - **TO THE EYE**
    - Child 6-17 years: Apply 4 times a day
    - Adult: Apply 4 times a day

- **SIDE-EFFECTS**
  - Distinctive taste • transient burning • transient stinging

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - EXCIPIENTS: May contain Benzalkonium chloride
    - Zaditen (Thea Pharmaceuticals Ltd)
      - Zaditen (as Ketotifen fumarate) 250 microgram per 1 ml Zaditen 250 micrograms/ml eye drops | 5 ml [POM] £7.80 DT price = £7.80
    - Opatanol (Alcon Laboratories (UK) Ltd)
      - Opatanol (as Opatanol hydrochloride) 1 mg per 1 ml Opatanol 1mg/ml eye drops | 5 ml [POM] £4.68 DT price = £4.68

Mast-cell stabilisers

- **Lodoxamide**
  - **INDICATIONS AND DOSE**
    - **Seasonal allergic conjunctivitis**
      - **TO THE EYE**
      - Child 3-17 years: Apply twice daily for maximum 4 months
      - Adult: Apply twice daily for maximum 4 months
  - **SIDE-EFFECTS**
    - Local irritation
    - Asthenia • dizziness • dry eye • headache • keratitis • local oedema • photophobia
    - Dry mouth • transient burning • transient stinging
    - Distinctive taste
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
      - Optrex Allergy
        - Sodium cromoglicate 20 mg per 1 ml Optrex Allergy 2% eye drops | 10 ml [POM] £3.57 DT price = £3.35
      - Opticrom Aqueous
        - Sodium cromoglicate 20 mg per 1 ml Opticrom Aqueous 2% eye drops | 10 ml [POM] £3.35 DT price = £3.35
      - Trometamol
        - Sodium cromoglicate 20 mg per 1 ml Trometamol 2% eye drops | 10 ml [POM] £3.35 DT price = £3.35
  - **Exceptions to Legal Category**
    - Sodium cromoglicate 2% eye drops can be sold to the public (in max. pack size of 10 ml) for treatment of acute seasonal and perennial allergic conjunctivitis.
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - Sodium cromoglicate (Non-proprietary)
        - Sodium cromoglicate 20 mg per 1 ml Sodium cromoglicate 2% eye drops | 13.5 ml [POM] £8.03 DT price = £1.72
      - Catacrom (Moornfields Pharmaceuticals)
        - Sodium cromoglicate 20 mg per 1 ml Catacrom 2% eye drops 0.3ml unit dose | 30 unit dose [P] £8.99 DT price = £8.99
      - Cromolux (Tublux Pharma Ltd)
        - Sodium cromoglicate 20 mg per 1 ml Cromolux 2% eye drops | 13.5 ml [POM] £3.20 DT price = £1.72
      - Opticrom (Sanofi)
        - Sodium cromoglicate 20 mg per 1 ml Opticrom Allergy 2% eye drops | 5 ml [P] £2.74 | 10 ml [P] £3.35
        - Opticrom Aqueous 2% eye drops | 13.5 ml [POM] £8.03 DT price = £1.72
      - Optrex Allergy (Reckitt Benckiser Healthcare (UK) Ltd)
        - Sodium cromoglicate 20 mg per 1 ml Optrex Allergy 2% eye drops | 10 ml [P] £3.88
      - Pollenase (sodium cromoglicate) (E M Pharma)
        - Sodium cromoglicate 20 mg per 1 ml Pollenase Allergy 2% eye drops | 10 ml [P] £2.08
      - Vividrin (Bausch & Lomb UK Ltd)
        - Sodium cromoglicate 20 mg per 1 ml Vividrin 2% eye drops | 13.5 ml [POM] £10.95 DT price = £1.72

Sodium cromoglicate (Sodium cromoglycate)

- **INDICATIONS AND DOSE**
  - **Allergic conjunctivitis | Seasonal keratoconjunctivitis**
    - **TO THE EYE**
    - Child: Apply 4 times a day
    - Adult: Apply 4 times a day
  - **SIDE-EFFECTS**
    - Transient burning • transient stinging
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops
1.2 Inflammatory eye conditions

**ANALGESICS > NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

**Nepafenac**

- **INDICATIONS AND DOSE**
  
  Prophylaxis and treatment of postoperative pain and inflammation associated with cataract surgery
  
  - **Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients**
  
  - **TO THE EYE**
  
  - **Adul:** (consult product literature)

- **CAUTIONS**
  
  Avoid sunlight - corneal epithelial breakdown (if evidence of, then discontinue immediately)

- **SIDE-EFFECTS**
  
  - **Common or very common**
    
    Punctate keratitis
  
  - **Uncommon**
    
    Allergic conjunctivitis - blurred vision - choroidal effusion - conjunctival hyperaemia - corneal deposits - corneal epithelium defect - dry eye - eye pruritus - headache - increased lacrimation - iritis - keratitis - nausea - ocular discomfort - photophobia
  
  - **Frequency not known**
    
    Corneal opacity - dermatochalasis - dizziness - eye swelling - impaired corneal healing - reduced visual acuity

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**

  - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
  
  - **Nepafenac** (Focus Pharmaceuticals Ltd)
    
    Nepafenac 1 mg per 1 ml
    
    Nevanac 1 mg/ml eye drops | 5 ml [Pos] £14.92

**CORTICOSTEROIDS**

**Betamethasone**

- **INDICATIONS AND DOSE**
  
  **Local treatment of inflammation (short-term)**

  - **TO THE EYE USING EYE DROP**
  
  - **Child:** Apply every 1–2 hours until controlled then reduce frequency
  
  - **Adult:** Apply every 1–2 hours until controlled then reduce frequency
  
  - **TO THE EYE USING EYE OINTMENT**
  
  - **Child:** Apply 2–4 times a day, alternatively apply at night when used in combination with eye drops
  
  - **Adult:** Apply 2–4 times a day, alternatively apply at night when used in combination with eye drops

- **SIDE-EFFECTS**
  
  Corneal thinning - scleral thinning

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Ear/eye/nose drops solution**

  - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
  
  - **Betamethasone (Non-proprietary)**
    
    Betamethasone sodium phosphate 1 mg per 1 ml Betamethasone 0.1% eye/ear/nose drops | 5 ml [Pos] no price available
  
  - **Betnesol (Focus Pharmaceuticals Ltd)**
    
    Betamethasone sodium phosphate 1 mg per 1 ml Betnesol 0.1% eye/ear/nose drops | 10 ml [Pos] £2.32 DT price = £2.32
  
  - **Vistamethasone (Martindale Pharmaceuticals Ltd)**
    
    Betamethasone sodium phosphate 1 mg per 1 ml Vistamethasone 0.1% eye/ear/nose drops | 5 ml [Pos] £0.87 | 10 ml [Pos] £0.99 DT price = £2.32

**Dexamethasone**

- **INDICATIONS AND DOSE**
  
  **Local treatment of inflammation (short-term)**

  - **TO THE EYE USING EYE DROP**
  
  - **Child:** Apply 4–6 times a day
  
  - **Adult:** Apply every 30–60 minutes until controlled, then reduced to 4–6 times a day

  **Short term local treatment of inflammation (severe conditions)**

  - **TO THE EYE USING EYE DROP**
  
  - **Child:** Apply every 30–60 minutes until controlled, reduce frequency when control achieved

- **CAUTIONS**
  
  - **Macular oedema following either branch retinal vein occlusion or central retinal vein occlusion (specialist use only)**
    
    Visual impairment due to diabetic macular oedema in adults who are pseudophakic, or who are insufficiently responsive to, or unsuitable for non-corticosteroid therapy (specialist use only)

  - **For the treatment of inflammation of the posterior segment of the eye presenting as non-infectious uveitis (specialist use only)**

  - **BY INTRAVITREAL INJECTION**
  
  - **Adult:** 700 micrograms, to be administered into the affected eye, concurrent administration to both eyes not recommended. For further information on pre-treatment, administration and repeat dosing, consult product literature

- **UNLICENSED USE**

  - **Maxidex®** not licensed for use in children under 2 years. **Dropeedex®** not licensed for use in children.

- **CONTRA-INDICATIONS**

  - **With intravitreal use**
    
    Active ocular herpes simplex - active or suspected ocular infection - active or suspected periocular infection - rupture of the posterior lens capsule in patients with aphakia, iris or transcleral fixated intra-ocular lens or anterior chamber intra-ocular lens - uncontrolled advanced glaucoma

- **CAUTIONS**

  - **With intravitreal use**
    
    History of ocular viral infection (including herpes simplex) - posterior capsule tear or iris defect (risk of implant migration into the anterior chamber which may cause corneal oedema and, in persistent severe cases, the need for corneal transplantation) - retinal vein occlusion with significant retinal ischaemia

- **INTERACTIONS**

  - **With intravitreal use**
    
    Caution with concomitant administration of anticoagulant or antiplatelet drugs—increased risk of haemorrhagic events.

- **SIDE-EFFECTS**

  - **Uncommon**

    - **With intravitreal use**
      
      Eyelid pruritus - glaucoma - migraine - necrotising retinitis
    
  - **Frequency not known**

    - **When used by eye**
      
      Corneal thinning - scleral thinning
    
  - **With intravitreal use**

    - **Blepharitis - cataract - headache - ocular hypertension - raised intra-ocular pressure - secondary ocular infection - visual disturbance

- **PREGNANCY**

  - **Dexamethasone readily crosses the placenta.**

  - **With intravitreal use**
    
    Manufacturer advises avoid unless potential benefit outweighs risk—no information available.
**MEDICINAL FORMS**

- **Dexamethasone intravitreal implant for treating diabetic macular oedema (July 2015) NICE TA349**
  - Dexamethasone intravitreal implant is recommended as an option for treating diabetic macular oedema only if:
    - the implant is to be used in an eye with an intraocular (pseudophakic) lens and
    - the diabetic macular oedema does not respond to non-corticosteroid treatment, or such treatment is unsuitable.
  - www.nice.org.uk/TA349

**Scottish Medicines Consortium (SMC) Decisions**

The *Scottish Medicines Consortium* has advised (May 2012) that dexamethasone intravitreal implant (Ozurdex®) is accepted for restricted use within NHS Scotland for the treatment of adults with macular oedema (i) following central retinal vein occlusion, and (ii) with branch retinal vein occlusion who are not clinically suitable for laser treatment, including patients with dense macular haemorrhage, or patients who have received and failed on previous laser treatment.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

- **Dexmedetomidine (Non-proprietary)**
  - Dexamethasone sodium phosphate 1 mg per 1 ml
    - Dexamethasone 0.1% eye drops 0.4ml unit dose preservative free | 20 unit dose (Pom) £3.75 DT price = £3.75
    - Dexafree (Thea Pharmaceuticals Ltd)
      - Dexamethasone sodium phosphate 1 mg per 1 ml
        - Dexafree 1mg/1ml eye drops 0.4ml unit dose | 30 unit dose (Pom) £9.70
    - **Dropodex** (Moorefields Pharmaceuticals)
      - Dexamethasone sodium phosphate 1 mg per 1 ml
        - Dropodex Dexamethasone 0.1% eye drops 0.4ml unit dose | 20 unit dose (Pom) £9.75 DT price = £9.75
      - **Maxidex** (Alicon Laboratories (UK) Ltd)
        - Dexamethasone 1 mg per 1 ml
          - Maxidex 0.1% eye drops | 5 ml (Pom) £1.42 DT price = £1.42 | 10 ml (Pom) £2.80 DT price = £2.80

**Fluorometholone**

- **INDICATIONS AND DOSE**
  - Local treatment of inflammation (short term)
    - TO THE EYE
      - Child: 2-7 years: Apply every 1 hour for 24-48 hours, then reduced to 2–4 times a day
      - Adult: Apply every 1 hour for 24–48 hours, then reduced to 2–4 times a day

**Prednisolone**

- **INDICATIONS AND DOSE**
  - Local treatment of inflammation (short-term)
    - TO THE EYE
      - Child: Apply every 1–2 hours until controlled then reduce frequency
      - Adult: Apply every 1–2 hours until controlled then reduce frequency

**SIDE-EFFECTS** Corneal thinning - scleral thinning

- **MEDITICIAN FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPENTS:** May contain Benzalkonium chloride, disodium edetate, polysorbates
  - FML Liquifilm (Allergan Ltd)
    - Fluorometholone 1 mg per 1 ml FML Liquifilm 0.1% ophthalmic suspension | 5 ml (Pom) £1.71 DT price = £1.71 | 10 ml (Pom) £2.95 DT price = £2.95

**Predsol (Focus Pharmaceuticals Ltd)**

- **Prednisolone sodium phosphate 5 mg per 1 ml**
  - Predsol 0.5% eye/ear drops | 10 ml (Pom) £2.00 DT price = £2.00

**Ear/eye drops solution**

- **EXCIPENTS:** May contain Benzalkonium chloride, disodium edetate, polysorbates
  - Predsol (Focus Pharmaceuticals Ltd)
    - Prednisolone sodium phosphate 1 mg per 1 ml Predsol 0.1% eye drops preservative free | 10 ml (Pom) £27.68 DT price = £27.68
    - Prednisolone sodium phosphate 3 mg per 1 ml Prednisolone sodium phosphate 0.3% eye drops preservative free | 10 ml (Pom) £23.02 DT price = £23.02
    - Prednisolone sodium phosphate 5 mg per 1 ml
      - Prednisolone sodium phosphate 0.5% eye drops 0.5ml unit dose | 20 unit dose (Pom) £11.78 DT price = £11.78
Rimexolone

**INDICATIONS AND DOSE**

Local treatment of postoperative inflammation (short term use)

- TO THE EYE
- Adult: Apply 4 times a day for 2 weeks, treatment to begin 24 hours after surgery

Local treatment of steroid-responsive inflammation (short term use)

- TO THE EYE
- Adult: Apply in at least 4 times a day divided doses for up to 4 weeks

Uveitis (short term use)

- TO THE EYE
- Adult: Apply every 1 hour during the day time for week 1, then apply every 2 hours for week 2, then apply 4 times a day for week 3, then apply twice daily for the first 4 days of week 4, then apply once daily for the remaining 3 days of week 4

**SIDE-EFFECTS** Corneal thinning; scleral thinning

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

No licensed medicines identified.

CORTICOSTEROIDS > CORTICOSTEROID COMBINATIONS WITH ANTI-INFECTIVES

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1019.

**INDICATIONS AND DOSE**

Local treatment of eye inflammation and bacterial infection (short-term)

- TO THE EYE USING EYE DROP
- Adult: Apply up to 6 times a day

**LESS SUITABLE FOR PRESCRIBING** Betamethasone with neomycin eye-drops are less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Ear/eye/nose drops solution

- Betnesol-N (Focus Pharmaceuticals Ltd)
  - Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml, Neomycin sulfate 5 mg per 1 ml Betnesol-N ear/eye/nose drops | 10 ml (Pod) £2.39 DT price = £2.39

Dexamethasone with framcyetin sulfate and gramicidin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 1019.

**INDICATIONS AND DOSE**

Local treatment of inflammation (short-term)

- TO THE EYE
- Child: Apply 4–6 times a day, may be administered every 30–60 minutes until severe conditions until controlled, then reduce frequency
- Adult: Apply 4–6 times a day, may be administered every 30–60 minutes in severe conditions until controlled, then reduce frequency

**LESS SUITABLE FOR PRESCRIBING** Sofradex® is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Ear/eye drops solution

EXCIPIENTS: May contain Polysorbates

- Sofradex® (Sanofi)
  - Dexamethasone (as Dexamethasone sodium metasulfobenzoate) 500 microgram per 1 ml, Framycetin sulfate 5 mg per 1 ml, Gramicidin 50 microgram per 1 ml Sofradex ear/eye drops | 10 ml (Pod) £7.50

Dexamethasone with hypropemellose, neomycin and polymyxin B sulfate

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 1019.

**INDICATIONS AND DOSE**

Local treatment of inflammation (short-term)

- TO THE EYE USING EYE DROP
- Adult: Apply every 30–60 minutes until controlled, then reduced to 4–6 times a day

Local treatment of inflammation (short-term)

- TO THE EYE USING EYE OINTMENT
- Adult: Apply 3–4 times a day, alternatively, apply at night when used with eye drops

**LESS SUITABLE FOR PRESCRIBING** Dexamethasone with neomycin and polymyxin B sulfate is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

EXCIPIENTS: May contain Benzalkonium chloride, polysorbates

- Maxitrol® (Alcon Laboratories (UK) Ltd)
  - Dexamethasone 1 mg per 1 ml, Neomycin (as Neomycin sulfate) 3.5 mg per 1 ml, Hypropemellose 5 mg per 1 ml, Polymyxin B sulfate 6000 unit per 1 ml Maxitrol eye drops | 5 ml (Pod) £1.68

Eye ointment

EXCIPIENTS: May contain Hydroxybenzoates (parabens), wool fat and related substances including lanolin

- Maxitrol® (Alcon Laboratories (UK) Ltd)
  - Dexamethasone 1 mg per 1 gram, Neomycin (as Neomycin sulfate) 3500 unit per 1 gram, Polymyxin B sulfate 6000 unit per 1 gram Maxitrol eye ointment | 3.5 g (Pod) £1.44
### Dexamethasone with tobramycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 1019

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#### INDICATIONS AND DOSE

**Local treatment of inflammation (short-term)**
- **TO THE EYE**
- Adult: (consult product literature)

#### MEDICINE FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **EXCIPIENTS**: May contain Benzalkonium chloride, disodium edetate
  - **Tobradex** (Alcon Laboratories (UK) Ltd)
    - Dexamethasone 1 mg per 1 ml, Tobramycin 3 mg per ml
      - **5 ml POM**: £5.37 DT price = £5.37

#### IMMUNOSUPPRESSANTS

**IMMUNOSUPPRESSANTS > CALCINEURIN INHIBITORS AND RELATED DRUGS**

### Ciclosporin

(Cyclosporin)

**DRUG ACTION** Ciclosporin inhibits production and release of lymphokines, thereby suppressing cell-mediated immune response.

#### INDICATIONS AND DOSE

**Severe keratitis in dry eye disease that has not responded to tear substitutes (initiated by a specialist)**
- **TO THE EYE**
  - Adult: Apply 1 drop once daily, to be applied to the affected eye(s) at bedtime, review treatment at least every 6 months

#### CONTRA-INDICATIONS

Active or suspected ocular or peri-ocular infection

#### CAUTIONS

Glucoma—limited information available · history of ocular herpes—no information available

#### SIDE-EFFECTS

- Common or very common: Blurred vision · instillation site pain · local erythema · local irritation · local oedema · local pain · ocular hyperaemia
- Uncommon: Bacterial keratitis · blepharitis · chalazion · conjunctivitis · corneal decompensation · corneal infiltrates · corneal scar · eye discharge · herpes zoster (ophthalmic) · iridocyclitis · keratitis · local pruritus

#### CONCEPTION AND CONTRACEPTION

Manufacturer recommends effective contraception during treatment in women of child-bearing potential.

#### PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

#### BREAST FEEDING

Manufacturer advises avoid—limited information.

#### DIRECTIONS FOR ADMINISTRATION

Keep eyes closed for 2 minutes after using Ikervis® eye drops, to increase local drug action and reduce systemic absorption.

### Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears (December 2015)

NICE TA369

Ciclosporin (Ikervis®) is recommended as an option for treating dry eye disease that has not improved despite treatment with tear substitutes.

[www.nice.org.uk/TA369](http://www.nice.org.uk/TA369)

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Ikervis** (Santen UK Ltd)
  - Ciclosporin 1 mg per 1 ml
    - Ikervis 0.1% eye drops 0.3ml unit dose
      - **30 unit dose POM**: £72.00 DT price = £72.00

### 1.2a Anterior uveitis

#### ANTIMUSCARINICS

**Antimuscarinics (eye)**

- **CAUTIONS**: Children under 3 months owing to the possible association between cycloplegia and the development of amblyopia (in children) · darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage · mydriasis can precipitate acute angle-closure glaucoma (usually in those aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber) (in adults) · mydriasis can precipitate acute angle-closure glaucoma (usually in those who are predisposed to the condition because of a shallow anterior chamber) (in children)

- **SIDE-EFFECTS**: Conjunctivitis (on prolonged administration) · contact dermatitis · eye oedema (on prolonged administration) · hyperaemia (on prolonged administration) · local irritation (on prolonged administration) · raised intraocular pressure · transient stinging

- **PATIENT AND CARER ADVICE**: Patients may not be able to undertake skilled tasks until vision clears after mydriasis.

### Atropine sulfate

**INDICATIONS AND DOSE**

**Cycloplegia**
- **TO THE EYE USING EYE DROP**
- Adult: (consult product literature)

**Anterior uveitis**
- **TO THE EYE USING EYE DROP**
- Adult: (consult product literature)

**SIDE-EFFECTS** Systemic side-effects can occur, particularly in children and the elderly.

**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose atropine sulfate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**
- **Atropine sulfate (Non-proprietary)**
  - Atropine sulfate 10 mg per 1 ml
    - Atropine 1% eye drops
      - **10 ml POM**: £64.55 DT price = £59.28
2 Dry eye conditions

Dry eye

Tear deficiency, ocular lubricants, and astringents

Chronic soreness of the eyes associated with reduced or abnormal tear secretion (e.g. in Sjögren’s syndrome) often responds to tear replacement therapy or pilocarpine p. 1062 given by mouth in adults. The severity of the condition and patient preference will often guide the choice of preparation.

Hypromellose p. 1024 is the traditional choice of treatment for tear deficiency. It may need to be instilled frequently (e.g. hourly) for adequate relief. Ocular surface mucin is often abnormal in tear deficiency and the combination of hypromellose with a mucolytic such as acetylcysteine below can be helpful.

The ability of carbomers to cling to the eye surface may help reduce frequency of application to 4 times daily.

Polyvinyl alcohol p. 1025 increases the persistence of the tear film and is useful when the ocular surface mucin is reduced.

Sodium hyaluronate eye drops p. 1026 are also used in the management of tear deficiency.

Sodium chloride 0.9% drops p. 1026 are sometimes useful in tear deficiency, and can be used as ‘comfort drops’ by contact lens wearers, and to facilitate lens removal. They are also used to irrigate the eye. Special presentations of sodium chloride 0.9% and other irrigation solutions are used routinely for intra-ocular surgery. Sodium chloride 5% eye drops are used for the short-term treatment of corneal oedema in adults.

Eye ointments containing a paraffin can be used to lubricate the eye surface, especially in cases of recurrent corneal epithelial erosion. They may cause temporary visual disturbance and are best suited for application before sleep. Ointments should not be used during contact lens wear.

OCULAR LUBRICANTS

Acetylcysteine

**INDICATIONS AND DOSE**

Tear deficiency | Impaired or abnormal mucus production

▶ TO THE EYE
▶ Adult: Apply 3–4 times a day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

Eye drops

EXCIPIENTS: May contain Benzalkonium chloride

Acetylcysteine 50 mg per 1 ml Ilube 5% eye drops | 10 ml [POM]

£14.93 DT price = £14.93

Ilube (Moorfields Pharmaceuticals)

Carbomers

(Polycrylic acid)

**INDICATIONS AND DOSE**

Dry eyes including keratoconjunctivitis sicca, unstable tear film

▶ TO THE EYE
▶ Child: Apply 3–4 times a day or when required
▶ Adult: Apply 3–4 times a day or when required

**UNLICENSED USE** Some preparations not licensed for use in children.

**PRESCRIBING AND DISPENSING INFORMATION** Synthetic high molecular weight polymers of acrylic acid cross-linked with either allyl ethers of sucrose or allyl ethers of pentaerithritol.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

▶ Carbomers (Non-proprietary)
  Carbomer 980 2 mg per 1 gram Carbomer ‘980’ 0.2% eye drops | 10 gram [POM]

£2.80 DT price = £2.80
### Medicated Forms

- **Artelac Nighttime** (Bausch & Lomb UK Ltd)
  - Carborol 980 2 mg per 1 gram Artelac Nighttime 0.2% eye gel
    - 10 ml £2.96 DT price = £2.80

- **Clinitas Carborol** (Allergan Ltd)
  - Carborol 980 2 mg per 1 gram Clinitas Carborol 0.2% eye gel
    - 10 ml £1.49 DT price = £2.80

- **GelTears** (Bausch & Lomb UK Ltd)
  - Carborol 980 2 mg per 1 gram GelTears 0.2% gel
    - 10 gram (£2.80 DT price = £2.80)

- **Lumecare Long Lasting** (Medicom Healthcare Ltd)
  - Carborol 980 2 mg per 1 gram Lumecare Carborol 0.2% eye gel
    - 10 gram £1.51 DT price = £2.80

- **Viscotears** (Alcon Laboratories (UK) Ltd)
  - Carborol 980 2 mg per 1 gram Viscotears 2mg/g liquid gel
    - 10 gram (£1.59 DT price = £2.80
  - Viscotears 0.5mg/g eye gel 0.6ml unit dose | 30 unit dose (£5.42

- **Xailin Fresh** (Nicov Pharma)
  - Carborol 980 2 mg per 1 gram Xailin 0.2% eye gel
    - 10 gram £3.25 DT price = £2.80

### Eye Gel

**Excipients:** May contain Benzalkonium chloride, cetrimide, disodium edetate

- **Blephagel** (Thea Pharmaceuticals Ltd)
  - Carborol 3.5 mg per 1 gram Blephagel 0.35% eye gel
    - 40 gram £6.66
  - Carborol 3.6 mg per 1 gram Blephagel 0.36% eye gel preservative free | 30 gram £7.53

- **Liquivisc** (Thea Pharmaceuticals Ltd)
  - Carborol 974P 2.5 mg per 1 gram Liquivisc 0.25% eye gel
    - 10 gram (£4.50 DT price = £4.50

### Carmellose Sodium

#### Indications and Dose

**Dry eye conditions**

- **Adult:** Apply as required
- **Child:** Apply as required

#### Prescribing and Dispensing Information

Some preparations are contained units which are resealable and may be used for up to 12 hours.

#### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

### Eye Drops

- **Carmellose Sodium (Non-proprietary)**
  - Carmellose 0.5% eye drops | 10 ml £7.49
  - Carmellose 1% eye drops 0.4ml unit dose preservative free | 30 unit dose (£3.00 | 30 unit dose £3.00 DT price = £3.00 | 30 unit dose (£3.00 | 60 unit dose (£3.00
  - Carmellose 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose (£3.00 | 30 unit dose (£3.00 DT price = £3.00 | 60 unit dose (£3.00
  - Carmellose 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose (£3.00 | 30 unit dose (£3.00 DT price = £3.00 | 60 unit dose (£3.00

- **Carmeleze** (Martindale Pharmaceuticals Ltd)
  - Melophtal 1% eye drops 0.4ml unit dose | 30 unit dose £3.00 DT price = £3.00
  - Melophtal 0.5% eye drops 0.4ml unit dose | 30 unit dose £3.00 DT price = £3.00

- **Carbolmose** (Moorfields Pharmaceuticals, Medicom Healthcare Ltd)
  - PF Drops Carmellose 0.5% eye drops preservative free | 10 ml £7.49
  - PF Drops Carmellose 0.5% eye drops preservative free | 10 ml £7.49
  - Lurecare Advance Carmellose 0.5% eye drops | 10 ml £5.99

- **Carmize** (Aspire Pharma Ltd)
  - Carmize 1% eye drops | 10 ml £8.49
  - Carmize 1% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.00 DT price = £3.00 | 60 unit dose £6.00
  - Carmize 0.5% eye drops | 10 ml £7.49
  - Carmize 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £5.75 DT price = £4.80

- **Cellusan** (Farmiga S.p.A.)
  - Cellusan 1% eye drops preservative free | 10 ml £4.80
  - Cellusan 1% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.00 DT price = £3.00
  - Cellusan Light 0.5% eye drops preservative free | 10 ml £4.80
  - Cellusan Light 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £5.75 DT price = £4.80

- **Celluvisc** (Allergan Ltd)
  - Celluvisc 1% eye drops 0.4ml unit dose | 30 unit dose (£3.00 DT price = £3.00 | 60 unit dose (£10.99
  - Celluvisc 0.5% eye drops 0.4ml unit dose | 30 unit dose (£4.80 DT price = £4.80 | 90 unit dose (£15.53

- **Lumecare (Carmellose)** (Medicom Healthcare Ltd)
  - Lumecare sodium 5 mg per 1 ml Lumecare Singles Carmellose 0.5% eye drops 0.4ml unit dose | 30 unit dose £4.60 DT price = £4.80

- **Optive (Allergan Ltd)**
  - Optive 0.5% eye drops | 10 ml £7.49

- **Optive Plus** (Allergan Ltd)
  - Optive Plus 0.5% eye drops | 10 ml £7.49

- **Xailin Fresh** (Nicov Pharma)
  - Carmellose sodium 5 mg per 1 ml Xailin Fresh 0.5% eye drops 0.4ml unit dose | 30 unit dose £3.84 DT price = £4.80

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### Hydroxyethylcellulose

#### Indications and Dose

**Tear deficiency**

- **Adult:** Apply as required
  - **Child:** Apply as required

#### Prescribing and Dispensing Information

Although multi-dose hydroxyethylcellulose eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

#### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

### Eye Drops

- **Artificial tears** (Bausch & Lomb UK Ltd)
  - Hydroxyethylcellulose 4.4 mg per 1 ml Minims artificial tears 0.44% eye drops 0.5ml unit dose | 20 unit dose (£8.97

### Hydroxypropyl Guar with Polyethylene Glycol and Propylene Glycol

(Formulated as an ocular lubricant)

#### Indications and Dose

**Dry eye conditions**

- **Adult:** Apply as required
  - **Child:** Apply as required

#### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

### Eye Drops

- **Systane** (Alcon Laboratories (UK) Ltd)
  - Systane Gel eye drops | 10 ml £7.49

### Hypermellose

#### Indications and Dose

**Tear deficiency**

- **Adult:** Apply as required
  - **Child:** Apply as required

#### Prescribing and Dispensing Information

The Royal Pharmaceutical Society has stated that where it is not possible to ascertain the strength of hypermellose prescribed, the prescriber should be contacted to clarify the strength intended.

Although multi-dose hypermellose eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
**Liquid paraffin with white soft paraffin and wool alcohols**

**INDICATIONS AND DOSE**

**Dry eye conditions**

- **TO THE EYE**
  - Child: Apply as required, best suited for application before sleep
  - Adult: Apply as required, best suited for application before sleep

**PATIENT AND CARER ADVICE**

- May cause temporary visual disturbance. Should not be used during contact lens wear.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye ointment**

- **Lacri-Lube** (Allergan Ltd)
  
  - Wool alcohols 2 mg per 1 gram, Liquid paraffin 425 mg per 1 gram, White soft paraffin 573 mg per 1 gram

**Paraffin, yellow, soft**

**INDICATIONS AND DOSE**

**Eye surface lubrication**

- **TO THE EYE**
  - Child: Apply every 2 hours as required
  - Adult: Apply every 2 hours as required

**PATIENT AND CARER ADVICE**

- Ophthalmic preparations may cause temporary visual disturbance. Should not be used during contact lens wear.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye ointment**

- **Paraffin, yellow, soft (Non-proprietary)**
  
  - Liquid paraffin 100 mg per 1 gram, Wool fat 100 mg per 1 gram, Yellow soft paraffin 800 mg per 1 gram

**Polyvinyl alcohol**

**INDICATIONS AND DOSE**

**Tear deficiency**

- **TO THE EYE**
  - Child: Apply as required
  - Adult: Apply as required

**PRESCRIBING AND DISPENSING INFORMATION**

- Although multi-dose polyvinyl alcohol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

- **Tear-Lac** (Scope Ophthalmics Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml

- **PVA** (Tubilux Pharma Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml

**Hypermellose with dextran 70**

The properties listed below are those particular to the combination only. For the properties of the components please consider, hypermellose p. 1024.

**INDICATIONS AND DOSE**

**Tear deficiency**

- **TO THE EYE**
  - Adult: Apply as required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS**: May contain Benzalkonium chloride, cetrimide, disodium edetate
  
  - **Tears Naturale** (Alcon Laboratories (UK) Ltd)
    
    - Dextran 70 I mg per 1 ml, Hypermellose 3 mg per 1 ml
      
      - Tears Naturale eye drops: 15 ml £1.89
      
      - Tears Naturale eye drops 0.4ml unit dose: 28 unit dose £13.26

- **Tear-Lac Hypromellose** (Medicom Healthcare Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Lumecare Tear Drops** (Medicom Healthcare Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Isopto Alkaline** (Alcon Laboratories (UK) Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Brolene Cool Eyes** (Non-proprietary)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Liquifilm Tears** (Non-proprietary)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

**Eye drops**

- **EXCIPIENTS**: May contain Benzalkonium chloride, disodium edetate
  
  - **Tears Naturale** (Alcon Laboratories (UK) Ltd)
    
    - Dextran 70 I mg per 1 ml, Hypermellose 3 mg per 1 ml
      
      - Tears Naturale eye drops: 15 ml £1.89
      
      - Tears Naturale eye drops 0.4ml unit dose: 28 unit dose £13.26

- **Tear-Lac Hypromellose** (Medicom Healthcare Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Isopto Alkaline** (Alcon Laboratories (UK) Ltd)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Brolene Cool Eyes** (Non-proprietary)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram

- **Liquifilm Tears** (Non-proprietary)
  
  - Polyvinyl alcohol 14 mg per 1 ml, White soft paraffin 573 mg per 1 gram
Retinol palmitate with white soft paraffin and light liquid paraffin and liquid paraffin and wool fat
(Formulated as an ocul ar lubricant)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**INDICATIONS AND DOSE**

- **Dry eye conditions**
  - **TO THE EYE**
  - **Adult:** consult product literature

**Prescribing and dispensing information**

Although multi-dose sodium hyaluronate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**INDICATIONS AND DOSE**

- **Tear deficiency | Ocular lubricants and astringents | Irrigation, including first-aid removal of harmful substances | Intra-ocular or topical irrigation during surgical procedures**
  - **TO THE EYE**
  - **Child:** Apply as required, use 0.9% eye preparations
  - **Adult:** Apply as required, use 0.9% eye preparations

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- Sodium hyaluronate (Non-proprietary)
  - Vislude 0.18% eye drops 0.3ml unit dose preservative free | 20 unit dose no price available
  - Artelac Rebalance (Bausch & Lomb UK Ltd)
    - Artelac Rebalance 0.15% eye drops | 10 ml £4.00
  - Artelac Splash (Bausch & Lomb UK Ltd)
    - Artelac Splash 0.2% eye drops 0.5ml unit dose | 30 unit dose £7.00 | 60 unit dose £11.20
  - Blink Intensive (AMO UK Ltd)
    - Blink Intensive Tears 0.2% eye drops 0.4ml unit dose | 20 unit dose £2.97
    - Blink Intensive Tears 0.2% eye drops | 10 ml £2.97
  - Clinitas (Altacor Ltd)
    - Clinitas Multi 0.4% eye drops preservative free | 10 ml £6.99
    - Clinitas Multi 0.4% eye drops 0.5ml unit dose | 30 unit dose £5.70
  - Evolve HA (Medicom Healthcare Ltd)
    - Evolve HA 0.2% eye drops preservative free | 10 ml £5.99
  - Hy-Opti (Allissia Healthcare Research Ltd)
    - Hy-Opti 0.1% eye drops preservative free | 10 ml £5.50
    - Hy-Opti 0.2% eye drops preservative free | 10 ml £9.90
  - Hyabak (Thea Pharmaceuticals Ltd)
    - Hyabak 0.15% eye drops preservative free | 10 ml £7.99
    - Hyabak UD 0.15% eye drops 0.4ml unit dose preservative free | 30 unit dose £4.99
  - Hycosan (Scope Ophthalmics Ltd)
    - Hycosan Extra 0.2% eye drops | 7.5 ml no price available
    - Hycosan 0.1% eye drops | 7.5 ml no price available
  - HydraMed (Farmigea S.p.A.)
    - HydraMed 0.2% eye drops preservative free | 10 ml £5.60
    - HydraMed 0.2% eye drops 0.5ml unit dose preservative free | 30 unit dose £5.60
  - Hylo-Comod (Scope Ophthalmics Ltd)
    - Hylo-Comod 0.1% eye drops preservative free | 10 ml £8.50
    - Hylo-Comod 0.2% eye drops preservative free | 10 ml £3.50
  - Hylo-fresh (Scope Ophthalmics Ltd)
    - Hylo-Fresh 0.03% eye drops preservative free | 10 ml £4.95
  - Lubristil (Moorfields Pharmaceuticals)
    - Lubristil 0.15% eye drops 0.3ml unit dose preservative free | 20 unit dose £4.99
  - Ocusan (Agepha Pharma s.r.o.)
    - Ocusan 0.2% eye drops 0.5ml unit dose | 20 unit dose £5.37
  - Optive Fusion (Allergan Ltd)
    - Optive Fusion 0.1% eye drops | 10 ml £7.49
  - Oxyal (Bausch & Lomb UK Ltd)
    - Oxyal 0.15% eye drops | 10 ml £4.15
  - Vismed (TRB Chemidica (UK) Ltd)
    - Vismed Gel Multi 0.3% eye drops preservative free | 10 ml £7.95
    - Vismed Multi 0.18% eye drops preservative free | 10 ml £6.81
    - Vismed 0.18% eye drops 0.3ml unit dose preservative free | 20 unit dose £5.10
  - Xailin HA (Nicof Pharma)
    - Xailin HA 0.2% eye drops preservative free | 10 ml £7.13

**INDICATIONS AND DOSE**

- **Eye drops**
  - Sodium hyaluronate (Non-proprietary)
    - Sodium chloride 50 mg per 1 ml Sodium chloride 5% eye drops | 10 ml £25.25
  - Hypersal (Ennogen Healthcare Ltd)
    - Sodium chloride 50 mg per 1 ml Hypersal 5% eye drops | 10 ml £25.25
  - ODMS (Kestrel Ophthalmics Ltd)
    - Sodium chloride 50 mg per 1 ml ODMS 5% eye drops preservative free | 10 ml £24.00 DT price = £0.00
  - Saline (Bausch & Lomb UK Ltd)
    - Sodium chloride 9 mg per 1 ml Minimum saline 0.9% eye drops 0.5ml unit dose | 20 unit dose (£) £7.14 DT price = £7.14
  - Sodium chloride (Essential Pharmaceuticals Ltd, Moorfields Pharmaceuticals)
    - Sodium chloride 50 mg per 1 ml NaCl 5% eye drops 0.45ml unit dose preservative free | 20 unit dose £19.70
    - PF Drops Sodium Chloride 5% eye drops preservative free | 10 ml £25.20 DT price = £9.00
  - Eye ointment
    - Sodium chloride (Non-proprietary)
      - Sodium chloride 50 mg per 1 ml Sodium chloride 5% eye ointment preservative free | 5 gram £22.50
      - Sodium chloride 50 mg per 1 gram Muro 128 5% eye ointment | 3.5 gram (Pam) no price available
    - Sodium chloride 14 mg per 1 ml Refresh Ophthalmic 1.4% eye drops 0.4ml unit dose | 30 unit dose £2.25
  - Sno Tears (Bausch & Lomb UK Ltd)
    - Sodium chloride 14 mg per 1 ml Sno Tears 1.4% eye drops | 10 ml £1.06

**Sodium chloride**

- **INDICATIONS AND DOSE**
  - **Dry eye conditions**
  - **TO THE EYE**
  - **Adult:** Apply as required

**Tear deficiency | Ocular lubricants and astringents | Irrigation, including first-aid removal of harmful substances | Intra-ocular or topical irrigation during surgical procedures**

**PRESCRIBING AND DISPENSING INFORMATION**

Some preparations are contained in units which are resealable and may be used for up to 12 hours.

Although multi-dose sodium hyaluronate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Soybean oil

- INDICATIONS AND DOSE
  - Dry eye conditions
    - TO THE EYE
    - Child: Apply up to 4 times a day
    - Adult: Apply up to 4 times a day

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**
  - Emustil (Moorfields Pharmaceuticals)
    Emustil eye drops 0.3ml unit dose preservative free | 20 unit dose £5.22

3 Eye infections

Eye, infections of

Eye infections

Most acute superficial eye infections can be treated topically. Blepharitis and conjunctivitis are often caused by staphylococci; keratitis and endophthalmitis may be bacterial, viral, or fungal. Bacterial blepharitis is treated by application of an antibacterial eye ointment to the conjunctival sac or to the lid margins. Systemic treatment may occasionally be required and is usually undertaken after culturing organisms from the lid margin and determining their antimicrobial sensitivity; antibiotics such as the tetracyclines given for 3 months or longer may be appropriate.

Most cases of acute bacterial conjunctivitis are self limiting; where treatment is appropriate, antibacterial eye drops or an eye ointment are used. A poor response might indicate viral or allergic conjunctivitis.

Corneal ulcer and keratitis require specialist treatment and may call for hospital admission for intensive therapy. Endophthalmitis is a medical emergency which also calls for specialist management and requires intravitreal administration of antimiicrobials; concomitant systemic treatment is required in some cases. Surgical intervention, such as vitrectomy, is sometimes indicated.

Antibacterials

Bacterial eye infections are generally treated topically with eye drops and eye ointments. Systemic administration is sometimes appropriate in blepharitis.

Chloramphenicol p. 1030 has a broad spectrum of activity and is the drug of choice for superficial eye infections. Chloramphenicol eye drops are well tolerated and the recommendation that chloramphenicol eye drops should be avoided because of an increased risk of aplastic anaemia is not well founded.

Other antibacterials with a broad spectrum of activity include the quinolones, ciprofloxacin p. 1028, levofloxacin p. 1029, moxifloxacin p. 1029, and ofloxacin p. 1029; the aminoglycosides, gentamicin p. 1028 and tobramycin p. 1028 are also active against a wide variety of bacteria. Gentamicin, tobramycin, quinolones (except moxifloxacin), and polymyxin B are effective for infections caused by *Pseudomonas aeruginosa*.

Ciprofloxacin eye drops are licensed for corneal ulcers; intensive application (especially in the first 2 days) is required throughout the day and night.

Azithromycin eye drops p. 1028 are licensed for trachomatous conjunctivitis caused by *Chlamydia trachomatis* and for purulent bacterial conjunctivitis. Trachoma which results from chronic infection with *Chlamydia trachomatis* can be treated with azithromycin by mouth [unlicensed indication].

Fusidic acid is useful for staphylococcal infections.

Propamidine isethionate p. 1030 is of little value in bacterial infections but is used by specialists to treat the rare, but potentially sight-threatening, condition of *Acanthamoeba keratitis* [unlicensed indication].

Cefuroxime p. 1028 can be administered by intracameral injection for the prophylaxis of endophthalmitis following cataract surgery.

With corticosteroids

Many antibacterial preparations also incorporate a corticosteroid but such mixtures should not be used unless a patient is under close specialist supervision. In particular they should not be prescribed for undiagnosed ‘red eye’ which is sometimes caused by the herpes simplex virus and may be difficult to diagnose.

Administration

Frequency of application depends on the severity of the infection and the potential for irreversible ocular damage; antibacterial eye preparations are usually administered as follows:

- **Eye drops**, apply 1 drop at least every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing.
- **Eye ointment**, apply either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).

Antifungals

Fungal infections of the cornea are rare but can occur after agricultural injuries, especially in hot and humid climates. Orbital mycosis is rarer, and when it occurs it is usually because of direct spread of infection from the paranasal sinuses. Increasing age, debility, or immunosuppression can encourage fungal proliferation. The spread of infection through blood occasionally produces metastatic endophthalmitis.

Many different fungi are capable of producing ocular infection; they can be identified by appropriate laboratory procedures.

Antifungal preparations for the eye are not generally available. Treatment will normally be carried out at specialist centres, but requests for information about supplies of preparations not available commercially should be addressed to the Strategic Health Authority (or equivalent), or to the nearest hospital ophthalmology unit, or to Moorfields Eye Hospital, 162 City Road, London EC1V 2PD (tel. (020) 7253 3411) or www.moorfields.nhs.uk.

Antivirals

Herpes simplex infections producing, for example, dendritic corneal ulcers can be treated with aciclovir p. 1031 or ganciclovir p. 1031. Aciclovir eye ointment is used in combination with systemic treatment for ophthalmic zoster.

Slow-release ocular implants containing ganciclovir (available on a named-patient basis from specialist importing companies) may be inserted surgically to treat immediate sight-threatening CMV retinitis. Local treatments do not protect against systemic infection or infection in the other eye. See systemic treatment of CMV retinitis.
3.1 Bacterial eye infection

**ANTIBACTERIALS > AMINOGYCOSIDES**

**Gentamicin**

- **INDICATIONS AND DOSE**
  - **Bacterial eye infections**
    - **TO THE EYE**
      - Child: Apply 1 drop at least every 2 hours in severe infection, reduce frequency as infection is controlled and continue for 48 hours after healing, frequency of eye drops depends on the severity of the infection and the potential for irreversible ocular damage; for less severe infection 3–4 times daily is generally sufficient.
      - Adult: Apply 1 drop at least every 2 hours, reduce frequency as infection is controlled and continue for 48 hours after healing; frequency of eye drops depends on the severity of the infection and the potential for irreversible ocular damage; for less severe infection 3–4 times daily is generally sufficient.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Eye drops may be sourced as a manufactured special or from specialist importing companies.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops
    - **Ear/eye drops solution**
      - **EXCIPIENTS**: May contain Benzalkonium chloride
        - **Gentamicin (Non-proprietary)**
          - Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml
          - Gentamicin 0.3% ear/eye drops | 10 ml (POSm) no price available DT price = £2.27
          - Gentamicin 0.3% eye/ear drops | 10 ml (POSm) £2.13–£2.27 DT price = £2.27

**Tobramycin**

- **INDICATIONS AND DOSE**
  - **Local treatment of infections**
    - **TO THE EYE**
      - Child: 1–17 years: Apply twice daily for 6–8 days
      - Adult: Apply twice daily for 6–8 days
  - **Local treatment of infections (severe infection)**
    - **TO THE EYE**
      - Child: 1–17 years: Apply 4 times a day for first day, then apply twice daily for 5–7 days
      - Adult: Apply 4 times a day for first day, then apply twice daily for 5–7 days

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **EXCIPIENTS**: May contain Benzododecinium bromide
    - **Tobradisc (Alcon Laboratories (UK) Ltd)**
      - Tobramycin 3 mg per 1 ml Tobradisc 3mg/ml eye drops | 5 ml (POSm) £4.74

**Ciprofloxacin**

- **INDICATIONS AND DOSE**
  - **Superficial bacterial eye infection**
    - **TO THE EYE USING EYE DROP**
      - Child: Apply 4 times a day for maximum duration of treatment 21 days
      - Adult: Apply 4 times a day for maximum duration of treatment 21 days
    - **TO THE EYE USING EYE OINTMENT**
      - Child 1–17 years: Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
      - Adult: Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days

**Azithromycin**

- **INDICATIONS AND DOSE**
  - **Trachomatous conjunctivitis caused by Chlamydia trachomatis**
    - **Purulent bacterial conjunctivitis**
      - **TO THE EYE**
        - Child: Apply twice daily for 3 days, review if no improvement after 3 days of treatment
        - Adult: Apply twice daily for 3 days, review if no improvement after 3 days of treatment
  - **SIDE-EFFECTS**
    - **Common or very common**
      - Blurred vision
      - Ocular burning
      - Ocular discomfort
      - Ocular pruritus
    - **Uncommon**
      - Conjunctival hyperaemia
      - Eyelid eczema
      - Eyelid erythema
      - Eyelid oedema
      - Keratitis

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **Azyter (Thea Pharmaceuticals Ltd)**
      - Azithromycin dihydrate 15 mg per 1 gram
      - Azyter 15mg/g eye drops 0.25g unit dose | 6 unit dose (POSm) £6.99 DT price = £6.99

**Cefuroxime**

- **INDICATIONS AND DOSE**
  - **PROKAM® INTRACAMERAL INJECTION**
    - **Prophylaxis of endophthalmitis after cataract surgery**
      - **BY INTRACAMERAL INJECTION**
        - Adult: 1 mg, dose to be injected into the anterior chamber of the eye at the end of cataract surgery
  - **CAUTIONS**
    - Combined operations with cataract surgery - complicated cataracts - reduced corneal endothelial cells (less than 2000) - severe risk of infection - severe thyroid disease
  - **PREGNANCY**
    - Not known to be harmful.
  - **BREAST FEEDING**
    - Present in milk in low concentration, but appropriate to use.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for injections**
    - **Aprokam (Thea Pharmaceuticals Ltd)**
      - Cefuroxime sodium 50 mg
      - Aprokam powder for solution for injection | 10 vial (POSm) £49.95

**ANTIBACTERIALS > MACROLIDES**

**Ciprofloxacin**

- **INDICATIONS AND DOSE**
  - **Superficial bacterial eye infection**
    - **TO THE EYE USING EYE DROP**
      - Child: Apply 4 times a day for maximum duration of treatment 21 days
      - Adult: Apply 4 times a day for maximum duration of treatment 21 days
    - **TO THE EYE USING EYE OINTMENT**
      - Child 1–17 years: Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
      - Adult: Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days

**Azithromycin**

- **INDICATIONS AND DOSE**
  - **Trachomatous conjunctivitis caused by Chlamydia trachomatis**
    - **Purulent bacterial conjunctivitis**
      - **TO THE EYE**
        - Child: Apply twice daily for 3 days, review if no improvement after 3 days of treatment
        - Adult: Apply twice daily for 3 days, review if no improvement after 3 days of treatment
  - **SIDE-EFFECTS**
    - **Common or very common**
      - Blurred vision
      - Ocular burning
      - Ocular discomfort
      - Ocular pruritus
    - **Uncommon**
      - Conjunctival hyperaemia
      - Eyelid eczema
      - Eyelid erythema
      - Eyelid oedema
      - Keratitis

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **Azlyter (Thea Pharmaceuticals Ltd)**
      - Azithromycin dihydrate 15 mg per 1 gram
      - Azlyter 15mg/g eye drops 0.25g unit dose | 6 unit dose (POSm) £6.99 DT price = £6.99

**ANTIBACTERIALS > QUINOLONES**

**Ciprofloxacin**

- **INDICATIONS AND DOSE**
  - **Superficial bacterial eye infection**
    - **TO THE EYE USING EYE DROP**
      - Child: Apply 4 times a day for maximum duration of treatment 21 days
      - Adult: Apply 4 times a day for maximum duration of treatment 21 days
    - **TO THE EYE USING EYE OINTMENT**
      - Child 1–17 years: Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
      - Adult: Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
Superficial bacterial eye infection (severe infection)

- **TO THE EYE USING EYE DROP**
- Adult: Apply every 2 hours during waking hours for 2 days, then apply 4 times a day for maximum duration of treatment 21 days
- Child: Apply every 2 hours during waking hours for 2 days, then apply 4 times a day for maximum duration of treatment 21 days

**Corneal ulcer**

- **TO THE EYE USING EYE DROP**
- Adult: Apply every 30 minutes for the remainder of day 1, then apply every 4 hours on days 3–14, maximum duration of treatment 21 days, to be administered throughout the day and night
- Child: Apply every 15 minutes for 6 hours, then apply every 30 minutes for the remainder of day 1, then apply every 4 hours on days 3–14, maximum duration of treatment 21 days, to be administered throughout the day and night

**Side-effects**

- **Common or very common** Corneal deposits (reversible after completion of treatment) • ocular discomfort • ocular hyperaemia • taste disturbance
- **Uncommon** Increased lacrimation • blurred vision • conjunctival hyperaemia • corneal infiltrates • corneal staining • eye dryness • eye irritation • eye pain • eye pruritus • eye swelling • eyelid disorders • eyelid erythema • eyelid exfoliation • eyelid oedema • headache • keratopathy • pruritus • rash • photophobia
- **Rare** Abdominal pain • asthenopia • corneal disorders • corneal epithelium defect • dermatitis • diarrhoea • diplopia • dizziness • ear pain • eye hypoesthesia • keratitis • parasanal sinus hyperssecretion • rhinitis

**Pregnancy** Manufacturer advises use only if potential benefit outweighs risk.

**Breastfeeding** Manufacturer advises caution.

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug.
- **Eye drops**
  - EXCIPIENTS: May contain Benzalkonium chloride
  - *Levofoxacin (Non-proprietary)*
    - Levofoxacin (as Levofoxacin hemihydrate) 5 mg per 1 ml
    - Levofoxacin 5 mg/ml eye drops | 5 ml £6.25
  - Oftaquix (Santen UK Ltd)
    - Levofoxacin (as Levofoxacin hemihydrate) 5 mg per 1 ml
    - Oftaquix 5 mg/ml eye drops | 5 ml £6.95

**Eye ointment**

- *Ciprofloxacin* (as Ciprofloxacin hydrochloride) 3 mg per 1 gram
  - Ciprofloxacin 3 mg/g eye ointment | 3.5 gram £5.22

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**Moxifloxacin**

**Indications and dose**

**Local treatment of infections**

- **To the eye**
- Child: Apply 3 times a day continue treatment for 2–3 days after infection improves; review if no improvement within 5 days
- Adult: Apply 3 times a day continue treatment for 2–3 days after infection improves; review if no improvement within 5 days

**Side-effects**

- **Common or very common** Hyperaemia • ocular discomfort • ocular dryness • ocular irritation • eye pain • taste disturbances
- **Uncommon** Conjunctival haemorrhage • corneal disorders • corneal erosion • corneal keratitis • corneal staining • eyelid erythema • headache • nasal discomfort • paraesthesia • pharyngolaryngeal pain • visual disturbances • vomiting
- **Frequency not known** Dizziness • dyspnoea • nausea • palpitation • photophobia • pruritus • raised intra-ocular pressure • rash

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug.
- **Eye drops**
  - *Moxivig* (Alcon Laboratories (UK) Ltd)
    - Moxifloxacin (as Moxifloxacin hydrochloride) 5 mg per 1 ml
    - Moxivig 0.5% eye drops | 5 ml £9.80

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**Levofoxacin**

**Indications and dose**

**Local treatment of eye infections**

- **To the eye**
- Child: Apply every 2 hours for first 2 days, to be applied maximum 8 times a day, then apply 4 times a day for 3 days

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**Oftloxacin**

**Indications and dose**

**Local treatment of infections**

- **To the eye**
- Child: Apply every 2–4 hours for the first 2 days, then reduced to 4 times a day for maximum 10 days treatment
**CHLORAMPHENICOL**  
**DRUG ACTION** Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**

**TO THE EYE USING EYE DROP**

- **Adult:** Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient.
- **Child:** Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient.

**SIDE-EFFECTS** Transient stinging

**PREGNANCY** Avoid unless essential—no information on topical use but risk of neonatal grey-baby syndrome with oral use in third trimester.

**BREAST FEEDING** Avoid unless essential— theoretical risk of bone-marrow toxicity.

**EXCIPIENTS:** May contain Benzalkonium chloride

- **Exocin (Allergan Ltd)**
- **Oflloxacin 3 mg per 1 ml** Exocin 0.3% eye drops | 5 ml | £2.17

**MEDICINAL FORMS**

- Chloramphenicol 10 mg per 1 gram
- Chloramphenicol 5 mg per 1 ml
- Opitex Infected Eyes (Reckitt Benckiser Healthcare (UK) Ltd)

**SIDE-EFFECTS**

- Common or very common: Eye irritation, ocular discomfort
- Frequency not known: Dry eyes, facial oedema, increased lacrimation, keratitis, ocular hyperaemia, ocular oedema, photophobia, visual disturbances

**PREGNANCY**

- **Frequency not known:** Eye irritation, ocular discomfort
- **Common or very common:** Dry eyes, facial oedema, increased lacrimation, keratitis, ocular hyperaemia, ocular oedema, photophobia, visual disturbances

**BREAST FEEDING**

- **Frequency not known:** Eye irritation, ocular discomfort
- **Common or very common:** Dry eyes, facial oedema, increased lacrimation, keratitis, ocular hyperaemia, ocular oedema, photophobia, visual disturbances

**Indications and dose**

- **Superficial eye infections**
- **Propamidine isetionate**
- **Klorafect**
- **Chloramphenicol 10 mg per 1 ml**
- **Chloramphenicol 5 mg per 1 ml**
- **Optrex Infected Eyes**
- **Acanthamoeba keratitis infections (specialist use only)**

**Expiry**

- **Chloramphenicol 5 mg per 1 ml**
- **Chloramphenicol 10 mg per 1 gram**
- **Chloramphenicol 0.3% eye drops**
- **Ofloxacin 3 mg per 1 ml**
- **Exocin (Allergan Ltd)**

**Price**

- **Chloramphenicol 5 mg per 1 ml**
- **Chloramphenicol 10 mg per 1 gram**
- **Chloramphenicol 0.3% eye drops**
- **Ofloxacin 3 mg per 1 ml**

**Prescribing and dispensing information**

- There can be variation in the licensing of different medicines containing the same drug.

**Uses**

- **Systemic quinolones have caused arthropathy in animal studies.**

**Unlicensed use**

- Not licensed for Acanthamoeba keratitis infections.

**Side-effects**

- Eye irritation, eye pain

**Pharmacology**

- **Pharmacodynamic action:**
  - **Antibacterial:**
  - **Antimicrobial:**
  - **Antifungal:**
  - **Antiviral:**

**Pharmacokinetics**

- **Absorption:**
- **Distribution:**
- **Metabolism:**
- **Excretion:**

**Contraindications**

- **Contraindicated in patients with a history of cholestatic jaundice and yellowing of the skin or eyes.**

**Precautions**

- **Caution in patients with a history of cholestasis or yellowing of the skin or eyes.**

**Interactions**

- **Other antibiotics:**
- **Antacids:**
- **Sulphonamides:**
- **Dapsone:**
- **Probenecid:**

**Drug interactions**

- **Cimetidine:**
- **Sulphamethoxazole:**
- **Antacids:**
- **Sulphonamides:**
- **Dapsone:**
- **Probenecid:**

**Special precautions**

- **Pregnancy and lactation:**
- **Children:**
- **The elderly:**

**Patient and carer advice**

- **Eye irritation:**
- **Ocular discomfort:**
- **Pain:**
- **Photophobia:**
- **Visual disturbances:**

**Medicinal forms**

- **Chloramphenicol 10 mg per 1 ml**
- **Chloramphenicol 5 mg per 1 ml**
- **Chloramphenicol 0.3% eye drops**
- **Ofloxacin 3 mg per 1 ml**

**Excipients**

- **Benzalkonium chloride:**
- **Disodium edetate:**
- **Glycine:**
- **Sodium chloride:**
- **Sodium hydroxide:**
- **Water for injections:**

**Antibacterials**

- **Chloramphenicol:**
- **Ciprofloxacin:**
- **Levofloxacin:**
- **Moxifloxacin:**
- **Ofloxacin:**
- **Cefuroxime axetil:**
- **Clarithromycin:**
- **Erythromycin:**
- **Linezolid:**
- **Tigecycline:**
- **Vancomycin:**

**Antimicrobial**

- **Chloramphenicol:**
- **Ciprofloxacin:**
- **Levofloxacin:**
- **Moxifloxacin:**
- **Ofloxacin:**
- **Cefuroxime axetil:**
- **Clarithromycin:**
- **Erythromycin:**
- **Linezolid:**
- **Tigecycline:**
- **Vancomycin:**

**Antifungal**

- **Chloramphenicol:**
- **Ciprofloxacin:**
- **Levofloxacin:**
- **Moxifloxacin:**
- **Ofloxacin:**
- **Cefuroxime axetil:**
- **Clarithromycin:**
- **Erythromycin:**
- **Linezolid:**
- **Tigecycline:**
- **Vancomycin:**

**Antiviral**

- **Chloramphenicol:**
- **Ciprofloxacin:**
- **Levofloxacin:**
- **Moxifloxacin:**
- **Ofloxacin:**
- **Cefuroxime axetil:**
- **Clarithromycin:**
- **Erythromycin:**
- **Linezolid:**
- **Tigecycline:**
- **Vancomycin:**

**Drug interactions**

- **Antacids:**
- **Sulphonamides:**
- **Dapsone:**
- **Probenecid:**

**Special precautions**

- **Pregnancy and lactation:**
- **Children:**
- **The elderly:**

**Patient and carer advice**

- **Eye irritation:**
- **Ocular discomfort:**
- **Pain:**
- **Photophobia:**
- **Visual disturbances:**
3.2 Viral eye infection

3.2a Ophthalmic herpes simplex

**ANTIVIRALS > NUCLEOSIDE ANALOGUES**

**Aciclovir** *(Acyclovir)*

- **INDICATIONS AND DOSE**
  - **Herpes simplex infection (local treatment)**
    - **TO THE EYE USING EYE OINTMENT**
    - Child: Apply 1 centimetre 5 times a day continue for at least 3 days after complete healing
    - Adult: Apply 1 centimetre 5 times a day continue for at least 3 days after complete healing

- **SIDE-EFFECTS**
  - Common or very common  Local inflammation - local irritation - superficial punctate keratopathy
  - Rare  Blepharitis
  - Very rare  Angioedema - hypersensitivity reactions

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Aciclovir eye ointment for herpes simplex infections www.medicinesforchildren.org.uk/aciclovir-eye-ointment-for-herpes-simplex-infection

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye ointment**
    - **Zovirax** *(GlaxoSmithKline UK Ltd)*
      - **Aciclovir 30 mg per 1 gram**  Zovirax 3% ophthalmic ointment  |  4.5 gram  |  £9.34 DT price  =  £9.34

**Ganciclovir**

- **INDICATIONS AND DOSE**
  - **Local treatment of herpes simplex infections**
    - **TO THE EYE**
    - Adult:  Apply 5 times a day until healing complete, then apply 3 times a day for a further 7 days

- **SIDE-EFFECTS**  Burning sensation - superficial punctate keratitis - tingling

- **ALLERGY AND CROSS-SENSITIVITY**  Contra-indicated in patients hypersensitive to valganciclovir, aciclovir, or aciclovir.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **EXCIPIENTS:**  May contain Benzalkonium chloride
    - **Ganciclovir 1.5 mg per 1 gram**  Virgan 0.15% eye gel  |  5 gram  |  £19.99 DT price  =  £19.99

### 4 Eye procedures

#### Mydriatics and cycloplesics

**Overview**

Antimuscarinics dilate the pupil and paralyse the ciliary muscle; they vary in potency and duration of action.

- Short-acting, relatively weak mydriatics, such as tropicamide 0.5%, below, (action lasts for 4–6 hours), facilitate the examination of the fundus of the eye. Longer-acting options include cyclopentolate hydrochloride 1% p. 1023 (action up to 24 hours) or atropine sulfate p. 1022 (action up to 7 days).

- Phenylephrine hydrochloride p. 1032 is used for mydriasis in diagnostic or therapeutic procedures; mydriasis occurs within 60–90 minutes and lasts up to 5–7 hours.

- Mydriatics and cycloplesics are used in the treatment of anterior uveitis, usually as an adjunct to corticosteroids.

- Atropine sulfate is used in anterior uveitis mainly to prevent posterior synechiae and to relieve ciliary spasm; cyclopentolate hydrochloride or homatropine hydrobromide p. 1023 (action up to 3 days) can also be used and may be preferred because they have a shorter duration of action.

**Other drugs used for Eye procedures** *Apraclonidine p. 1043
- Lidocaine hydrochloride, p. 97*

#### Antimuscarinics

**Tropicamide**

- **INDICATIONS AND DOSE**
  - **Fundoscopy**
    - **TO THE EYE**
    - Child:  0.5% eye drops to be applied 20 minutes before examination
    - Adult:  (consult product literature)

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Although multi-dose tropicamide eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **EXCIPIENTS:**  May contain Benzalkonium chloride, edetic acid (edta)
    - **Mydriacyl** *(Alcon Laboratories (UK) Ltd)*
      - **Tropicamide 5 mg per 1 ml**  Mydriacyl 0.5% eye drops  |  5 ml  |  £1.29
      - **Tropicamide 10 mg per 1 ml**  Mydriacyl 1% eye drops  |  5 ml  |  £1.60
    - **Tropicamide** *(Bausch & Lomb UK Ltd)*
      - **Tropicamide 5 mg per 1 ml**  Minims tropicamide 0.5% eye drops 0.5ml unit dose  |  20 unit dose  |  £0.75
      - **Tropicamide 10 mg per 1 ml**  Minims tropicamide 1% eye drops 0.5ml unit dose  |  20 unit dose  |  £1.00

  Combinations available:  *Phenylephrine with tropicamide, p. 1033*
Eye procedures

Povidone-iodine

**INDICATIONS AND DOSE**
Cutaneous peri-ocular and conjunctival antisepsis before ocular surgery
- **TO THE EYE**
- **Adult:** Apply, leave for 2 minutes, then irrigate thoroughly with sodium chloride 0.9%

**CONTRA-INDICATIONS**
Concomitant use of ocular antimicrobial drugs - concomitant use of ocular formulations containing mercury-based preservatives

**SIDE-EFFECTS**
- **Rare** Conjunctival hyperaemia - superficial punctuate keratitis
- **Frequency not known** Cytotoxicity on deep tissue - cytotoxicity on mucous membranes - residual yellow coloration of the conjunctiva

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose povidone iodine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Lidocaine and Fluorescein** (Bausch & Lomb UK Ltd)
  - **Fluorescein sodium 2.5 mg per 1 ml, Lidocaine hydrochloride 40 mg per 1 ml.** Minims lidocaine and fluorescein eye drops 0.5ml unit dose | 20 unit dose | £1.24

Fluorescein sodium

**INDICATIONS AND DOSE**
Detection of lesions and foreign bodies
- **TO THE EYE**
- **Adult:** Use sufficient amount to stain damaged areas

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose fluorescein eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Minims fluorescein sodium 2.5 mg per 1 ml, Lidocaine hydrochloride 40 mg per 1 ml.** Minims lidocaine and fluorescein eye drops 0.5ml unit dose | 20 unit dose | £1.24

Fluorescein with lidocaine

**INDICATIONS AND DOSE**
Local anaesthesia
- **TO THE EYE**
- **Adult:** Apply as required

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose lidocaine and fluorescein eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Lidocaine and Fluorescein** (Bausch & Lomb UK Ltd)
  - **Fluorescein sodium 2.5 mg per 1 ml, Lidocaine hydrochloride 40 mg per 1 ml.** Minims lidocaine and fluorescein eye drops 0.5ml unit dose | 20 unit dose | £1.24
4.1 Post-operative pain and inflammation

Eye, surgical and peri-operative drug use

Ocular peri-operative drugs

Drugs used to prepare the eye for surgery, drugs that are injected into the anterior chamber at the time of surgery, and those used after eye surgery are included here.

Oxybuprocaine hydrochloride p. 1032, flurbiprofen p. 1034, ketorolac trometamol p. 1035, and nepafenac p. 1019, are used for the prophylaxis and treatment of inflammation, pain, and other symptoms associated with ocular surgery or laser treatment of the eye. Bromfenac p. 1034 is used for the treatment of postoperative inflammation following cataract surgery. Diclofenac sodium and flurbiprofen are also used to prevent miosis during ocular surgery.

Apraclonidine p. 1043, an alpha₂-adrenoreceptor agonist, reduces intra-ocular pressure possibly by reducing the production of aqueous humour. It is used to control increases in intra-ocular pressure associated with ocular surgery and as short-term treatment to reduce intraocular pressure prior to surgery.

Acetylcholine chloride p. 1032, administered into the anterior chamber of the eye during surgery, rapidly produces miosis which lasts approximately 20 minutes. If prolonged miosis is required, it can be applied again.

Intra-ocular sodium hyaluronate p. 1026 and balanced salt solution are used during surgical procedures on the eye. Povidone-iodine p. 1032 is used for peri-ocular and conjunctival antisepsis before ocular surgery to support postoperative infection control.

Local anaesthetics

Oxybuprocaine hydrochloride, below, and tetracaine p. 1034 are widely used topical local anaesthetics. Proxymetacaine hydrochloride, p. 1034 causes less initial stinging and is useful for children. Oxybuprocaine hydrochloride or a combined preparation of lidocaine hydrochloride and fluorescein sodium p. 1032 is used for tonometry. Tetracaine produces a more profound anaesthesia and is suitable for use before minor surgical procedures, such as the removal of corneal sutures. It has a temporary disruptive effect on the corneal epithelium. Lidocaine hydrochloride, with or without adrenaline/epinephrine p. 211, is injected into the eyelids for minor surgery. Local anaesthetics should never be used for the management of ocular symptoms.

ANAESTHETICS, LOCAL

<table>
<thead>
<tr>
<th>Oxybuprocaine hydrochloride</th>
<th>(Benoxinate hydrochloride)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDICATIONS AND DOSE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Local anaesthetic</strong></td>
<td></td>
</tr>
<tr>
<td>▶ TO THE EYE</td>
<td></td>
</tr>
<tr>
<td>▶ Adult: Apply as required</td>
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</tbody>
</table>

Phenylephrine with tropicamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, phenylephrine hydrochloride p. 1032, tropicamide p. 1031.

**INDICATIONS AND DOSE**

Pre-operative mydriasis | Diagnostic procedures when monotherapy insufficient
▶ TO THE EYE
▶ Adult: One insert to be applied into the lower conjunctival sac up to max. 2 hours before procedure; remove insert within 30 minutes of satisfactory mydriasis, and within 2 hours of application

**DIRECTIONS FOR ADMINISTRATION**

Patients with severe dry eyes may require a drop of saline to improve insert tolerance.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Ophthalmic insert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mydriasant (Thea Pharmaceuticals Ltd)</td>
</tr>
<tr>
<td>Tropicamid 0.28 mg, Phenylephrine hydrochloride 5.4 mg</td>
</tr>
</tbody>
</table>
preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Oxybuprocaine hydrochloride** (Bausch & Lomb UK Ltd)
  Oxybuprocaine hydrochloride 4 mg per 1 ml Minims oxybuprocaine hydrochloride 0.4% eye drops 0.5ml unit dose | 20 unit dose £11.15

**Proxymetacaine hydrochloride**

**INDICATIONS AND DOSE**
Local anaesthetic
- TO THE EYE
- Adult: Apply as required

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose proxymetacaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Proxymetacaine** (Bausch & Lomb UK Ltd)
  Proxymetacaine hydrochloride 5 mg per 1 ml Minims proxymetacaine 0.5% eye drops 0.5ml unit dose | 20 unit dose £11.54

**Tetracaine**
(Amethocaine)

**INDICATIONS AND DOSE**
Local anaesthetic
- TO THE EYE
- Adult: Apply as required

**SIDE-EFFECTS**
Local skin reactions

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose tetracaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Tetracaine** (Non-proprietary)
  Tetracaine hydrochloride 5 mg per 1 ml Minims tetracaine hydrochloride 0.5% eye drops 0.5ml unit dose | 20 unit dose £10.16
  Tetracaine hydrochloride 10 mg per 1 ml Minims tetracaine hydrochloride 1% eye drops 0.5ml unit dose | 20 unit dose £10.16

**Analgesics**

**Non-steroidal anti-inflammatory drugs**

**Diclofenac sodium**

**INDICATIONS AND DOSE**
Inhibition of intra-operative miosis during cataract surgery (but does not possess intrinsic mydriatic properties) | Postoperative inflammation in cataract surgery, strabismus surgery or argon laser trabeculoplasty | Pain in corneal epithelial defects after photorefractive keratectomy, radial keratotomy or accidental trauma | Seasonal allergic conjunctivitis
- TO THE EYE
- Adult: (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Diclofenac sodium** 1 mg per 1 ml Diclofenac sodium 1 mg per 1 ml Voltarol Ophtha 0.1% eye drops 0.3ml unit dose | 5 unit dose £4.00 | 40 unit dose £32.00
- **Diclofenac sodium** 1 mg per 1 ml Voltarol Ophtha Multidose 0.1% eye drops | 5 ml £6.68

**Bromfenac**

**INDICATIONS AND DOSE**
Postoperative inflammation following cataract surgery
- TO THE EYE
- Adult: (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Bromfenac** (Non-proprietary)
  Bromfenac (as Bromfenac sodium sesquihydrate) 900 microgram per 1 ml Bromfenac 900micrograms/ml eye drops | 5 ml £8.50
  Yellox (Bausch & Lomb UK Ltd)
  Bromfenac (as Bromfenac sodium sesquihydrate) 900 microgram per 1 ml Yellox 900micrograms/ml eye drops | 5 ml £5.28

**Flurbiprofen**

**INDICATIONS AND DOSE**
Inhibition of intra-operative miosis (but does not possess intrinsic mydriatic properties) | Control of anterior segment inflammation following postoperative and post-laser trabeculoplasty when corticosteroids contra-indicated
- TO THE EYE
- Adult: (consult product literature)

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Flurbiprofen** 200 microgram per 1 ml Flurbiprofen (as Flurbiprofen sodium) 200 micrograms/ml eye drops | 20 unit dose £11.05
  Voluntarol Ophtha (Thea Pharmaceuticals Ltd)
  Flurbiprofen sodium 200 microgram per 1 ml Flurbiprofen Ophtha 0.2% eye drops 0.3ml unit dose | 5 unit dose £4.00 | 40 unit dose £32.00
  Voltarol Ophtha (Thea Pharmaceuticals Ltd)
  Flurbiprofen sodium 200 microgram per 1 ml Voltarol Ophtha Multidose 0.2% eye drops | 5 ml £6.68
5 Glaucoma and ocular hypertension

Glaucoma

Overview

Glaucoma describes a group of disorders characterised by a loss of visual field associated with cupping of the optic disc and optic nerve damage. While glaucoma is generally associated with raised intra-ocular pressure, it can occur when the intra-ocular pressure is within the normal range. The most common form of glaucoma is primary open-angle glaucoma (chronic open-angle glaucoma), where drainage of the aqueous humour through the trabecular meshwork is restricted. The condition is often asymptomatic, but the patient may present with significant loss of visual field. Patients with ocular hypertension are at high risk of developing primary open-angle glaucoma.

Drugs that reduce intra-ocular pressure by different mechanisms are available for managing ocular hypertension and glaucoma. A topical beta-blocker or a prostaglandin analogue is usually the drug of first choice for the treatment of ocular hypertension. A prostaglandin analogue should be used to manage patients with early or moderate primary open-angle glaucoma. After checking compliance and eye drop instillation technique, it may be necessary to combine these drugs or add others, such as sympathomimetics, carbonic anhydrase inhibitors, or miotics to control intra-ocular pressure.

Acute angle-closure glaucoma

Acute angle-closure glaucoma occurs when the outflow of aqueous humour from the eye is obstructed by bowing of the iris against the trabecular meshwork; it is a medical emergency that requires urgent reduction of intra-ocular pressure to prevent loss of vision. Patients with acute angle-closure glaucoma should be referred immediately for specialist ophthalmology assessment and treatment.

Standard antiglaucoma therapy is used if supplementary treatment is required after iridotomy, iridectomy, laser treatment, or drainage surgery in either primary open-angle or acute angle-closure glaucoma.

Beta-blockers

Topical application of a beta-blocker to the eye reduces intra-ocular pressure effectively in primary open-angle glaucoma, probably by reducing the rate of production of aqueous humour. Administration by mouth also reduces intra-ocular pressure but this route is not used since side-effects may be troublesome.

Beta-blockers used as eye drops include betaxolol p. 1037, carteolol hydrochloride p. 1036, levobunolol hydrochloride p. 1036, and timolol maleate p. 1036.

Prostaglandin analogues and prostanamides

The prostaglandin analogues latanoprost p. 1041, tafluprost and travoprost p. 1043, and the synthetic prostanamide, bimatoprost, increase uveoscleral outflow and subsequently reduce intra-ocular pressure. They are used to reduce intra-ocular pressure in ocular hypertension or open-angle glaucoma.

Sympathomimetics

Brimonidine tartrate, a selective alpha2-adrenoceptor agonist, is thought to lower intra-ocular pressure by reducing aqueous humour formation and increasing uveoscleral outflow. It is licensed for the reduction of intra-ocular pressure in open-angle glaucoma or ocular hypertension in patients for whom beta-blockers are inappropriate; it may also be used as adjunctive therapy when intra-ocular pressure is inadequately controlled by other anti-glaucoma therapy.

Apraclonidine p. 1043 is another alpha2-adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. Eye drops containing apraclonidine 0.5% are used short-term to delay laser treatment or surgery in patients with glaucoma not adequately controlled by another drug; eye drops containing 1% are used for control of intra-ocular pressure after anterior segment laser surgery. Apraclonidine may not provide additional benefit in patients already using two drugs that suppress the production of aqueous humour.

Carbonic anhydrase inhibitors and systemic drugs

The carbonic anhydrase inhibitors, acetazolamide p. 1037, brinzolamide p. 1038, and dorzolamide p. 1039, reduce intra-ocular pressure.
ocular pressure by reducing aqueous humour production. Systemic use of acetazolamide also produces weak diuresis. Acetazolamide is given by mouth or by intravenous injection (intramuscular injections are painful because of the alkaline pH of the solution). It is used as an adjunct to other treatment for reducing intra-ocular pressure. Acetazolamide is not generally recommended for long-term use.

Dorzolamide and brinzolamide are topical carbonic anhydrase inhibitors. They are licensed for use in patients resistant to beta-blockers or those in whom beta-blockers are contra-indicated. They are used alone or as an adjunct to a topical beta-blocker. Brinzolamide can also be used as an adjunct to a prostaglandin analogue or the alpha2-adrenoceptor agonist, brimonidine tartrate p. 1044.

Systemic absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.

The osmotic diuretics, intravenous hypertonic mannitol p. 217 or glycerol by mouth are useful short-term ocular hypotensive drugs.

**Miotics**
Miotics act by opening the inefficient drainage channels in the trabecular meshwork.

Pilocarpine p. 1039, a miotic, is not commonly used for the treatment of primary open-angle glaucoma because side-effects are poorly tolerated. It is used mainly in the treatment of primary angle-closure glaucoma and in some secondary glaucomas.

**BETA-ADRENOCETOR BLOCKERS > NON-SELECTIVE**

**Carteolol hydrochloride**

- **INDICATIONS AND DOSE**
  - Primary open-angle glaucoma
    - **TO THE EYE**
    - Adult: Apply twice daily

- **CONTRA-INDICATIONS** Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

- **CAUTIONS** Patients with corneal disease

  **CAUTIONS, FURTHER INFORMATION**
  Systemic absorption can follow topical application to the eyes; consider cautions listed for systemically administered beta blockers.

- **INTERACTIONS** → Appendix 1 (beta-blockers). Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

- **SIDE-EFFECTS** Anaphylaxis - anterior uveitis - blepharoconjunctivitis - burning - corneal disorders - dry eyes - erythema - itching - ocular stinging - pain

  **SIDE-EFFECTS, FURTHER INFORMATION**
  Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

- **PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose (Levobunolol) eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**
  EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate, sodium metabisulphite
  → Betagan (Allergan Ltd)
  | Levobunolol hydrochloride 5 mg per 1 ml Betagan 0.5% eye drops | 5 ml | £1.85 DT price = £1.85
  Betagan Unit Dose 0.5% eye drops 0.4ml unit dose | 30 unit dose | £0.98

**Timolol maleate**

- **INDICATIONS AND DOSE**
  Reduction of intra-ocular pressure in primary open-angle glaucoma
  → TO THE EYE
  → Adult: Apply twice daily

  **TIMOPTOL-LA®**
  Reduction of intra-ocular pressure in primary open-angle glaucoma
  → TO THE EYE
  → Adult: Apply once daily

  **TIOPLEX®**
  Reduction of intra-ocular pressure in primary open-angle glaucoma
  → TO THE EYE
  → Adult: Apply once daily, to be applied in the morning

- **CONTRA-INDICATIONS** Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

- **CAUTIONS** Consider also cautions listed for systemically administered beta blockers - patients with corneal disease

- **INTERACTIONS** Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.
CAUTIONS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

INTERACTIONS

Appendix 1 (beta-blockers).

Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

SIDE-EFFECTS

Anaphylaxis, blepharoconjunctivitis, burning, corneal disorders, dry eyes, erythema, itching, ocular stinging, pain

SYSTEMIC ABSORPTION

Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose timolol eye drops commonly contain preservatives, preserved formulation unit dose vials may be available.

NATIONAL FUNDING/ACCESS DECISIONS

TIOPLEX®

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2014) that timolol gel eye drops (TIOPLEX®) are accepted for restricted use within NHS Scotland for the reduction of elevated intraocular pressure in patients with ocular hypertension or chronic open angle glaucoma who have proven sensitivity to preservatives.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

Eye drops

EXCIPIENTS: May contain Benzalkonium chloride

- Timolol maleate (Non-proprietary)
  - Timolol (as Timolol maleate) 2.5 mg per 1 ml Timolol 0.25% eye drops | 5 ml (Pom) £1.76 DT price = £1.07
  - Timolol (as Timolol maleate) 5 mg per 1 ml Timolol 0.5% eye drops | 5 ml (Pom) £1.95 DT price = £1.01
- Timoptic (Santen UK Ltd)
  - Timolol (as Timolol maleate) 2.5 mg per 1 ml Timoptic 0.25% eye drops | 5 ml (Pom) £3.12 DT price = £1.07
  - Timoptic Unit Dose 0.25% ophthalmic solution 0.2ml unit dose | 30 unit dose (Pom) £8.45
- Timolol (as Timolol maleate) 5 mg per 1 ml Timolol 0.5% eye drops | 5 ml (Pom) £3.12 DT price = £1.01
  - Timoptic Unit Dose 0.5% ophthalmic solution 0.2ml unit dose | 30 unit dose (Pom) £9.65 DT price = £9.65
- Tiopex (Thea Pharmaceuticals Ltd)
  - Timolol (as Timolol maleate) 1 mg per 1 gram Tiopex 1mg/g eye gel 0.4g unit dose | 30 unit dose (Pom) £7.49 DT price = £7.49

Eye gel

EXCIPIENTS: May contain Benzododecinium bromide

- Timolol-LA (Santen UK Ltd)
  - Timolol (as Timolol maleate) 2.5 mg per 1 ml Timolol-LA 0.25% ophthalmic gel-forming solution | 2.5 ml (Pom) £3.13 DT price = £3.13
  - Timolol (as Timolol maleate) 5 mg per 1 ml Timolol-LA 0.5% ophthalmic gel-forming solution | 2.5 ml (Pom) £3.12 DT price = £3.12


BETA-ADRENOCEPTOR BLOCKERS

Betaxolol

INDICATIONS AND DOSE

Primary open-angle glaucoma
- TO THE EYE
- Adult: Apply twice daily

CONTRA-INDICATIONS

Also consider contra-indications listed for systemically administered beta blockers: bradycardia, heart block

CAUTIONS

Patients with corneal disease

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide

INDICATIONS AND DOSE

Reduction of intra-ocular pressure in open-angle glaucoma / Reduction of intra-ocular pressure in secondary glaucoma / Reduction of intra-ocular pressure perioperatively in angle-closure glaucoma
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES, OR BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
- Adult: 0.25–1 g daily in divided doses, intramuscular injection preferably avoided because of alkalinity

Glaucma
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: 250–500 mg daily

Epilepsy
- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES, OR BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
- Adult: 0.25–1 g daily in divided doses, intramuscular injection preferably avoided because of alkalinity

CONTRA-INDICATIONS

Adrenocortical insufficiency · hyperchloremaic acidosis · hypokalaemia · hyponatraemia · long-term administration in chronic angle-closure glaucoma

CAUTIONS

Avoid extravasation at injection site (risk of necrosis) · diabetes mellitus · elderly · impaired alveolar ventilation (risk of acidosis) · not generally recommended for long-term use · pulmonary obstruction (risk of acidosis) · renal calculi

INTERACTIONS

Appendix 1 (diuretics).
Brinzolamide with brimonidine 27-Sep-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, brinzolamide, above, brimonidine tartrate p. 1044.

**INDICATIONS AND DOSE**
**Raised intra-ocular pressure in open-angle glaucoma and in ocular hypertension when monotherapy is inadequate**

**TO THE EYE**

Adult: Apply 1 drop twice daily

**SIDE-EFFECTS**
- Common or very common Somnolence
- Uncommon Dermatitis - dry throat - hypotension - vertigo

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
**EXCIPIENTS:** May contain Sodium chloride, sodium propionate, gluconic acid, hydrogenated castor oil, polysorbate 80.

**Brinzolamide**
- **Brinzolamide 10 mg per 1 ml** Brinzolamide 10mg/ml eye drops | 5 ml POM £6.92 DT price = £2.24
- **Azopt** (Alcon Laboratories (UK) Ltd) Brinzolamide 10 mg per 1 ml Azopt 10mg/ml eye drops | 5 ml POM £6.92 DT price = £2.24

**Brimonidine**
- **Brimonidine 0.2 mg per 1 ml** Brimonidine 0.2 mg/ml eye drops | 5 ml POM £6.45 DT price = £2.24
- **Simbrinza** (Alcon Laboratories (UK) Ltd) Brimonidine 0.2 mg/ml + Brinzolamide 0.12 mg/ml eye drops | 5 ml POM £6.45 DT price = £2.24

**Brinzolamide**
- **Indications and dose**
  - Reduction of intra-ocular pressure in ocular hypertension and open-angle glaucoma either as adjunct to beta-blockers or prostaglandin analogues or used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated
  - **TO THE EYE**
  - Adult: Apply twice daily, then increased if necessary up to 3 times a day

**Contra-Indications**
- Hyperchloraeic acidosis

**CAUTIONS**
- Renal tubular immaturity or abnormality - systemic absorption follows topical application

**INTERACTIONS**
Since systemic absorption may follow topical application of brinzolamide to the eye, the possibility of interactions should be borne in mind.

**SIDE-EFFECTS**
- **Common or very common** Corneal erosion - corneal oedema - dry mouth - headache - ocular disturbances - photophobia - reduced visual acuity - taste disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**
Systemic absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated if history of sulfonamide hypersensitivity.

**PREGNANCY**
Avoid - toxicity in animal studies.

**BREAST FEEDING**
Use only if benefit outweighs risk.

**HEPATIC IMPAIRMENT**
Manufacturer advises avoid.

**RENAL IMPAIRMENT**
Avoid - risk of metabolic acidosis.

**Monitoring Requirements**
Monitor blood count and plasma electrolyte concentrations with prolonged use.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 3
  - **Acetazolamide (Non-proprietary)**
  - Acetazolamide 250 mg Acetazolamide 250mg tablets | 112 tablet | £3.00

**Modified-release capsule**
- CAUTIONARY AND ADVISORY LABELS 3, 25
  - **Diamox SR (AMCo)**
  - Acetazolamide 250 mg Diamox SR 250mg capsules | 30 capsule | £6.66 DT price = £16.66
  - **Eytafox** (Teva UK Ltd)
  - Acetazolamide 250 mg Eytafox 250mg modified-release capsules | 30 capsule | £7.56 DT price = £16.66

**Powder for solution for injection**
- **Diamox** (AMCo)
  - Acetazolamide 500 mg Diamox Sodium Parenteral 500mg powder for solution for injection vials | 1 vial POM £1.76

**Brinzolamide**
- **INDICATIONS AND DOSE**
  - Reduction of intra-ocular pressure in ocular hypertension and open-angle glaucoma either as adjunct to beta-blockers or prostaglandin analogues or used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated
  - **TO THE EYE**
  - Adult: Apply twice daily

**Contra-Indications**
- Hyperchloraeic acidosis

**CAUTIONS**
- Renal tubular immaturity or abnormality - systemic absorption follows topical application
**Brinzolamide with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, brinzolamide p. 1038, timolol maleate p. 1036.

**INDICATIONS AND DOSE**

**Raised intraocular pressure in open-angle glaucoma or ocular hypertension when beta-blocker alone not adequate**

- TO THE EYE
- Adult: Apply twice daily

**INDICATIONS AND DOSE**

**Raised intraocular pressure in ocular hypertension used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated**

- TO THE EYE
- Adult: Apply 3 times a day

**MEDICINAL FORMS**

- **Eye drops**
  - **EXCIPIENTS**: May contain Benzalkonium chloride, disodium edetate
    - Azarga (Alcon Laboratories (UK) Ltd)
      - Timolol (as Timolol maleate) 5 mg per 1 ml, Brinzolamide 10 mg per 1 ml

**Dorzolamide**

**INDICATIONS AND DOSE**

**Raised intraocular pressure in ocular hypertension as adjunct to beta-blocker**

- TO THE EYE
- Adult: Apply twice daily

**CONTRA-INDICATIONS**

- **Hyperchloremic acidosis**
- **CAUTIONS**
  - Chronic corneal defects • history of intraocular surgery • history of renal calculi • low endothelial cell count • systemic absorption follows topical application
- **INTERACTIONS**
  - Appendix 1 (dorzolamide).
  - Since systemic absorption may follow topical application of dorzolamide to the eye, the possibility of interactions should be borne in mind.

**SIDE-EFFECTS**

- **Common or very common**
  - Asthenia • bitter taste • blurred vision • conjunctivitis • eyelid inflammation • headache • lacrimation • nausea • ocular irritation • superficial punctate keratitis
- **Uncommon**
  - Iridocyclitis
- **Rare**
  - Contact dermatitis • corneal oedema • dizziness • dry mouth • epistaxis • eyelid crusting • paraesthesia • Stevens-Johnson syndrome • throat irritation • toxic epidermal necrolysis • transient myopia • urolithiasis

**SIDE-EFFECTS, FURTHER INFORMATION**

- Systemic absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.

**ALLERGY AND CROSS-SENSITIVITY**

- Contra-indicated if history of sulfonamide hypersensitivity.

**PREGNANCY**

- Manufacturer advises avoid—no information available.

**BREAST FEEDING**

- Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution—no information available.

**RENAL IMPAIRMENT**

- Avoid if eGFR less than 30 ml/minute/1.73 m².

**PRESCRIBING AND DISPENSING INFORMATION**

- Although multi-dose dorzolamide eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS**: May contain Benzalkonium chloride
  - Dorzolamide (Non-proprietary)
    - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
      - Dorzolamide 2% eye drops | 5 ml £6.33 DT price = £1.96
      - Trusopt (Santen UK Ltd)
        - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
          - Trusopt 2% eye drops | 5 ml £6.33 DT price = £1.96
          - Trusopt 2% eye drops 0.2ml unit dose preservative free | 60 unit dose £24.18 DT price = £24.18

**Dorzolamide with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, dorzolamide, above, timolol maleate p. 1036.

**INDICATIONS AND DOSE**

**Raised intraocular pressure in ocular hypertension when beta-blockers alone not adequate**

- TO THE EYE
- Adult: Apply twice daily

**PRESCRIBING AND DISPENSING INFORMATION**

- Although multi-dose dorzolamide with timolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS**: May contain Benzalkonium chloride
  - Dorzolamide with timolol (Non-proprietary)
    - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
      - Dorzolamide 2% / Timolol 0.5% eye drops | 5 ml £27.16 DT price = £1.94
      - Dorzolamide 2% / Timolol 0.5% eye drops 0.2ml unit dose preservative free | 60 unit dose £27.16 DT price = £28.59
      - Cosopt (Santen UK Ltd)
        - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
          - Cosopt eye drops 0.2ml unit dose preservative free | 60 unit dose £28.59 DT price = £28.59
          - Cosopt eye drops | 5 ml £10.05 DT price = £1.94

**PARESYPATHOMIMETICS**

**Pilocarpine**

**INDICATIONS AND DOSE**

**Primary angle-closure glaucoma • Some secondary glaucomas**

- TO THE EYE
- Adult: Apply up to 4 times a day

**CONTRA-INDICATIONS**

- Acute inflammatory disease of the anterior segment • acute iritis • anterior uveitis • conditions
where pupillary constriction is undesirable - some forms of secondary glaucoma (where pupillary constriction is undesirable)

- **CAUTIONS** A darkly pigmented iris may require a higher concentration of the miotic or more frequent administration and care should be taken to avoid overdosage • asthma • cardiac disease • care in conjunctival damage • care in corneal damage • epilepsy • gastrointestinal spasm • hypertension • hyperthyroidism • hypotension • marked vasomotor instability • Parkinson’s disease • peptic ulceration • retinal detachment has occurred in susceptible individuals and those with retinal disease • urinary-tract obstruction

- **INTERACTIONS** → Appendix 1 (parasympathomimetics).
- **Systemic effects** rare following application to the eye.

- **SIDE-EFFECTS**
  - **Rare** Parasympathomimetics systemic side effects
  - **Frequency not known** Blurred vision • ciliary spasm (leads to headache and browache which may be more severe in the initial 2–4 weeks of treatment—a particular disadvantage in patients under 40 years of age) • conjunctival vascular congestion • lens changes (with chronic use) • myopia • ocular burning • ocular itching • pupillary block • smarting • vitreous haemorrhage

- **PREGNANCY** Avoid unless the potential benefit outweighs risk—limited information available.
- **BREAST FEEDING** Avoid unless the potential benefit outweighs risk—no information available.
- **PRE-TREATMENT SCREENING** Fundus examination is advised before starting treatment with a miotic (retinal detachment has occurred).
- **MONITORING REQUIREMENTS** Intra-ocular pressure and visual fields should be monitored in those with chronic simple glaucoma and those receiving long-term treatment with a miotic.
- **PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose pilocarpine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops
  
  **Eye drops**

  **EXCEPTANTS:** May contain Benzalkonium chloride

  - **Pilocarpine (Non-proprietary)**
    - Pilocarpine hydrochloride 10 mg per 1 ml
    - Pilocarpine hydrochloride 1% eye drops | 10 ml PPM | £9.54 DT price = £8.77
    - Pilocarpine hydrochloride 20 mg per 1 ml
    - Pilocarpine hydrochloride 2% eye drops | 10 ml PPM | £11.72 DT price = £10.76
    - Pilocarpine hydrochloride 40 mg per 1 ml
    - Pilocarpine hydrochloride 4% eye drops | 10 ml PPM | £13.04 DT price = £11.97
    - Pilocarpine nitrate (Bausch & Lomb UK Ltd)
      - Pilocarpine nitrate 20 mg per 1 ml
      - Minims pilocarpine nitrate 2% eye drops 0.5 ml unit dose | 20 unit dose PPM | £1.99

- **PROSTAGLANDIN ANALOGUES AND PROSTAMIDES**

  **Bimatoprost**

  - **INDICATIONS AND DOSE**
    - **Raised intra-ocular pressure in open-angle glaucoma**
    - **Ocular hypertension**
      - **TO THE EYE**
      - **Adult:** Apply once daily, to be administered preferably in the evening

  - **CAUTIONS** Angle-closure glaucoma (no experience of use) • aphakia • asthma • chronic obstructive pulmonary disease • compromised respiratory function • congenital glaucoma (no experience of use) • contact lens wearers • history of significant ocular viral infections • inflammatory ocular conditions (no experience of use) • narrow-angle glaucoma (no experience of use) • neovascular glaucoma (no experience of use) • predisposition to bradycardia • predisposition to hypotension • pseudophakia with torn posterior lens capsule or anterior chamber lenses • risk factors for cystoid macular oedema • risk factors for iritis • risk factors for uveitis

  - **SIDE-EFFECTS**
    - **Common or very common** Blepharitis • blood pressure changes • brown pigmentation particularly in those with mixed-colour irides • conjunctival disorders • corneal erosion • darkening, thickening and lengthening of eye lashes • eyelash and vellus hair changes • headache • ocular discomfort • photophobia • pigmentation of periocular skin • punctate keratitis • reduced visual acuity • transient punctate epithelial erosion
    - **Uncommon** Asthenopia • dizziness • skin rash
    - **Rare** Arthralgia • darkening of palpebral skin • facial oedema • iritis • macular oedema • myalgia • uveitis
    - **Very rare** Chest pain • exacerbation of angina • palpitation • periorbital changes resulting in deepening of the eyelid sulcus
    - **Frequency not known** Asthma • blepharospasm • bradycardia • dyspnoea • exacerbation of asthma • exacerbation of COPD • eyelid retraction • malaise • myopia • ocular infection • reactivation of previous corneal infiltrates • retinal haemorrhage
    - **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
    - **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
    - **HEPATIC IMPAIRMENT** Use with caution in moderate to severe impairment—no information available.
    - **RENAL IMPAIRMENT** Use with caution—no information available.
    - **PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose bimatoprost eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
    - **PATIENT AND CARER ADVICE** Changes to eye colour Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed colour irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

  - **NATIONAL FUNDING/ACCESS DECISIONS**

  **LUMIGAN®**

  Scottish Medicines Consortium (SMC) Decisions

  The Scottish Medicines Consortium has advised (March 2013) that bimatoprost 300 micrograms/mL preservative-free eye drops (Lumigan® single-dose eye drops) are accepted for restricted use within NHS Scotland for the reduction of elevated intra-ocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers) in adults who have proven sensitivity to benzalkonium chloride.
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- Lumigan (Allergan Ltd)
- Bimatoprost 100 microgram per 1 ml Lumigan 100 micrograms/ml eye drops 3 ml (POM) £11.71 DT price = £11.71 | 9 ml (POM) £35.13
- Bimatoprost 300 microgram per 1 ml Lumigan 300 micrograms/ml eye drops 0.4 ml unit dose | 30 unit dose (POM) £13.75 DT price = £13.75

**INDICATIONS AND DOSE**

**Bimatoprost with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bimatoprost p. 1040, timolol maleate p. 1036.

**NATIONAL FUNDING/ACCESS DECISIONS**

**GANFORT® SINGLE USE**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (October 2013) that Ganfort™ unit dose eye drops are accepted for restricted use within NHS Scotland for the reduction of intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension insufficiently responsive to topical beta-blockers or prostaglandin analogues who have proven sensitivity to preservatives.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- Ganfort (Allergan Ltd)
- Bimatoprost 300 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml Ganfort 0.3 mg/ml / 5 mg/ml eye drops | 3 ml (POM) £13.95 DT price = £13.95 | 9 ml (POM) £37.59
- Ganfort 0.3 mg/ml / 5 mg/ml eye drops 0.4 ml unit dose | 30 unit dose (POM) £17.50

**Latanoprost**

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in open-angle glaucoma or ocular hypertension

- TO THE EYE
- Adult: Apply once daily

**NATIONAL FUNDING/ACCESS DECISIONS**

**MONOPOST®**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (June 2013) that Monopost™ is accepted for restricted use within NHS Scotland for the reduction of elevated intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension who have proven sensitivity to benzalkonium chloride.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- Monopost (Thea Pharmaceuticals Ltd)
- Latanoprost 50 microgram per 1 ml Latanoprost 50 micrograms/ml eye drops 2.5 ml (POM) £12.48 DT price = £12.48
- Monopost (Thea Pharmaceuticals Ltd) Latanoprost 50 microgram per 1 ml Monopost 50 micrograms/ml eye drops 0.2 ml unit dose | 30 unit dose (POM) £8.49 DT price = £8.49 | 90 unit dose (POM) £25.47 DT price = £25.47
**Latanoprost with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, latanoprost p. 1041, timolol maleate p. 1036.

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate

- **TO THE EYE**
- **Adult:** Apply once daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- *Latanoprost with timolol (Non-proprietary)*
  - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops 2.5 ml \( \text{PoM} \) £14.32 DT price = £2.73
- *Xalacom* (Pfizer Ltd)
  - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml xalacom eye drops 2.5 ml \( \text{PoM} \) £14.32 DT price = £2.73

**Tafluprost**

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in open-angle glaucoma

- **Ocular hypertension**
  - **TO THE EYE**
  - **Adult:** Apply once daily, to be administered preferably in the evening

**CAUTIONS**

- Angle-closure glaucoma (no experience of use)
- - aphakia • astigmatism • chronic obstructive pulmonary disease
- - compromised respiratory function • congenital glaucoma (no experience of use) • contact lens wearers • history of significant ocular viral infections • inflammatory ocular conditions (no experience of use) • narrow-angle glaucoma (no experience of use) • neovascular glaucoma (no experience of use) • pseudophakia with torn posterior lens capsule or anterior chamber lenses • risk factors for cystoid macular oedema • risk factors for iritis • risk factors for uveitis

**SIDE-EFFECTS**

- **Common or very common**
  - Blurred vision • ocular hyperaemia
  - Anterior chamber inflammation • conjunctivitis

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Blurred vision may affect performance of skilled tasks (e.g. driving or operating machinery).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (September 2015) that Taptiqom™ (talfuprost with timolol) is accepted for restricted use within NHS Scotland, within the licensed indications, in patients who have proven sensitivity to preservatives.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Disodium edetate

- *Tafloprost (Non-proprietary)*
  - Tafloprost 15 microgram per 1 ml Tafloprost 15micrograms/ml eye drops 2.5 ml \( \text{PoM} \) no price available
- *Saflutan* (Santen UK Ltd)
  - Tafloprost 15 microgram per 1 ml Saflutan 15micrograms/ml eye drops 0.3ml unit dose 30 unit dose \( \text{PoM} \) £12.20 DT price = £12.20

**Tafloprost with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, tafloprost, above, timolol maleate p. 1036.

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in open-angle glaucoma and ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate

- **TO THE EYE**
- **Adult:** Apply 1 drop once daily

**SIDE-EFFECTS**

- **Common or very common**
  - Blurred vision • ocular hyperaemia
  - Anterior chamber inflammation • conjunctivitis

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

Blurred vision may affect performance of skilled tasks (e.g. driving or operating machinery).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Disodium edetate

- *Tafloprost (Non-proprietary)*
  - Tafloprost 15 microgram per 1 ml Tafloprost 15micrograms/ml eye drops 2.5 ml \( \text{PoM} \) no price available
- *Saflutan* (Santen UK Ltd)
  - Tafloprost 15 microgram per 1 ml Saflutan 15micrograms/ml eye drops 0.3ml unit dose 30 unit dose \( \text{PoM} \) £12.20 DT price = £12.20

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Disodium edetate

- *Tafloprost (Non-proprietary)*
  - Tafloprost 15 microgram per 1 ml Tafloprost 15micrograms/ml eye drops 2.5 ml \( \text{PoM} \) no price available
- *Saflutan* (Santen UK Ltd)
  - Tafloprost 15 microgram per 1 ml Saflutan 15micrograms/ml eye drops 0.3ml unit dose 30 unit dose \( \text{PoM} \) £12.20 DT price = £12.20
Travoprost

**INDICATIONS AND DOSE**

**Raised intra-ocular pressure in open-angle glaucoma**

**Ocular hypertension**

- **TO THE EYE**
- **Adult:** Apply once daily, to be administered preferably in the evening

**CAUTIONS**

- History of significant ocular viral infections - angle-closure glaucoma (no experience of use) - aphakia - asthma - chronic obstructive pulmonary disease - compromised respiratory function - congenital glaucoma (no experience of use) - contact lens wearers - inflammatory ocular conditions (no experience of use) - narrow-angle glaucoma (no experience of use) - neovascular glaucoma (no experience of use) - pseudophakia with torn posterior lens capsule or anterior chamber lenses - risk factors for cytokoid macular oedema - risk factors for iris - risk factors for uveitis

**SIDE-EFFECTS**

- **Common or very common**
  - Blepharitis - blood pressure changes - brown pigmentation particularly in those with mixed-colour irides - conjunctival disorders - corneal erosion - darkening, thickening and lengthening of eye lashes - eyelash and vellus hair changes - headache - ocular discomfort - photophobia - pigmentation of perilous skin - punctate keratitis - reduced visual acuity - transient punctate epithelial erosion
- **Uncommon**
  - Asthenopia - dizziness - skin rash
- **Rare**
  - Arthralgia - darkening of palpebral skin - facial oedema - iritis - macular oedema - myalgia - uveitis
- **Very rare**
  - Chest pain - exacerbation of angina - palpitation - periorbital changes resulting in deepening of the eyelid sulcus
- **Frequency not known**

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

**BREAST FEEDING**

Present in milk in animal studies; manufacturer advises avoid.

**PATIENT AND CARER ADVICE**

Changes to eye colour

Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS:** May contain Propylene glycol
- **Travatan** (Alcon Laboratories (UK) Ltd)
  - Travoprost 40 microgram per 1 ml Travatan 40micrograms/ml eye drops
    - **2.5 ml (POD)** £10.95 DT price = £10.95
    - **5 ml (POD)** £17.95 DT price = £17.95

**Travoprost with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, travoprost, above, timolol maleate p. 1036.

**INDICATIONS AND DOSE**

**Raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate**

- **TO THE EYE**
- **Adult:** Apply once daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS:** May contain Propylene glycol
  - **DuoTrav** (Alcon Laboratories (UK) Ltd)
    - Timolol (as Timolol maleate) 5 mg per 1 ml, Travoprost 40 microgram per 1 ml
    - **DuoTrav 40micrograms/ml / 5mg/ml eye drops**
      - **2.5 ml POD** £13.95 DT price = £13.95
      - **7.5 ml POD** £39.68

**SYMPATHOMIMETICS > ALPHA 2-ADRENOCEPTOR AGONISTS**

Apraclonidine

**DRUG ACTION**

Apraclonidine is an alpha,2-adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. It is a derivative of clonidine.

**INDICATIONS AND DOSE**

Control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery

- **TO THE EYE**
- **Adult:** Apply 1 drop, 1 hour before laser procedure, then 1 drop, immediately after completion of procedure, 1% eye drops to be administered

Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug

- **TO THE EYE**
- **Adult:** Apply 1 drop 3 times a day usually for maximum 1 month, 0.5% eye drops to be administered, may not provide additional benefit if patient already using two drugs that suppress the production of aqueous humour

**CONTRA-INDICATIONS**

History of severe or unstable and uncontrolled cardiovascular disease

**CAUTIONS**

Cerebrovascular disease - depression - heart failure - history of angina - hypertension - loss of effect may occur over time - Parkinson’s syndrome - Raynaud’s syndrome - recent myocardial infarction - reduction in vision in end-stage glaucoma (suspend treatment) - severe coronary insufficiency - thromboangiitis obliterans - vasovagal attack

**INTERACTIONS**

Appendix 1 (apraclonidine).

**SIDE-EFFECTS**

- **Common or very common**
  - Conjunctivitis - dry eye - ocular intolerance - rhinitis - taste disturbance
- **Uncommon**
  - Asthma - blepharitis - blepharospasm - chest pain - conjunctival vascular disorders - corneal erosion and infiltrates - dyspnoea - eyelid ptosis or retraction - impaired co-ordination - irritability - keratitis - keratopathy - myalgia - mydriasis - nervousness - parosmia - photophobia - rhinorrhoea - throat irritation - visual impairment

**SIDE-EFFECTS, FURTHER INFORMATION**

- Ocular intolerance
  - Withdraw if eye pruritus, ocular hyperaemia, increased lacrimation, or oedema of the eyelids and conjunctiva occur.
- Systemic effects
  - Since absorption may follow topical application, see clonidine hydrochloride p. 136.
Brimonidine tartrate

- **DRUG ACTION** Brimonidine, an alpha2-adrenoceptor agonist, is thought to lower intra-ocular pressure by reducing aqueous humour formation and increasing uveoscleral outflow.

- **INDICATIONS AND DOSE**
  - Raised intra-ocular pressure in open-angle glaucoma in patients for whom beta-blockers are inappropriate
  - Ocular hypertension in patients for whom beta-blockers are inappropriate
  - Adjunctive therapy when intra-ocular pressure is inadequately controlled by other antiglaucoma therapy

  - **TO THE EYE**
  - Adult: Apply twice daily

- **CAUTIONS**
  - Cerebral insufficiency
  - Coronary insufficiency
  - Depression
  - Postural hypotension
  - Raynaud’s syndrome
  - Severe cardiovascular disease
  - Thromboangiitis obliterans

- **INTERACTIONS** ➔ Appendix 1 (brimonidine).

- **SIDE-EFFECTS**
  - Common or very common
    - Burning sensation at application site
    - Conjunctival blanching
    - Conjunctival disturbances
    - Conjunctival follicles
    - Conjunctival infection
    - Corneal erosion
    - Corneal staining
    - Dizziness
    - Drowsiness
    - Dry mouth
    - Eyelid inflammation
    - Gastro-intestinal disturbances
    - Headache
    - Malaise
    - Ocular disturbances
    - Ocular dryness
    - Ocular hyperaemia
    - Ocular pain
    - Ocular pruritus
    - Photophobia
    - Stinging at application site
    - Taste disturbances
    - Upper respiratory symptoms
    - Visual disturbances
  - Uncommon
    - Arrhythmia
    - Bradycardia
    - Depression
    - Nasal dryness
    - Palpitation
    - Tachycardia
  - Rare
    - Drowsiness
  - Very rare
    - Hypertension
    - Hypotension
    - Insomnia
    - Iritis
    - Miosis
    - Syncope

- **PREGNANCY** Limited information available; manufacturer advises use only if benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises use with caution.

- **RENAL IMPAIRMENT** Manufacturer advises use with caution.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Drowsiness may affect performance of skilled tasks (e.g. driving).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **EXCIPIENTS:** May contain Benzalkonium chloride
    - Iopidine (Alcon Laboratories (UK) Ltd)
      - Apraclonidine (as Apraclonidine hydrochloride) 5 mg per 1 ml Iopidine 5mg/eye drops | 5 ml (POD) £10.88 DT price = £10.88
      - Apraclonidine (as Apraclonidine hydrochloride) 10 mg per 1 ml Iopidine 1% eye drops 0.25ml unit dose | 24 unit dose (POD) £77.85 DT price = £77.85

**Brimonidine with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, brimonidine tartrate, above, timolol maleate p. 1036.

- **INDICATIONS AND DOSE**
  - Raised intra-ocular pressure in open-angle glaucoma and for ocular hypertension when beta-blocker alone not adequate
    - **TO THE EYE**
    - Adult: Apply twice daily

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **EXCIPIENTS:** May contain Benzalkonium chloride
    - **Brimonidine tartrate (Non-proprietary)**
      - Brimonidine tartrate 2 mg per 1 ml Brimonidine 0.2% eye drops | 5 ml (POD) £6.85 DT price = £6.85
      - Alphagan (Allergan Ltd)
        - Brimonidine tartrate 2 mg per 1 ml Alphagan 0.2% eye drops | 5 ml (POD) £6.85 DT price = £6.85
      - Brymont (Blumont Pharma Ltd)
        - Brimonidine tartrate 2 mg per 1 ml Brymont 2mg/ml eye drops | 5 ml (POD) £2.27 DT price = £2.27
    - **Combinations available:** *Brinzolamide with brimonidine*, p. 1038

**6 Retinal disorders**

6.1 Macular degeneration

**Subfoveal choroidal neovascularisation**

**Treatment**

Aflibercept p. 1045, pegaptanib sodium p. 1046 and ranibizumab p. 1046 are vascular endothelial growth factor inhibitors licensed for the treatment of neovascular (wet) age-related macular degeneration. Aflibercept is also licensed for the treatment of macular oedema secondary to central retinal vein occlusion, and diabetic macular oedema; ranibizumab is also licensed for the treatment of visual impairment due to diabetic macular oedema, macular oedema secondary to branch or central retinal vein occlusion, and choroidal neovascularisation secondary to pathologic myopia. Ranibizumab can be administered...
concomitantly with laser photocoagulation for the treatment of diabetic macular oedema and for macular oedema secondary to branch retinal vein occlusion.

ANTINEOVASCULARISATION DRUGS

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Aflibercept

**DRUG ACTION** Aflibercept is a recombinant fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factors A and B (VEGF-A, VEGF-B) and placental growth factor (PIGF). Aflibercept inhibits the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

**INDICATIONS AND DOSE**

Neovascular (wet) age-related macular degeneration (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: Initially 2 mg once a month for 3 months, to be injected into the affected eye, then 2 mg every 2 months, review treatment frequency after 12 months

Macular oedema secondary to central retinal vein occlusion (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: Initially 2 mg once a month, to be injected into the affected eye, monitor visual and anatomic outcomes monthly; continue treatment until visual and anatomic outcomes are stable for 3 monthly assessments (discontinue treatment if no improvement in visual and anatomic outcomes after initial 3 injections); if necessary subsequent doses may be given at least 1 month apart

Diabetic macular oedema (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: Initially 2 mg once a month for 5 months, then maintenance 2 mg every 2 months, to be injected into the affected eye, review treatment frequency after 12 months (discontinue treatment if no improvement in visual and anatomic outcomes)

**CONTRA-INDICATIONS** Clinical signs of irreversible ischaemic visual function loss - ocular or periorcular infection - severe intra-ocular inflammation

**CAUTIONS** Active systemic infection - diabetic patients with uncontrolled hypertension - discontinue treatment if stage 3 or 4 macular holes develop - consult product literature for full details - discontinue treatment in the event of a retinal break - consult product literature for full details - discontinue treatment in the event of rhegmatogenous retinal detachment - consult product literature for full details - patients at risk of retinal pigment epithelial tear - poorly controlled glaucoma - recent history of myocardial infarction - recent history of stroke - recent history of transient ischaemic attack

**CAUTIONS, FURTHER INFORMATION** Aflibercept is given by intravitreal injection by specialists experienced in the management of this condition. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections - patients should be advised to report any signs of infection immediately.

**SIDE-EFFECTS**

- Common or very common - Blurred vision - cataract formation - conjunctival haemorrhage - conjunctival hyperaemia - corneal abrasion or oedema - corneal erosion - eye pain - eyelid oedema - foreign body sensation in eye - increased lacrimation - injection-site haemorrhage - injection-site pain - ocular hyperaemia - punctate keratitis - raised intra-ocular pressure - reduced visual acuity - retinal degeneration - retinal pigment epithelium detachment - retinal pigment epithelium tear - vitreous detachment - vitreous floaters - vitreous haemorrhage
- Uncommon - Anterior chamber flare - blindness - corneal epithelial defect - eyelid irritation - iridocyclitis - iritis - lenticular opacities - retinal detachment - retinal tear - uveitis
- Rare - Hypopyon - viritis

**CONCEPTION AND CONTRACEPTION** Manufacturer recommends women use effective contraception during and for at least 3 months after treatment.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**MONITORING REQUIREMENTS** Monitor intra-ocular pressure following injection.

**DIRECTIONS FOR ADMINISTRATION** For further information on administration, consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Aflibercept solution for injection for treating wet age-related macular degeneration (July 2013) NICE TA294
  - Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:
    - it is used in accordance with the recommendations for ranibizumab in NICE TA 155 and
    - the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme
  [www.nice.org.uk/TA294](http://www.nice.org.uk/TA294)

- Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion (February 2014) NICE TA305
  - Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme
  [www.nice.org.uk/TA305](http://www.nice.org.uk/TA305)

- Aflibercept for treating diabetic macular oedema (July 2015) NICE TA346
  - Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if:
    - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
    - the company provides aflibercept with the discount agreed in the patient access scheme
  [www.nice.org.uk/TA346](http://www.nice.org.uk/TA346)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Eylea (Bayer Plc) ▼
- **Aflibercept 40 mg per 1 ml** Eylea 2mg/50 microlitres solution for injection vials | 1 vial [POM] £816.00
**Pegaptanib sodium**

- **INDICATIONS AND DOSE**
  - Treatment of neovascular (wet) age-related macular degeneration (specialist use only)
    - By intravitreal injection
    - Adult: 300 micrograms every 6 weeks, to be administered into the affected eye, review treatment if no benefit after 2 consecutive injections

- **CONTRA-INDICATIONS** Ocular or periocular infection
- **CAUTIONS** Pegaptanib is given by intravitreal injection by specialists. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately.

- **SIDE-EFFECTS**
  - **Common or very common** Anterior chamber inflammation • cataract • conjunctival haemorrhage • conjunctivitis • corneal dystrophy • dry eye • eye discharge • eye irritation • eye pain • flashing lights • headache • local oedema • macular degeneration • mydriasis • periorbital haematoma • photophobia • punctate keratitis • raised intra-ocular pressure • retinal haemorrhage • rhinorrhoea • vitreous disorders • vitreous floaters
  - **Uncommon** Aortic aneurysm • asthenopia • back pain • blepharitis • chalazion • changes in hair colour • chest pain • corneal deposits • deafness • decreased intra-ocular pressure • depression • dyspepsia • ectropion • eczema • eye movement disorder • eyelid ptosis • hypertension • influenza-like symptoms • injection-site reactions • iritis • nasopharyngitis • night sweats • nightmares • occlusion of retinal blood vessels • optic nerve cupping • palpatation • pruritus • pupillary disorder • rash • retinal detachment • retinal exudates • vertigo • vitreous haemorrhage • vomiting

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **MONITORING REQUIREMENTS**
  - Monitor intra-ocular pressure (transient increase may occur following injection, and small, sustained increases reported after repeated dosing).
  - Monitor for vitreous haemorrhage and for signs of ocular infection for 2 weeks following injection.
- **DIRECTIONS FOR ADMINISTRATION** For further information on administration, consult product literature.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NICE technology appraisals (TAs)
    - Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (updated May 2012) NICE TA155
    - Pegaptanib is not recommended for the treatment of wet age-related macular degeneration; patients currently receiving pegaptanib for any lesion type can continue therapy until they and their specialist consider it appropriate to stop.
    - www.nice.org.uk/TA155

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

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**Ranibizumab**

- **INDICATIONS AND DOSE**
  - Neovascular (wet) age-related macular degeneration (specialist use only)
    - By intravitreal injection
    - Adult: 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months, thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart

- **Diabetic macular oedema / Macular oedema secondary to retinal vein occlusion (specialist use only)**
  - By intravitreal injection
  - Adult: Initially 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months (discontinue treatment if no improvement in visual acuity after initial 3 injections), thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart

- **Choroidal neovascularisation secondary to pathologic myopia (specialist use only)**
  - By intravitreal injection
  - Adult: Initially 500 micrograms, to be administered as a single injection into the affected eye, monitor for disease activity monthly for first 2 months, then at least every 3 months thereafter during the first year, then as required, if necessary subsequent doses may be given at least 1 month apart

- **Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photoacoagulation (specialist use only)**
  - By intravitreal injection
  - Adult: 500 micrograms, to be administered at least 30 minutes after laser photoacoagulation

- **CONTRA-INDICATIONS** Ocular or periocular infection • severe intra-ocular inflammation • signs of irreversible ischaemic visual function loss in patients with retinal vein occlusion

- **CAUTIONS** Active systemic infection • diabetic macular oedema due to type 1 diabetes (limited information available) • diabetic patients with HbA1c over 12% • history of stroke • history of transient ischaemic attack • patients at risk of retinal pigment epithelial tear • previous intravitreal injections • proliferative diabetic retinopathy • retinal detachment or macular hole (discontinue treatment if rhegmatogenous retinal detachment or stage 3 or 4 macular holes develop) • uncontrolled hypertension

- **CAUTIONS, FURTHER INFORMATION**
  - Ranibizumab is given by intravitreal injection by specialists. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately.

- **SIDE-EFFECTS**
  - **Common or very common** Allergic skin reactions • anaemia • anterior chamber flare • anxiety • arthralgia • blepharitis • cataract • conjunctival disorders • conjunctivitis • cough • eye haemorrhage • eyelid oedema • headache • iridocyclitis • iritis • nasopharyngitis • nausea • ocular discomfort • photophobia • photopsia • posterior capsule opacification • punctuate keratitis • raised intra-ocular pressure • retinal disorders • urinary tract infection • uveitis • visual disturbance • vitreous disorders
Ranibizumab for the treatment of diabetic macular oedema

**NATIONAL FUNDING/ACCESS DECISIONS**

Monitor visual acuity, see individual indications and dose

Monitor intra-ocular pressure, perfusion of the optic nerve

**MONITORING REQUIREMENTS**

Uncommon information available.

www.nice.org.uk/TA274

It is appropriate to stop.

Visual impairment due to diabetic macular oedema whose best corrected visual acuity is between 6/12 and 6/96;

the lesion size is less than or equal to 12 disc areas in greatest linear dimension;

there is evidence of recent disease progression;

the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).

Ranibizumab should only be continued in patients who maintain adequate response to therapy.

www.nice.org.uk/TA155

**Scottish Medicines Consortium (SMC) Decisions**

The **Scottish Medicines Consortium** has advised (May 2007) that ranibizumab (Lucentis®) is accepted for use within NHS Scotland for the treatment of neovascular (wet) age-related macular degeneration.

The **Scottish Medicines Consortium** has advised (October 2011 and April 2013) that ranibizumab (Lucentis®) is accepted for use within NHS Scotland for the treatment of macular oedema secondary to branch or central retinal vein occlusion, and (November 2012) for restricted use for the treatment of visual impairment due to diabetic macular oedema in adults with best corrected visual acuity 75 Early Treatment Diabetic Retinopathy Study letters or less at baseline, and (October 2013) for the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia in adults; SMC advice is contingent upon the continuing availability of ranibizumab at the price agreed in the patient access scheme.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for Injection**

**Lucentis** (Novartis Pharmaceuticals UK Ltd)

Ranibizumab 10 mg per 1 ml

Lucentis 2.3mg/0.23ml solution for injection vials 1 vial (Pom) £551.00 (Hospital only) Lucentis 1.65mg/0.165ml solution for injection pre-filled syringes 1 pre-filled disposable injection (Pom) £551.00

**PHOTOSENSITISERS**

**Verteporfin**

**DRUG ACTION**

Following intravenous infusion, verteporfin is activated by local irradiation using non-thermal red light to produce cytotoxic derivatives.

**INDICATIONS AND DOSE**

Photodynamic treatment of age-related macular degeneration associated with predominantly classic subfoveal choroidal neovascularisation or with pathological myopia (specialist use only)

> **BY INTRAVENOUS INFUSION**

> Adult: 6 mg/m², dose to be given over 10 minutes

**CONTRA-INDICATIONS** Acute porphyria p. 930

**CAUTIONS** Avoid extravasation · biliary obstruction · photosensitivity

**INTERACTIONS** Caution on concomitant use with other photosensitising drugs.

**SIDE-EFFECTS**

Common or very common Back pain · flashlights · hypercholesterolaemia · malaise · nausea · photosensitivity · reduced visual acuity · visual disturbances · visual-field defects

Uncommon Hyperaesthesia · hypertension · pyrexia · retinal detachment · subretinal, retinal or vitreous haemorrhage

Rare Retinal or choroidal vessel non-perfusion

Frequency not known Chest pain · macular oedema · myocardial infarction · retinal oedema · vasovagal reactions

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk (teratogenic in animal studies).
Eye

6.2 Macular oedema

**Other drugs used for Macular oedema**
- Afibercept p. 1045
- Dexamethasone p. 1019
- Ranibizumab p. 1046

**Fluocinolone acetonide**

- **INDICATIONS AND DOSE**
  Treatment of visual impairment associated with chronic diabetic macular oedema which is insufficiently responsive to available therapies (specialist use only)
  - **BY INTRAVITREAL INJECTION**
    - Adult: 190 micrograms, to be administered into the affected eye

- **CONTRA-INDICATIONS**
  - Active or suspected ocular infection
  - Raised baseline intra-ocular pressure

- **CAUTIONS**
  - Anticoagulant or antiplatelet drugs (higher incidence of conjunctival haemorrhage).

- **SIDE-EFFECTS**
  - Common or very common: Blurred vision, cataract, conjunctival haemorrhage, glaucoma, ocular discomfort, raised intra-ocular pressure, reduced visual acuity, vitreous floats, vitreous haemorrhage

- **Uncommon**
  - Conjunctival ulcer, endophthalmitis, eye discharge, eye pruritus, headache, iris adhesions, iritis, neovascularisation, maculopathy, ocular hyperaemia, optic atrophy, optic nerve disorder, posterior capsule opacification, retinal exudates, retinal vascular occlusion, sclera thinning, vitreous degeneration, vitreous detachment

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

- **BREAST FEEDING**
  - Manufacturer advises avoid unless essential.

- **MONITORING REQUIREMENTS**
  - Monitor for raised intra-ocular pressure (particularly if raised at baseline), retinal detachment, endophthalmitis, vitreous haemorrhage or detachment within 2–7 days following the procedure.
  - Monitor intra-ocular pressure at least every 3 months thereafter (for approximately 36 months).

- **DIRECTIONS FOR ADMINISTRATION**
  - Concurrent administration to both eyes not recommended. For further information on administration and repeat dosing, consult product literature.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NICE technology appraisals (TAs)
    - Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (November 2013) NICE TA301
      - Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if:
        - the implant is to be used in an eye with a intra-ocular (pseudophakic lens) and
        - the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme.
    - Scottish Medicines Consortium (SMC) Decisions
      - The Scottish Medicines Consortium has advised (February 2014) that fluocinolone acetonide intravitreal implant (Iluvien®) is recommended for restricted use within NHS Scotland for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies, only in patients in whom the affected eye is pseudophakic (has an artificial lens after cataract surgery), and retreatment would take place only if the patient had previously responded to treatment with fluocinolone acetonide and subsequently best corrected visual acuity had deteriorated to less than 20/32.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Implant**
  - Iluvien (Alimera Sciences Ltd)
    - Flucinolone acetonide 190 microgram ILUVIEN 190microgram intravitreal implant in applicator | 1 device £5,500.00
6.3 Vitreomacular traction

RECOMBINANT PROTEOLYTIC ENZYMES

Ocriplasmin

- **INDICATIONS AND DOSE**
  Treatment of vitreomacular traction, including when associated with a macular hole of diameter less than or equal to 400 microns (specialist use only)
  ▶ BY INTRAVITREAL INJECTION
  ▶ Adult: 125 micrograms for 1 dose, to be administered into the affected eye, concurrent administration to both eyes is not recommended

- **CONTRA-INDICATIONS**
  Active or suspected ocular or periocular infection • aphakia • exudative age-related macular degeneration • high myopia • history of rhegmatogenous retinal detachment • ischaemic retinopathies • large diameter macular hole (> 400 microns) • lens zonule instability • proliferative diabetic retinopathy • recent intra-ocular injection (including laser therapy) • recent ocular surgery • retinal vein occlusions • vitreous haemorrhage

- **CAUTIONS**
  History of uveitis (including severe active inflammation) • non-proliferative diabetic retinopathy • significant eye trauma

- **SIDE-EFFECTS**
  ▶ Common or very common
    Abnormal retinograph • anterior chamber cell or flare • chromatopsia • conjunctival disorders • eyelid oedema • iris • macular degeneration • macular hole • macular oedema • metamorphopsia • ocular discomfort • ocular hyperaemia • photophobia • photopsia • raised intra-ocular pressure • reduced visual acuity • retinal disorders • retinal pigment epitheliopathy • vitreous disorders
  ▶ Uncommon
    Anterior chamber inflammation • corneal abrasion • diplopia • eye inflammation • hyphaema • lens subluxation • miosis • scotoma • transient blindness • unequal pupils • visual field defect

- **PREGNANCY**
  Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING**
  Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **MONITORING REQUIREMENTS**
  Monitor intra-ocular pressure, visual acuity, and for signs of intra-ocular inflammation or infection following injection.

- **DIRECTIONS FOR ADMINISTRATION**
  For further information on administration, consult product literature.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  **NICE technology appraisals (TAs)**
  Ocriplasmin for treating vitreomacular traction (October 2013) NICE TA297
  Ocriplasmin is recommended as an option for treating vitreomacular traction in adults, only if:
  ▶ an epiretinal membrane is not present and
  ▶ they have a stage II full-thickness macular hole with a diameter of 400 microns or less and/or
  ▶ they have severe symptoms.
  www.nice.org.uk/TA297

  **Scottish Medicines Consortium (SMC) Decisions**
  The Scottish Medicines Consortium has advised (July 2014) that ocriplasmin (Jetrea®) is accepted for restricted use within NHS Scotland for the treatment of patients with vitreomacular traction plus macular hole, regardless of whether they have epiretinal membrane formation, and in patients with vitreomacular traction alone (no epiretinal membrane and no macular hole).

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Solution for injection**
  ▶ Jetrea (Alcon Laboratories (UK) Ltd)
  Ocriplasmin 2.5 mg per 1 ml Jetrea 0.5mg/0.2ml concentrate for solution for injection vials | 1 vial £2,500.00
Chapter 12
Ear, nose and oropharynx

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Ear

Otitis externa

Otitis externa is an inflammatory reaction of the meatal skin. It is important to exclude an underlying chronic otitis media before treatment is commenced. Many cases recover after thorough cleansing of the external ear canal by suction or dry mopping. A frequent problem in resistant cases is the difficulty in applying lotions and ointments satisfactorily to the rela
cessively affected skin. The most effective method is to introduce a ribbon gauze dressing or sponge wick soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution p. 1054. When this is not practical, the ear should be gently cleansed with a probe covered in cotton wool and the patient encouraged to lie with the affected ear uppermost for ten minutes after the canal has been filled with a liberal quantity of the appropriate solution.

If infection is present, a topical anti-infective which is not used systemically (such as neomycin sulfate p. 1052 or clioquinol) may be used, but for only about a week as excessive use may result in fungal infections; these may be difficult to treat and require expert advice. Sensitivity to the anti-infective or solvent may occur and resistance to antibacterials is a possibility with prolonged use. Aluminium acetate ear drops are also effective against bacterial infection and inflammation of the ear. Chloramphenicol p. 1052 may be used but the ear drops contain propylene glycol and cause hypersensitivity reactions in about 10% of patients.

Solutions containing an anti-infective and a corticosteroid are used for treating cases where infection is present with inflammation and eczema.

In view of reports of ototoxicity, manufacturers contra-indicate treatment with topical aminoglycosides or polymyxins in patients with a perforated tympanic membrane (eardrum) or patent grommet. However, some specialists do use these drops cautiously in the presence of a perforation or patent grommet in patients with chronic supplicative otitis media and when other measures have failed for otitis externa; treatment should be considered only by specialists in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;
- patients should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances.

A solution of acetic acid 2% acts as an antifungal and antibacterial in the external ear canal. It may be used to treat mild otitis externa but in severe cases an antiinflammatory preparation with or without an anti-infective drug is required. A proprietary preparation containing acetic acid 2% (EarCalm® spray) is on sale to the public.

For severe pain associated with otitis externa, a simple analgesic, such as paracetamol, may be used. A systemic antibacterial can be used if there is spreading cellulitis or if the patient is systemically unwell.

When a resistant staphylococcal infection (a boil) is present spreading cellulitis or if the patient is systemically unwell.

Otitis media

Acute otitis media

Acute otitis media is the commonest cause of severe aural pain in small children. Many infections, especially those accompanying coryza, are caused by viruses. Most uncomplicated cases resolve without antibacterial treatment and a simple analgesic, such as paracetamol, may be sufficient. In children without systemic features, a systemic antibacterial may be started after 72 hours if there is no improvement, or earlier if there is deterioration, if the patient is systemically unwell, if the patient is at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis), if mastoiditis is present, or in children under 2 years of age with bilateral otitis media. Perforation of the tympanic membrane in patients with acute otitis media usually heals spontaneously without treatment; if there is no improvement, e.g. pain or discharge persists, a systemic antibacterial can be given. Topical treatment of acute otitis media is ineffective and there is no place for drops containing a local anaesthetic.
Otitis media with effusion
Otitis media with effusion (glue ear) occurs in about 10% of children and in 90% of children with cleft palates. Systemic antibacterials are not usually required. If glue ear persists for more than a month or two, the child should be referred for assessment and follow up because of the risk of long-term hearing impairment which can delay language development. Untreated or resistant glue ear may be responsible for some types of chronic otitis media.

Chronic otitis media
Opportunistic organisms are often present in the debris, keratin, and necrotic bone of the middle ear and mastoid in patients with chronic otitis media. The mainstay of treatment is thorough cleansing with aural microsuction which may completely resolve long-standing infection. Local cleansing of the meatal and middle ear may be followed by treatment with a sponge wick or ribbon gauze dressing soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution; this is particularly beneficial for discharging ears or infections of the mastoid cavity. An antibacterial ear ointment may also be used. Acute exacerbations of chronic infection may also require systemic treatment with amoxicillin p. 506 (or erythromycin p. 497 if penicillin-allergic); treatment is adjusted according to the results of sensitivity testing.

In view of reports of ototoxicity, manufacturers contraindicate topical treatment with ototoxic antibacterials in the presence of a tympanic perforation or patent grommet. Ciprofloxacin or ofloxacin eye drops used in the ear [unlicensed use] or ear drops [both unlicensed; available from ‘special-order’ manufacturers or specialist importing companies] are an effective alternative to such ototoxic ear drops for chronic otitis media in patients with perforation of the tympanic membrane.

However, some specialists do use ear drops containing aminoglycosides or polymyxins [unlicensed indications] cautiously in patients with chronic suppurative otitis media and a perforation of the tympanic membrane, if the otitis media has failed to settle with systemic antibacterials; treatment should be considered only by specialists in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;
- patients should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances. It is considered that the pus in the middle ear associated with otitis media also carries a risk of ototoxicity.

Removal of ear wax
Ear wax (cerumen) is a normal bodily secretion which provides a protective film on the meatal skin and need only be removed if it causes hearing loss or interferes with a proper view of the ear drum.

Ear wax can be softened using simple remedies such as olive oil ear drops or almond oil ear drops; sodium bicarbonate ear drops p. 1054 are also effective, but may cause dryness of the ear canal. If the wax is hard and impacted, the drops can be used twice daily for several days and this may reduce the need for mechanical removal of the wax. The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Some proprietary preparations containing organic solvents can irritate the meatal skin, and in most cases the simple remedies indicated above are just as effective and less likely to cause irritation. Docusate sodium p. 1054 or urea hydrogen peroxide p. 1055 are ingredients in a number of proprietary preparations for softening ear wax.

If necessary, wax may be removed by irrigation with water (warmed to body temperature). Ear irrigation is generally best avoided in young children, in patients unable to cooperate with the procedure, in those with otitis media in the last six weeks, in otitis externa, in patients with cleft palate, a history of ear drum perforation, or previous ear surgery. A person who has hearing in one ear only should not have that ear irrigated because even a very slight risk of damage is unacceptable in this situation.

1 Otitis externa
Other drugs used for Otitis externa Hydrocortisone with miconazole, p. 1107

ANTIBACTERIALS > AMINOGLYCOSIDES

Framycetin sulfate

- INDICATIONS AND DOSE
  - Bacterial infection in otitis externa
    - TO THE EAR
    - Adult: (consult product literature)

- CONTRA-INDICATIONS
  - Perforated tympanic membrane

- CAUTIONS
  - Avoid prolonged use

- Side-effects
  - Local sensitivity

Gentamicin

- INDICATIONS AND DOSE
  - Bacterial infection in otitis externa
    - TO THE EAR
    - Child: Apply 2–3 drops 4–5 times a day, (including a dose at bedtime)
    - Adult: Apply 2–3 drops 4–5 times a day, (including a dose at bedtime)

- CONTRA-INDICATIONS
  - Patent grommet (although may be used by specialists, see Ear p. 1050) - perforated tympanic membrane (although may be used by specialists, see Ear p. 1050)

- CAUTIONS
  - Avoid prolonged use

- SIDE-EFFECTS
  - Local sensitivity

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

Combinations available: Dexamethasone with framycetin sulfate and gramicidin, p. 1053

Ear, nose and oropharynx
Gentamicin with hydrocortisone

- **INDICATIONS AND DOSE**
  - **Eczematous inflammation in otitis externa**
    - **TO THE EAR**
    - **Child:** Apply 2–4 drops 4–5 times a day, (including a dose at bedtime)
    - **Adult:** Apply 2–4 drops 4–5 times a day, (including a dose at bedtime)

- **CONTRA-INDICATIONS** Patent grommet (although may be used by specialists, see Ear p. 1050) • perforated tympanic membrane (although may be used by specialists, see Ear p. 1050)
- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS** Local sensitivity reactions
- **PATIENT AND CARER ADVICE**

**ANTIBACTERIALS 〉 IMIDAZOLE ANTIFUNGALS**

Clotrimazole

- **INDICATIONS AND DOSE**
  - **Fungal infection in otitis externa**
    - **TO THE EAR**
    - **Child:** Apply 2–3 times a day continue for at least 14 days after disappearance of infection
    - **Adult:** Apply 2–3 times a day continue for at least 14 days after disappearance of infection

- **SIDE-EFFECTS** Local irritation • local sensitivity
- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
- **Ear drops**
  EXCIPIENTS: May contain Propylene glycol
  - **Chloramphenicol (Non-proprietary)**
    - Chloramphenicol 50 mg per 1 ml
    - Chloramphenicol 100 mg per 1 ml
    - Chloramphenicol 5% ear drops

**CORTICOSTEROIDS**

Betamethasone

- **INDICATIONS AND DOSE**
  - **BETNESOL®**
    - **ECZEMATOUS INFLAMMATION IN OTITIS EXTERNA**
      - **TO THE EAR**
      - **Adult:** Apply 2–3 drops every 2–3 hours, reduce frequency when relief obtained

**ANTIFUNGALS 〉 IMIDAZOLE ANTIFUNGALS**

Clotrimazole

- **INDICATIONS AND DOSE**
  - **Fungal infection in otitis externa**
    - **TO THE EAR**
    - **Child:** Apply 2–3 times a day continue for at least 14 days after disappearance of infection
    - **Adult:** Apply 2–3 times a day continue for at least 14 days after disappearance of infection

- **SIDE-EFFECTS** Local irritation • local sensitivity
- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
- **Liquid**
  - **Canesten (clotrimazole)** (Bayer Plc)
    - Clotrimazole 10 mg per 1 ml
    - Canesten 1% solution

**CORTICOSTEROIDS**

Betamethasone

- **INDICATIONS AND DOSE**
  - **BETNESOL®**
    - **ECZEMATOUS INFLAMMATION IN OTITIS EXTERNA**
      - **TO THE EAR**
      - **Adult:** Apply 2–3 drops every 2–3 hours, reduce frequency when relief obtained

- **CONTRA-INDICATIONS** Avoid alone in the presence of untreated infection (combine with suitable anti-infective)
- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS** Local sensitivity reactions
- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
- **Ear/eye/nose drops solution**
  EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
  - **Betnesol (Focus Pharmaceuticals Ltd)**
    - Betamethasone sodium phosphate 1 mg per 1 ml
      - Betnesol 0.1% eye/ear/nose drops

Neomycin sulfate

- **INDICATIONS AND DOSE**
  - **Bacterial infection in otitis externa**
    - **TO THE EAR**
    - **Child:** (consult product literature)
    - **Adult:** (consult product literature)

- **CONTRA-INDICATIONS** Patent grommet (although may be used by specialists, see Ear p. 1050) • perforated tympanic membrane (although may be used by specialists, see Ear p. 1050)
- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS** Local irritation
- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
- **Ear drops**
  EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
  - **Betamethasone with neomycin (Non-proprietary)**
    - Betamethasone sodium phosphate 1 mg per 1 ml
    - Hydrocortisone acetate 10 mg per 1 ml
    - Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml
      - Gentamicin 0.3% / Hydrocortisone acetate 1% ear drops
    - 10 ml [Pom] £23.92 DT price = £23.92
- **SIDE-EFFECTS** Local sensitivity reactions
- **MEDICATION FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
- **Chloramphenicol (Non-proprietary)**
  - Chloramphenicol 50 mg per 1 ml
  - Chloramphenicol 100 mg per 1 ml
  - Chloramphenicol 5% ear drops

**CONTRA-INDICATIONS**

- Avoid alone in the presence of untreated infection (combine with suitable anti-infective)
- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS** Local sensitivity reactions
- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
- **Ear drops**
  EXCIPIENTS: May contain Propylene glycol
  - **Chloramphenicol (Non-proprietary)**
    - Chloramphenicol 50 mg per 1 ml
    - Chloramphenicol 100 mg per 1 ml
  - Chloramphenicol 5% ear drops
  - Chloramphenicol 10% ear drops
  - Chloramphenicol 5% ear drops

**SIDE-EFFECTS**

- Common or very common High incidence of sensitivity reactions to vehicle
- **PATIENT AND CARER ADVICE**
  Medicines for Children leaflet: Chloramphenicol ear drops for ear infections (otitis externa) www.medicinesforchildren.org.uk/chloramphenicol-ear-drops-ear-infections-otitis-externa-0
- **LESS SUITABLE FOR PRESCRIBING** Chloramphenicol ear drops are less suitable for prescribing.

**SIDE-EFFECTS**

- Local sensitivity reactions
- Avoid prolonged use
CORTICOSTEROIDS CORTICOSTEROID COMBINATIONS WITH ANTI-INFECTIVES

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1052, neomycin sulfate p. 1052.

INDICATIONS AND DOSE

Eczematous inflammation in otitis externa

TO THE EAR

Child: Apply 2–3 drops 3–4 times a day

Adult: Apply 2–3 drops 3–4 times a day

CONTRA-INDICATIONS Patent grommet (although may be used by specialists, see Ear p. 1050) • perforated tympanic membrane (although may be used by specialists, see Ear p. 1050)

CAUTIONS Avoid prolonged use

SIDE-EFFECTS Local sensitivity

MEDICINAL FORMS

Ear/eye/nose drops solution

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

Betnesol-N (Focus Pharmaceuticals Ltd)

Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml, Neomycin sulfate 5 mg per 1 ml

Betnesol-N ear/eye/nose drops | 10 ml £0.39 DT price = £2.39

Dexamethasone with framycetin sulfate and gramicidin

The properties listed below are those particular to the combination only. For the properties of the components please consider, framycetin sulfate p. 1051.

INDICATIONS AND DOSE

Eczematous inflammation in otitis externa

TO THE EARDrops

Child: 2–3 drops 3–4 times a day

Adult: 2–3 drops 3–4 times a day

LESS SUITABLE FOR PRESCRIBING Sofradex® is less suitable for prescribing.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Ear/eye drops solution

EXCIPIENTS: May contain Polysorbates

Sofradex (Sanofi)

Gramicidin 50 micrograms per 1 ml, Dexamethasone (as Dexamethasone sodium metasulfobenzoate) 500 microgram per 1 ml, Framycetin sulfate 5 mg per 1 ml

Sofradex ear/eye drops | 10 ml £7.50

Dexamethasone with glacial acetic acid and neomycin sulfate

INDICATIONS AND DOSE

Eczematous inflammation in otitis externa

TO THE EAR

Child 2–17 years: Apply 1 spray 3 times a day

Adult: Apply 1 spray 3 times a day

CONTRA-INDICATIONS Patent grommet (although may be used by specialists, see Ear p. 1050) • perforated tympanic membrane
membrane (although may be used by specialists, see Ear p. 1050)

- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS** Local sensitivity

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Spray**
- **EXCIPIENTS**: May contain Hydroxybenzoates (parabens)
  - Otomize (Teva UK Ltd)
    - Dexamethasone 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram, Acetic acid glacial 20 mg per 1 gram
  - Otomize ear spray 5 ml £0.85 | 20 ml £1.73 | 200 ml £2.05 | 500 ml £11.67

**DERMATOLOGICAL DRUGS**

- **INDICATIONS AND DOSE**
  - **Removal of earwax**
  - **To the ear**
    - Adult: To be inserted into meatus or apply on a ribbon gauze dressing or sponge wick which should be kept saturated with the ear drops

**DIRECTIVES FOR ADMINISTRATION**
For ear drops 8%—dilute 8 parts aluminium acetate ear drops (13%) with 5 parts purified water. Must be freshly prepared.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ear drops

**2 Removal of earwax**

**BICARBONATE**

- **Sodium bicarbonate**

  - **INDICATIONS AND DOSE**
    - **Removal of earwax (with 5% ear drop solution)**
      - **To the ear**
      - **Child**: (consult product literature)
      - **Adult**: (consult product literature)

  - **SIDE-EFFECTS** Dryness of the ear canal

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Ear drops**
  - **Sodium bicarbonate (Non-proprietary)**
    - Sodium bicarbonate 50 mg per 1 ml
      - Sodium bicarbonate 5% ear drops 10 ml £1.25–£1.28

**SOFTENING DRUGS**

- **Almond oil**

  - **INDICATIONS AND DOSE**
    - **Removal of earwax**
      - **To the ear**
      - **Child**: Allow drops to warm to room temperature before use (consult product literature)
      - **Adult**: Allow drops to warm to room temperature before use (consult product literature)

  - **DIRECTIONS FOR ADMINISTRATION**
    - The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Liquid**
  - **Almond oil (Non-proprietary)**
    - Almond oil 1 ml per 1 ml
      - Almond oil liquid: 50 ml £0.85
      - 70 ml £1.73
      - 200 ml £2.37
      - 500 ml £11.67

**Arachis oil with chlorobutanol**

- **INDICATIONS AND DOSE**
  - **Removal of earwax**
    - **To the ear**
    - **Adult**: (consult product literature)

- **LESS SUITABLE FOR PRESCRIBING**
  - Arachis (peanut) oil with chlorobutanol ear drops are less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Ear drops**
  - **Cerumol (Thornton & Ross Ltd)**
    - Chlorobutanol 50 mg per 1 ml, Arachis oil 573 mg per 1 ml
      - Cerumol ear drops: 11 ml [£] £2.05

**Docusate sodium**

- **(Dioctyl sodium sulphosuccinate)**

  - **INDICATIONS AND DOSE**
    - **Removal of ear wax**
      - **To the ear**
      - **Adult**: (consult product literature)

  - **LESS SUITABLE FOR PRESCRIBING**
    - Ear drops less suitable for prescribing.

  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.

    **Ear drops**
    - **Molcer (Wallace Manufacturing Chemists Ltd)**
      - Docusate sodium 50 mg per 1 ml
        - Docusate sodium ear drops: 15 ml [£] £8.08
    - **Waxsol (Meda Pharmaceuticals Ltd)**
      - Docusate sodium 5 mg per 1 ml
        - Waxsol ear drops: 10 ml [£] £1.95

**Olive oil**

- **INDICATIONS AND DOSE**
  - **Removal of earwax**
    - **To the ear**
      - **Child**: Apply twice daily for several days (if wax is hard and impacted)
      - **Adult**: Apply twice daily for several days (if wax is hard and impacted)

  - **DIRECTIONS FOR ADMINISTRATION**
    - The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Allow ear drops to warm to room temperature before use.
Rhinitis and bacterial sinusitis

Rhinitis is often self-limiting but bacterial sinusitis may require treatment with antibiotics. There are few indications for nasal sprays and drops except in allergic rhinitis and perennial rhinitis. Many nasal preparations contain sympathomimetic drugs which may damage the nasal cilia. Sodium chloride 0.9% solution p. 914 may be used as a douche or ‘sniff’ following endonasal surgery.

Drugs used in nasal allergy

Mild allergic rhinitis is controlled by antihistamines (see under Antihistamines, allergen immunotherapy and allergic emergencies p. 259) or topical nasal corticosteroids; systemic nasal decongestants are of doubtful value. Topical nasal decongestants can be used for a short period to relieve congestion and allow penetration of a topical nasal corticosteroid.

More persistent symptoms and nasal congestion can be relieved by topical nasal corticosteroids; sodium cromoglicate p. 1061 is an alternative, but may be less effective. The topical antihistamine azelastine hydrochloride p. 1017 is useful for controlling breakthrough symptoms in allergic rhinitis. Topical antihistamines are considered less effective than topical corticosteroids but probably more effective than cromoglicate. In seasonal allergic rhinitis (e.g. hay fever), treatment should begin 2 to 3 weeks before the season commences and may have to be continued for several months; continuous treatment may be required for years in perennial rhinitis.

Montelukast p. 251 is less effective than topical nasal corticosteroids; montelukast can be used in patients with seasonal allergic rhinitis and concomitant asthma.

Sometimes allergic rhinitis is accompanied by vasomotor rhinitis. In this situation, the addition of topical nasal ipratropium bromide can reduce watery rhinorrhea. Very disabling symptoms occasionally justify the use of systemic corticosteroids for short periods, for example, in students taking important examinations. They may also be used at the beginning of a course of treatment with a corticosteroid spray to relieve severe mucosal oedema and allow the spray to penetrate the nasal cavity.

Corticosteroids

Corticosteroid nasal preparations should be avoided in the presence of untreated nasal infections, after nasal surgery (until healing has occurred), and in pulmonary tuberculosis. Patients transferred from systemic corticosteroids may experience exacerbation of some symptoms. Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; for cautions and side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays. The height of children receiving prolonged treatment with nasal corticosteroids should be monitored; if growth is slowed, referral to a paediatrician should be considered.

Nasal polyps

Short-term use of corticosteroid nasal drops helps to shrink nasal polyps; to be effective, the drops must be administered with the patient in the ‘head down’ position. A short course of a systemic corticosteroid may be required initially to shrink large polyps. A corticosteroid nasal spray can be used to maintain the reduction in swelling and also for the initial treatment of small polyps.

Pregnancy

If a pregnant woman cannot tolerate the symptoms of allergic rhinitis, treatment with nasal beclometasone dipropionate p. 1059, budesonide p. 1059, fluticasone p. 1060, or sodium cromoglicate may be considered.

Topical nasal decongestants

The nasal mucosa is sensitive to changes in atmospheric temperature and humidity and these alone may cause slight nasal congestion. The nose and nasal sinuses produce a litre of mucus in 24 hours and much of this finds its way silently into the stomach via the nasopharynx. Slight changes in the nasal airway, accompanied by an awareness of mucus passing along the nasopharynx causes some patients to be inaccurately diagnosed as suffering from chronic sinusitis. These symptoms are particularly noticeable in the later stages of the common cold. Sodium chloride 0.9% given as nasal drops or spray may relieve nasal congestion by helping to liquefy mucous secretions.

Inhalation of warm moist air is useful in the treatment of symptoms of acute infective conditions. The addition of volatile substances such as menthol and eucalyptus may encourage the use of warm moist air (see under Aromatic inhalations, cough preparations and systemic nasal decongestants p. 277).

Symptoms of nasal congestion associated with vasomotor rhinitis and the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays. These all contain sympathomimetic drugs which exert their effect by vasoconstriction of the mucosal blood vessels which in turn reduces oedema of the nasal passages.
nasal mucosa. They are of limited value because they can give rise to a rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilatation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events. Ephedrine hydrochloride nasal drops, below, are the safest sympathomimetic preparation and can give relief for several hours. The more potent sympathomimetic drugs oxymetazoline and xylometazoline hydrochloride p. 1057 are more likely to cause a rebound effect.

Non-allergic watery rhinorrhea often responds well to treatment with the antimuscarinic ipratropium bromide p. 1058.

Sinusitis and oral pain
Sinusitis affecting the maxillary antrum can cause pain in the upper jaw. Where this is associated with blockage of the opening from the sinus into the nasal cavity, it may be helpful to relieve the congestion with inhalation of warm moist air or with ephedrine hydrochloride nasal drops.

Systemic antibacterials may sometimes be required for sinusitis (see under Nose infections, bacterial p. 475).

Nasal preparations for infection
There is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis; see elimination of nasal staphylococci.

Nasal staphylococci
Elimination of organisms such as staphylococci from the nasal vestibule can be achieved by the use of a cream containing chlorhexidine and neomycin (Naseptin®), but re-colonisation frequently occurs. Coagulate-positive staphylococci are present in the noses of 40% of the population.

A nasal ointment containing mupirocin p. 1058 is also available; it should probably be held in reserve for resistant infections. In hospitals or in care establishments, mupirocin nasal ointment should be reserved for the eradication (in both patients and staff) of nasal carriage of meticillin-resistant Staphylococcus aureus (MRSA). A sample should be taken 2 days after treatment to confirm eradication. The course may be repeated if the sample is positive (and the throat is not colonised). To avoid the development of resistance, the treatment course should not exceed 7 days and the course should not be repeated on more than one occasion. If the MRSA strain is mupirocin-resistant or does not respond after 2 courses, consider alternative products such as chlorhexidine and neomycin cream.

1 Nasal congestion

SYMPATHOMIMETICS ▶ VASOCONSTRICTOR

Ephedrine hydrochloride

• INDICATIONS AND DOSE
  - Nasal congestion
    - Sinusitis affecting the maxillary antrum
      - BY INTRanasAL ADMINISTRATION
        - Child 12-17 years: Apply 1–2 drops up to 4 times a day as required for a maximum of 7 days, to be instilled into each nostril
        - Adult: Apply 1–2 drops up to 4 times a day as required for a maximum of 7 days, to be instilled into each nostril

  - Important Safety Information
    - CHM/MHRA Advice
      - The CHM/MHRA has stated that non-prescription cough and cold medicines containing ephedrine can be considered for up to 5 days’ treatment in children aged 6–12 years after basic principles of best care have been tried; these medicines should not be used in children under 6 years of age.

  - CAUTIONS
    - Avoid excessive or prolonged use:
      - cardiovascular disease (in children) - diabetes mellitus - elderly - hypertension - hyperthyroidism - ischaemic heart disease (in adults) - prostatic hypertrophy (risk of acute urinary retention) (in adults)

  - INTERACTIONS ▶ Appendix 1 (sympathomimetics).

  - SIDE-EFFECTS
    - Common or very common
      - Headache - nausea
    - Frequency not known
      - After excessive use tolerance with diminished effect - cardiovascular effect - local irritation - rebound congestion

  - PREGNANCY
    - Manufacturer advises avoid.

  - BREASTFEEDING
    - Present in milk; manufacturer advises avoid—irritability and disturbed sleep reported.

  - PRESCRIBING AND DISPENSING INFORMATION
    - For nasal drops, the BP directs that if no strength is specified 0.5% drops should be supplied.

  - PROFESSION SPECIFIC INFORMATION
    - Dental practitioners’ formulary
      - Ephedrine nasal drops may be prescribed.

  - EXCEPTIONS TO LEGAL CATEGORY
    - Ephedrine nasal drops can be sold to the public provided no more than 180 mg of ephedrine base (or salts) are supplied at one time, and pseudoephedrine salts are not supplied at the same time; for conditions that apply to supplies made at the request of a patient, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

  - MEDICINAL FORMS
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: nasal drops

  - Nasal drops
    - Ephedrine hydrochloride (Non-proprietary)
      - Ephedrine hydrochloride 5 mg per 1 ml Ephedrine 0.5% nasal drops ▶ 10 ml ▶ £1.75 DT price = £1.75
      - Ephedrine hydrochloride 10 mg per 1 ml Ephedrine 1% nasal drops ▶ 10 ml ▶ £1.81 DT price = £1.81

Pseudoephedrine hydrochloride

• INDICATIONS AND DOSE
  - Congestion of mucus membranes of upper respiratory tract
    - BY MOUTH
      - Child 6–11 years: 30 mg 3–4 times a day
      - Child 12–17 years: 60 mg 3–4 times a day
      - Adult: 60 mg 3–4 times a day

  - Important Safety Information
    - MHRA/CHM Advice (March 2008 and February 2009): Over-the-counter cough and cold medicines for children
      - Children under 6 years should not be given over-the-counter cough and cold medicines containing pseudoephedrine.

    - CAUTIONS
      - Diabetes - heart disease - hypertension - hyperthyroidism - ischaemic heart disease (in adults) - prostatic hypertrophy (in adults) - raised intra-ocular pressure (in children) - susceptibility to angle-closure glaucoma (in adults)

    - INTERACTIONS ▶ Appendix 1 (sympathomimetics).
      - Contra-indicated in patients taking monoamine oxidase inhibitors within the previous 2 weeks.
Xylometazoline hydrochloride

**DRUG ACTION** Xylometazoline is a sympathomimetic.

**INDICATIONS AND DOSE**

**Nasal congestion**

- **BY INTRANASAL ADMINISTRATION USING NASAL SPRAY**
  - Child 12–17 years: 1 spray 1–3 times a day as required for maximum duration of 7 days, to be administered into each nostril
  - Adult: 1 spray 1–3 times a day as required for maximum duration of 7 days, to be administered into each nostril

**IMPORTANT SAFETY INFORMATION**

The CHM/MHRA has stated that non-prescription cough and cold medicines containing oxymetazoline or xylometazoline can be considered for up to 5 days' treatment in children aged 6–12 years after basic principles of best care have been tried; these medicines should not be used in children under 6 years of age.

**SIDE-EFFECTS**

- Cardiovascular effects - hallucinations in small children - headache - local irritation - nausea - rebound congestion - restlessness in small children - sleep disturbances in small children - tolerance with diminished effect (after excessive use) - transient visual disturbances

**CAUTIONS**

- Hallucinations in small children - Discontinue treatment if the hallucinations occur.

**PREGNANCY**

- Manufacturer advises avoid.

**BREAST FEEDING**

- Manufacturer advises caution—no information available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Pseudoephedrine hydrochloride (Non-proprietary)
  - Pseudoephedrine hydrochloride 60 mg 60mg tablets | 12 tablet [P] no price available
  - Galpseud (Thornton & Ross Ltd)
    - Pseudoephedrine hydrochloride 60 mg Galpseud 60mg tablets | 24 tablet [PoSt] £2.25 | 100 tablet [PoSt] £5.42 DT price = £5.42
  - Sudafed Non-Drowsy Decongestant (pseudoephedrine) (McNeil Products Ltd)
    - Pseudoephedrine hydrochloride 60 mg Sudafed Decongestant 60mg tablets | 12 tablet [P] £2.04

**Oral solution**

EXCIPIENTS: May contain Alcohol

- Pseudoephedrine hydrochloride (Non-proprietary)
  - Pseudoephedrine hydrochloride 6 mg per 1 ml 30mg/5ml oral liquid sugar-free | 100 ml [P] £1.57 DT price = £1.57
  - Galpseud (Thornton & Ross Ltd)
    - Pseudoephedrine hydrochloride 6 mg per 1 ml Galpseud 30mg/5ml linctus sugar-free | 2000 ml [PoSt] £14.00
  - Sudafed Non-Drowsy Decongestant (pseudoephedrine) (McNeil Products Ltd)
    - Pseudoephedrine hydrochloride 6 mg per 1 ml Sudafed Decongestant 30mg/5ml liquid | 100 ml [P] £1.92

**Spray**

- Otrivine (Novartis Consumer Health UK Ltd)
  - Xylometazoline hydrochloride 1 mg per 1 ml Otrivine Congestion Relief 0.1% nasal spray | 10 ml | [GSL] £3.05 DT price = £2.18
  - Otrivine Adult Measured Dose Sinusitis spray | 10 ml | [GSL] £2.62 DT price = £2.18
  - Otrivine Allergy Relief 0.1% nasal spray | 10 ml | [GSL] £2.62 DT price = £2.18
  - Otrivine Adult nasal spray | 10 ml | [GSL] £2.18 DT price = £2.18
  - Otrivine Adult Metered Dose 0.1% nasal spray | 10 ml | [GSL] £2.62 DT price = £2.18
  - Sudafed Congestion Relief (McNeil Products Ltd)
    - Xylometazoline hydrochloride 1 mg per 1 ml Sudafed Congestion Relief 0.1% nasal spray | 10 ml | [GSL] £3.25 DT price = £2.18
  - Sudafed Mucus Relief (McNeil Products Ltd)
    - Xylometazoline hydrochloride 1 mg per 1 ml Sudafed Mucus Relief 0.1% nasal spray | 15 ml | [GSL] £2.37
  - Sudafed Non-Drowsy Decongestant (xylometazoline) (McNeil Products Ltd)
    - Xylometazoline hydrochloride 1 mg per 1 ml Sudafed Blocked Nose 0.1% spray | 15 ml | [GSL] £2.38

**Nasal drops**

- Otrivine (Novartis Consumer Health UK Ltd)
  - Xylometazoline hydrochloride 1 mg per 1 ml Otrivine Adult 0.1% nasal drops | 10 ml | [GSL] £2.18 DT price = £2.18
  - Xylometazoline hydrochloride 500 microgram per 1 ml Otrivine Child nasal drops | 10 ml | [P] £1.91 DT price = £1.91
2 Nasal infection

**ANTIBACTERIALS**  >  **AMINOGYCOSIDES**

### Chlorhexidine with neomycin

- **INDICATIONS AND DOSE**
  - **Eradication of nasal carriage of staphylococci**
    - **BY INTRanasAL ADMINISTRATION**
    - **Child:** Apply 4 times a day for 10 days
    - **Adult:** Apply 4 times a day for 10 days
  - **Preventing nasal carriage of staphylococci**
    - **BY INTRanasAL ADMINISTRATION**
    - **Child:** Apply twice daily
    - **Adult:** Apply twice daily

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - **EXCIPIENTS:** May contain Arachis (peanut) oil, cetostearyl alcohol (including cetyl and stearyl alcohol)
    - **Nasapen (Alliance Pharmaceuticals Ltd)**
      - Chlorhexidine hydrochloride 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram
      - Nasapen nasal cream | 15 gram | £2.24

### Mupirocin

- **INDICATIONS AND DOSE**
  - **BACTROBAN NASAL**
    - **FOR ERADICATION OF NASAL CARRIAGE OF STAPHYLOCOCCUS AUREUS (MRSA)**
      - **BY INTRanasAL ADMINISTRATION**
      - **Child:** Apply 2–3 times a day for 5 days; a sample should be taken 2 days after treatment to confirm eradication. Course may be repeated once if sample positive (and throat not colonised), dose to be applied to the inner surface of each nostril
      - **Adult:** Apply 2–3 times a day for 5 days; a sample should be taken 2 days after treatment to confirm eradication. Course may be repeated once if sample positive (and throat not colonised), dose to be applied to the inner surface of each nostril

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

### Other drugs used for Nasal inflammation, nasal polyps and rhinitis

- **Deslortatine**, p. 262
- **Fexofenadine hydrochloride**, p. 269

### AMINOSTEROLIDS  >  **AMINOGLYCOSIDES**

#### Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1052, neomycin sulfate p. 480.

- **INDICATIONS AND DOSE**
  - **Nasal infection**
  - **BY INTRanasAL ADMINISTRATION USING NASAL DROPS**
    - **Child:** Apply 2–3 drops 2–3 times a day, to be applied into each nostril
    - **Adult:** Apply 2–3 drops 2–3 times a day, to be applied into each nostril

- **LESS SUITABLE FOR PRESCRIBING**
  - Betamethasone with neomycin nasal-drops are less suitable for prescribing; there is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Ear/eye/nose drops solution**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
    - **Betnesol-N (Focus Pharmaceuticals Ltd)**
      - Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml, Neomycin sulfate 5 mg per 1 ml
      - Betnesol-N ear/eye/nose drops | 10 ml | £2.39

3 Nasal inflammation, nasal polyps and rhinitis

### Ipratropium bromide

24-Feb-2016

- **INDICATIONS AND DOSE**
  - **RHINORRHOEA ASSOCIATED WITH ALLERGIC AND NON-ALLERGIC RHINITIS**
  - **BY INTRanasAL ADMINISTRATION**
  - **Child 12–17 years:** 2 sprays 2–3 times a day, dose to be sprayed into each nostril
  - **Adult:** 2 sprays 2–3 times a day, dose to be sprayed into each nostril

- **DOSE EQUIVALENCE AND CONVERSION**
  - 1 metered spray of nasal spray = 21 micrograms.

- **CAUTIONS**
  - Avoid spraying near eyes, bladder outflow obstruction, cystic fibrosis, prostatic hyperplasia (in adults), susceptibility to angle-closure glaucoma

- **SIDE-EFFECTS**
  - **Common or very common**
    - Epistaxis, nasal dryness, nasal irritation
  - **Uncommon**
    - Headache, nausea
  - **Very rare**
    - Gastro-intestinal motility disturbances, palpitations, urinary retention

- **PREGNANCY**
  - Manufacturer advises only use if potential benefit outweighs the risk.

- **BREAST FEEDING**
  - No information available—manufacturer advises only use if potential benefit outweighs risks.
Corticosteroids (intranasal)

- **CAUTIONS** Avoid after nasal surgery (until healing has occurred) - avoid in pulmonary tuberculosis - avoid in the presence of untreated nasal infections - patients transferred from systemic corticosteroids may experience exacerbation of some symptoms

- **CAUTIONS, FURTHER INFORMATION**
  - Systemic absorption: Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; therefore also consider the cautions and side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays.

- **SIDE-EFFECTS**
  - Rare: Glaucoma - raised intra-ocular pressure
  - Very rare: Nasal septal perforation (usually following nasal surgery)

- **FREQUENCY NOT KNOWN**
  - Aggression (particularly in children) - anxiety (particularly in children) - bronchospasm - depression (particularly in children) - dryness - epistaxis - headache - hyperactivity (particularly in children) - hypersensitivity reactions - nasal irritation - nasal ulceration - sleep disturbances (particularly in children) - smell disturbances - taste disturbances - throat irritation

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Systemic absorption: Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged. Therefore also consider the side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays.

- **MONITORING REQUIREMENTS**
  - The height of children receiving prolonged treatment with nasal corticosteroids should be monitored; if growth is slowed, referral to a paediatrician should be considered.

**Betamethasone**

- **INDICATIONS AND DOSE**
  - **BETNESOL®**
    - Non-infected inflammatory conditions of nose
      - **BY INTRANASAL ADMINISTRATION**
        - Adult: Apply 2–3 drops 2–3 times a day, dose to be applied into each nostril
    - **VISTAMETHASONE®**
      - Non-infected inflammatory conditions of nose
        - **BY INTRANASAL ADMINISTRATION**
          - Adult: Apply 2–3 drops twice daily, dose to be applied into each nostril

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Ear/eye/nose drops solution**
    - **EXCIPIENTS**: May contain Benzalkonium chloride, disodium edetate
      - **Betnesol** (Focus Pharmaceuticals Ltd)
        - Betamethasone sodium phosphate 1 mg per 1 ml
          - Betnesol 0.1% ear/eye/nose drops | 10 ml £2.32 DT price = £2.32
      - **Vistamethasone** (Martinvale Pharmaceuticals Ltd)
        - Betamethasone sodium phosphate 1 mg per 1 ml
          - Vistamethasone 0.1% ear/eye/nose drops | 5 ml £0.87 | 10 ml £0.99 DT price = £2.32

**Budesonide**

- **INDICATIONS AND DOSE**
  - **BY INTRANASAL ADMINISTRATION**
    - Child 12–17 years: Initially 200 micrograms once daily, dose to be administered into each nostril in the morning, alternatively initially 100 micrograms twice daily, dose to be administered to each nostril; reduced to 100 micrograms once daily, dose to be administered into each nostril, dose can be reduced when control achieved continued
Ear, nose and oropharynx  

Adult: Initially 200 micrograms once daily, dose to be administered into each nostril in the morning, alternatively initially 100 micrograms twice daily, dose to be administered to each nostril; reduced to 100 micrograms once daily, dose to be administered into each nostril, dose can be reduced when control achieved.

**Nasal polyps**

- **BY INTRANASAL ADMINISTRATION**
  - Child 12-17 years: 100 micrograms twice daily for up to 3 months, dose to be administered into each nostril.
  - Adult: 100 micrograms twice daily for up to 3 months, dose to be administered into each nostril.

**RHINOCORT AQUA®**

**Rhinitis**

- **BY INTRANASAL ADMINISTRATION**
  - Adult: 128 micrograms once daily, dose to be administered into each nostril in the morning, alternatively 64 micrograms twice daily, dose to be administered into each nostril; reduced to 64 micrograms once daily when control achieved. Use for maximum 3 months, doses to be administered into each nostril.

**Nasal polyps**

- **BY INTRANASAL ADMINISTRATION**
  - Adult: 64 micrograms twice daily for up to 3 months, dose to be administered into each nostril.

**EXCEPTIONS TO LEGAL CATEGORY** Preparations of budesonide can be sold to the public for nasal administration as a nasal spray if supplied for the prevention and treatment of seasonal allergic rhinitis in adults over 18 years subject to max. single dose of 200 micrograms per nostril, max. daily dose of 200 micrograms per nostril for max. period of 3 months, and a pack size of 10 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

EXCIPIENTS: May contain Disodium edetate, polysorbates, potassium sorbate.

- Budesonide (Non-proprietary)
  - Budesonide 100 microgram per 1 dose
    - Budeflam Aquanase 100 micrograms/dose nasal spray | 150 dose | no price available
    - Rhinocort 100 micrograms/dose nasal spray | 200 dose | no price available
  - Rhinocort (AstraZeneca UK Ltd)
  - Budesonide 64 microgram per 1 dose
    - Rhinocort Aqua 64 microgram nasal spray | 120 dose | £3.49 DT price = £4.77

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**Fluticasone**

**04-Jan-2016**

**INDICATIONS AND DOSE**

**Prophylaxis and treatment of allergic rhinitis and perennial rhinitis**

- **BY INTRANASAL ADMINISTRATION USING NASAL SPRAY**
  - Child 4-11 years: 50 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 50 micrograms twice daily.
  - Child 12-17 years: 100 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 100 micrograms twice daily; reduced to 50 micrograms once daily, dose to be administered into each nostril, dose to be reduced when control achieved.
  - Adult: 100 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 100 micrograms twice daily; reduced to 50 micrograms once daily, dose to be administered into each nostril, dose to be reduced when control achieved.

**Nasal polyps**

- **BY INTRANASAL ADMINISTRATION USING NASAL SPRAY**
  - Child 16-17 years: 200 micrograms 1-2 times a day, to be administered into each nostril, alternative treatment should be considered if no improvement after 4–6 weeks, (200 micrograms is equivalent to approximately 6 drops).
  - Adult: 200 micrograms 1–2 times a day, to be administered into each nostril, alternative treatment should be considered if no improvement after 4–6 weeks, (200 micrograms is equivalent to approximately 6 drops).

**AVAMYS® SPRAY**

**Prophylaxis and treatment of allergic rhinitis**

- **BY INTRANASAL ADMINISTRATION**
  - Child 6-11 years: 27.5 micrograms once daily, dose to be sprayed into each nostril, then increased if necessary to 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 27.5 micrograms once daily, to be sprayed into each nostril, dose to be reduced once control achieved; use minimum effective dose.
  - Adult: 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 27.5 micrograms once daily, to be sprayed into each nostril, dose to be reduced once control achieved; use minimum effective dose.
  - Adult: 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 27.5 micrograms once daily, to be sprayed into each nostril, dose to be reduced once control achieved; use minimum effective dose.

**DOSE EQUIVALENCE AND CONVERSION**

- For Avamys® spray: 1 spray equivalent to 27.5 micrograms.

**SIDE-EFFECTS** Nasal ulceration occurs commonly with nasal preparations containing fluticasone furoate.

**EXCEPTIONS TO LEGAL CATEGORY**

Preparations of fluticasone propionate can be sold to the public for nasal administration (other than by pressurised nasal spray) if supplied for the prevention and treatment of allergic rhinitis in adults over 18 years, subject to max. single dose of 100 micrograms per nostril, max. daily dose of 200 micrograms per nostril for max. 3 months, and a pack size of 3 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate, polysorbates, propylene glycol.

- Fluticasone propionate 50 microgram per 1 dose
  - Pirinase 50 micrograms/dose aqueous nasal spray | 100 dose | £0.50
  - Nasofan 50 micrograms/dose aqueous nasal spray | 100 dose | no price available
  - Flixonase (GlaxoSmithKline Consumer Healthcare)
  - Fluticasone propionate 50 microgram per 1 dose
    - Nasofan Allergy 50 micrograms/dose nasal spray | 60 dose | £4.68
  - Avamys (GlaxoSmithKline UK Ltd)
  - Fluticasone furoate 27.5 microgram per 1 dose
    - 27.5 micrograms/dose nasal spray | 120 dose | £6.44 DT price = £6.44
  - Flixonase (GlaxoSmithKline UK Ltd)
  - Fluticasone propionate 50 microgram per 1 dose
    - 50 micrograms/dose aqueous nasal spray | 150 dose | £11.01 DT price = £11.01
  - Rhinocort (AstraZeneca UK Ltd)
  - Fluticasone propionate 50 microgram per 1 dose
    - 100 micrograms/dose nasal spray | 50 dose | £4.44
  - Fluticasone propionate 50 microgram per 1 dose
    - Nasofan Allergy 100 micrograms/dose nasal spray | 60 dose | £4.44
  - Flixonase (GlaxoSmithKline UK Ltd)
  - Flixonase (GlaxoSmithKline Consumer Healthcare)
Fluticasone with azelastine

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 1060, azelastine hydrochloride p. 1017.

- **INDICATIONS AND DOSE**
  - **Moderate to severe seasonal and perennial allergic rhinitis, if monotherapy with antihistamine or corticosteroid is inadequate**
    - **BY INTRANASAL ADMINISTRATION**
    - Child 12-17 years: 1 spray twice daily, dose to be administered into each nostril.
    - Adult: 1 spray twice daily, dose to be administered into each nostril.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Spray**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, polysorbates
    - **Fluticasone with azelastine (Non-proprietary)**
    - Fluticasone propionate 50 microgram per 1 actuation, Azelastine hydrochloride 137 microgram per 1 actuation
    - Fluticasone propionate 50 microgram per 1 actuation, Azelastine hydrochloride 137 microgram per 1 actuation
    - **Dymista** (Meda Pharmaceuticals Ltd)
      - Fluticasone propionate 50 microgram per 1 actuation, Azelastine hydrochloride 137 microgram per 1 actuation
      - **Dymista (Meda Pharmaceuticals Ltd)**
        - Fluticasone propionate 50 microgram per 1 actuation, Azelastine hydrochloride 137 microgram per 1 actuation
  - **Nasal drops**
    - **EXCIPIENTS:** May contain Polysorbates

Mometasone furoate

- **INDICATIONS AND DOSE**
  - **Prophylaxis and treatment of allergic rhinitis**
    - **BY INTRANASAL ADMINISTRATION**
      - **Child 6-11 years:** 55 micrograms once daily, dose to be sprayed into each nostril, reduced if necessary to 110 micrograms once daily, dose to be sprayed into each nostril; reduced to 55 micrograms once daily, dose to be sprayed into each nostril, reduced dose when control achieved; maximum duration of treatment 3 months
      - **Child 12-17 years:** 110 micrograms once daily, dose to be sprayed into each nostril, reduced to 55 micrograms once daily, dose to be sprayed into each nostril, reduced dose when control achieved.
      - **Adult:** 110 micrograms once daily, dose to be sprayed into each nostril, reduced to 55 micrograms once daily, dose to be sprayed into each nostril, reduced dose when control achieved.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Spray**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, polysorbates
    - **Mometasone furoate (Non-proprietary)**
    - **Mometasone furoate 50 microgram per 1 dose**
      - **Mometasone furoate 50 microgram per 1 dose**
    - **Nasonex** (Merck Sharp & Dohme Ltd)
      - **Mometasone furoate 50 microgram per 1 dose**

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Preparations of triamcinolone acetonide can be sold to the public for nasal administration as a non-presurised nasal spray if supplied for the symptomatic treatment of seasonal allergic rhinitis in adults over 18 years, subject to maximum daily dose of 110 micrograms per nostril for maximum 3 months, and a pack size of 3.575 mg.

- **SIDE-EFFECTS**
  - Nasal ulceration occurs commonly with preparations containing mometasone furoate.

Ear, nose and oropharynx

- **Sodium cromoglicate**
  - **(Sodium cromoglycate)**
    - **INDICATIONS AND DOSE**
      - **Prophylaxis of allergic rhinitis**
        - **BY INTRANASAL ADMINISTRATION**
          - **Child:** 1 spray 2–4 times a day, to be administered into each nostril.
          - **Adult:** 1 spray 2–4 times a day, to be administered into each nostril.
    - **UNLICENSED USE**
      - Licensed for use in children (age range not specified by manufacturers).
    - **SIDE-EFFECTS**
      - **Rare**
        - Transient bronchospasm
      - **Frequency not known**
        - Local irritation
Oropharynx

1 Dry mouth

Treatment of dry mouth

Overview
Dry mouth (xerostomia) may be caused by drugs with antimuscarinic (anticholinergic) side-effects (e.g. antispasmodics, tricyclic antidepressants, and some antipsychotics), by diuretics, by irradiation of the head and neck region or by damage to or disease of the salivary glands. Patients with a persistently dry mouth may develop a burning or scalded sensation and have poor oral hygiene; they may develop increased dental caries, periodontal disease, intolerance of dentures, and oral infections (particularly candidiasis). Dry mouth may be relieved in many patients by simple measures such as frequent sips of cool drinks or sucking pieces of ice or sugar-free fruit pastilles. Sugar-free chewing gum stimulates salivation in patients with residual salivary function.

Artificial saliva can provide useful relief of dry mouth. A properly balanced artificial saliva should be of a neutral pH and contain electrolytes (including fluoride) to correspond approximately to the composition of saliva. The acidic pH of some artificial saliva products may be inappropriate. Of the proprietary preparations, Agural®, Biôtène Oralbalance® gel or Xerolin® can be used for any condition giving rise to a dry mouth. BioXtra®, Glandosane®, Saliva Orthana®, and Saliveze®, have ACBS approval for dry mouth associated only with radiotherapy or sicca syndrome. Salivix® pastilles, which act locally as salivary stimulants, are also available for any condition leading to a dry mouth and SST tablets may be prescribed for dry mouth in patients with salivary gland impairment (and patent salivary ducts). Pilocarpine tablets, below, are licensed for the treatment of xerostomia following irradiation for head and neck cancer and for dry mouth and dry eyes (xerophthalmia) in Sjögren’s syndrome. They are effective only in patients who have some residual salivary gland function, and therefore should be withdrawn if there is no response.

LUBRICANTS

Artificial saliva products

● ARTIFICIAL SALIVA PRODUCTS
AS SALIVA ORTIANA® LOZENGES
Mucin 65 mg, xylitol 59 mg, in a sorbitol basis, pH neutral

● INDICATIONS AND DOSE
Dry mouth as a result of having (or having undergone) radiotherapy / Sicca syndrome

BY MOUTH
Adult: 5 mg twice daily; children and adults over 60 may be given 2.5 mg daily

AS SALIVA ORTIANA® SPRAY
Gastric mucin (porcine) 3.5%, xylitol 2%, sodium fluoride 4.2 mg/litre, with preservatives and flavouring agents, pH neutral.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified

● CONTRA-INDICATIONS
Acute iritis · chronic obstructive pulmonary disease (increased bronchial secretions and increased airways resistance) · uncontrolled asthma (increased bronchial secretions and increased airways resistance) · uncontrolled cardiorenal disease

● CAUTIONS
Asthma (avoid if uncontrolled) · biliary-tract disease · cardiovascular disease (avoid if uncontrolled) · cholelithiasis · chronic obstructive pulmonary disease (avoid if uncontrolled) · cognitive disturbances · maintain adequate fluid intake to avoid dehydration associated with excessive sweating · peptic ulceration · psychiatric disturbances · risk of increased renal colic · risk of increased urethral smooth muscle tone · susceptibility to angle-closure glaucoma

● INTERACTIONS
Appendix 1 (parasympathomimetics).

● SIDE-EFFECTS
Common or very common
Influenza-like symptoms · abdominal pain · asthenia · conjunctivitis · constipation · diarrhoea · dizziness · dyspepsia · flushing · headache · hypertension · increased urinary frequency · lacrimation · nausea · ocular pain · palpitation · pruritus · rash · rhinitis · sweating · visual disturbances · vomiting

Uncommon
Flatulence · urinary urgency

PREGNANCY
Avoid—smooth muscle stimulant; toxicity in animal studies.

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Reduce initial oral dose in moderate or severe cirrhosis.

RENAL IMPAIRMENT
Manufacturer advises caution with tablets.

PATIENT AND CARER ADVICE
Driving and skilled tasks
Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

Manufacturer advises caution with

Salagen® (Merus Labs Luxembourg S.A.R.L.)
Pilocarpine hydrochloride 5 mg, 84 tablet pack £41.14 DT price = £41.14

Patient and carer advice

Adult: 5 mg 3 times a day for 4 weeks, then increased if tolerated to up to 30 mg daily in divided doses if required, dose to be taken with or immediately after meals (last dose always with evening meal), maximum therapeutic effect normally within 4–8 weeks; discontinue if no improvement after 2–3 months

Dry mouth and dry eyes in Sjögren’s syndrome

BY MOUTH
Adult: 5 mg 4 times a day; increased if tolerated to up to 30 mg daily in divided doses if required, dose to be taken with meals and at bedtime, discontinue if no improvement after 2–3 months

Pilocarpine

INDICATIONS AND DOSE
Xerostomia following irradiation for head and neck cancer

BY MOUTH
Adult: 5 mg 3 times a day for 4 weeks, then increased if tolerated to up to 30 mg daily in divided doses if required, dose to be taken with or immediately after meals (last dose always with evening meal), maximum therapeutic effect normally within 4–8 weeks; discontinue if no improvement after 2–3 months

Dry mouth and dry eyes in Sjögren’s syndrome

BY MOUTH
Adult: 5 mg 4 times a day; increased if tolerated to up to 30 mg daily in divided doses if required, dose to be taken with meals and at bedtime, discontinue if no improvement after 2–3 months

PARASYMPATHOMIMETICS

Pilocarpine

Artificial saliva products

● ARTIFICIAL SALIVA PRODUCTS
AS SALIVA ORTIANA® LOZENGES
Mucin 65 mg, xylitol 59 mg, in a sorbitol basis, pH neutral

● INDICATIONS AND DOSE
Dry mouth as a result of having (or having undergone) radiotherapy / Sicca syndrome

BY MOUTH
Adult: 1 lozenge as required, allow to dissolve slowly in the mouth

AS Saliva Orthana® lozenges do not contain fluoride.

AS Saliva Orthana lozenges (A S Pharma Ltd)
30 lozenge(ACBS) · NHS indicative price = £3.50

AS SALIVA ORTIANA® SPRAY
Gastric mucin (porcine) 3.5%, xylitol 2%, sodium fluoride 4.2 mg/litre, with preservatives and flavouring agents, pH neutral.
Dry mouth may be a symptom of many diseases, may be associated with medical treatments or may be a side-effect of some medications. The products listed below are either commercially available products or they have been evaluated by the Medicines and Healthcare products Regulatory Agency (MHRA) as having potential benefit for the products listed below. In some cases, they may be used outside the licensed indications. The list is not exhaustive and prescribers should refer to the individual product literature for further information.

### Indications and Dose

**Symptomatic treatment of dry mouth**

- **BY MOUTH**
- Adult: Apply as required, spray onto oral and pharyngeal mucosa

#### Professional Specific Information

**Dental practitioners’ formulary**

**AS Saliva Orthana** Oral Spray may be prescribed.

**AS Saliva Orthanaspray** (CCMed Ltd) 50 ml - NHS indicative price = £4.924

**BioXtra** Lactoperoxidase, lactoferrin, lysozyme, whey colostrum, xylitol and other ingredients.

**BioXtra Dry Mouth oral gel** (R.U.S. Products Ltd) 40 ml - NHS indicative price = £3.94 - Drug Tariff (Part IXa)

**Biotene Oralbalance** Lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis

**Biotene Oralbalance Oral Spray** May be prescribed as Artificial Saliva Gel.

**BioXtra Oral Spray** May be prescribed.

**BioXtra Dry Mouth Oral Gel** Contains traces of milk protein and egg white protein.

**BNF 73**

**Salivix** Sugar-free, reddish-amber, acacia, malic acid and other ingredients in a sorbitol base.

**SST** Sugar-free, citric acid, malic acid and other ingredients in a sorbitol base.

**Saliveze** Carmellose sodium (sodium carboxymethylcellulose), calcium chloride, magnesium chloride, potassium chloride, sodium chloride, and dibasic sodium phosphate, pH neutral

**Glandosane** Synthetic saliva spray citrus (Fresenius Kabi Ltd) 50 ml(ACBS) - NHS indicative price = £5.58

**Saliveze mouth spray** (Wyvern Medical Ltd) 50 ml (ACBS) - NHS indicative price = £3.50

**Salivix** Spray, Sugar-free, water, sorbitol, carmellose (carboxymethylcellulose), potassium chloride, sodium...
Ear, nose and oropharynx

Mouthwash is ideal and can be prepared either by dissolving must be used frequently and vigorously. A warm saline cause some local hyperaemia. However, to be effective, they mouthwashes which have a mechanical cleansing effect and Super Mouthwashes, gargles, and dentifrices preparations also contain local anaesthetics which relieve and cause sore tongue and sore lips. Some of these Lozenges and sprays preparations for oropharyngeal use Mouthwashes and other preparations for oropharyngeal use

Lozenges and sprays
There is no convincing evidence that antiseptic lozenges and sprays have a beneficial action and they sometimes irritate and cause sore tongue and sore lips. Some of these preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

Mouthwashes, gargles, and dentifrices
Superficial infections of the mouth are often helped by warm mouthwashes which have a mechanical cleansing effect and cause some local hyperaemia. However, to be effective, they must be used frequently and vigorously. A warm saline mouthwash is ideal and can be prepared either by dissolving half a teaspoonful of salt in a glassful of warm water or by diluting compound sodium chloride mouthwash p. 1066 with an equal volume of warm water.

Mouthwashes containing an oxidising agent, such as hydrogen peroxide p. 1065, may be useful in the treatment of acute ulcerative gingivitis (Vincent’s infection) since the organisms involved are anaerobes. It also has a mechanical cleansing effect arising from frothing when in contact with oral debris.

Chlorhexidine, below, is an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth. It does not, however, completely control plaque deposition and is not a substitute for effective toothbrushing. Moreover, chlorhexidine preparations do not penetrate significantly into stagnation areas and are therefore of little value in the control of dental caries or of periodontal disease once pocketing has developed.

Chlorhexidine mouthwash is used in the treatment of denture stomatitis. It is also used in the prevention of oral candidiasis in immuno compromised patients. Chlorhexidine mouthwash reduces the incidence of alveolar osteitis following tooth extraction. Chlorhexidine mouthwash should not be used for the prevention of endocarditis in patients undergoing dental procedures.

Chlorhexidine can be used as a mouthwash, spray or gel for secondary infection in mucosal ulceration and for controlling gingivitis, as an adjunct to other oral hygiene measures. These preparations may also be used instead of toothbrushing where there is a painful periodontal condition (e.g. primary herpetic stomatitis) or if the patient has a haemorrhagic disorder, or is disabled.

Chlorhexidine preparations are of little value in the control of acute necrotising ulcerative gingivitis. With prolonged use, chlorhexidine causes reversible brown staining of teeth and tongue. Chlorhexidine may be incompatible with some ingredients in toothpaste, causing an unpleasant taste in the mouth; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing products.

There is no convincing evidence that gargles are effective in adults.

2 Oral hygiene

Mouthwashes and other preparations for oropharyngeal use


Chlorhexidine

**INDICATIONS AND DOSE**

**Symptomatic treatment of dry mouth**

- **By mouth**
  - Adult: 1 spray as required

**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulary**

Xerotin® Oral Spray may be prescribed as Artificial Saliva Oral Spray.

Xerotin spray (SpePharm UK Ltd)

100 ml - NHS indicative price = £6.86 - Drug Tariff (Part IXa)

**2 Oral hygiene**

**Mouthwashes and other preparations for oropharyngeal use**

**Lozenges and sprays**

There is no convincing evidence that antiseptic lozenges and sprays have a beneficial action and they sometimes irritate and cause sore tongue and sore lips. Some of these preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

**Mouthwashes, gargles, and dentifrices**

Superficial infections of the mouth are often helped by warm mouthwashes which have a mechanical cleansing effect and cause some local hyperaemia. However, to be effective, they must be used frequently and vigorously. A warm saline mouthwash is ideal and can be prepared either by dissolving half a teaspoonful of salt in a glassful of warm water or by diluting compound sodium chloride mouthwash p. 1066 with an equal volume of warm water.

Mouthwashes containing an oxidising agent, such as hydrogen peroxide p. 1065, may be useful in the treatment of acute ulcerative gingivitis (Vincent’s infection) since the organisms involved are anaerobes. It also has a mechanical cleansing effect arising from frothing when in contact with oral debris.

Chlorhexidine, below, is an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth. It does not, however, completely control plaque deposition and is not a substitute for effective toothbrushing. Moreover, chlorhexidine preparations do not penetrate significantly into stagnation areas and are therefore of little value in the control of dental caries or of periodontal disease once pocketing has developed.

Chlorhexidine mouthwash is used in the treatment of denture stomatitis. It is also used in the prevention of oral candidiasis in immuno compromised patients. Chlorhexidine mouthwash reduces the incidence of alveolar osteitis following tooth extraction. Chlorhexidine mouthwash should not be used for the prevention of endocarditis in patients undergoing dental procedures.

Chlorhexidine can be used as a mouthwash, spray or gel for secondary infection in mucosal ulceration and for controlling gingivitis, as an adjunct to other oral hygiene measures. These preparations may also be used instead of toothbrushing where there is a painful periodontal condition (e.g. primary herpetic stomatitis) or if the patient has a haemorrhagic disorder, or is disabled.

Chlorhexidine preparations are of little value in the control of acute necrotising ulcerative gingivitis. With prolonged use, chlorhexidine causes reversible brown staining of teeth and tongue. Chlorhexidine may be incompatible with some ingredients in toothpaste, causing an unpleasant taste in the mouth; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing products.

There is no convincing evidence that gargles are effective in adults.

**ANTISEPTICS AND DISINFECTANTS > OTHER**

**Chlorhexidine**

**INDICATIONS AND DOSE**

**Oral hygiene and plaque inhibition | Oral candidiasis | Gingivitis | Management of aphthous ulcers**

- **By mouth using mouthwash**
  - Child: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)
  - Adult: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)

**Denture stomatitis**

- **Mouthwash**
  - Adult: Cleanse and soak dentures in mouthwash solution for 15 minutes twice daily

**Oral hygiene and plaque inhibition and gingivitis**

- **By mouth using dental gel**
  - Child: Apply 1–2 times a day, to be brushed on the teeth
  - Adult: Apply 1–2 times a day, to be brushed on the teeth

**Oral candidiasis | Management of aphthous ulcers**

- **By mouth using dental gel**
  - Child: Apply 1–2 times a day, to affected areas
  - Adult: Apply 1–2 times a day, to affected areas

**Oral hygiene and plaque inhibition | Oral candidiasis | Gingivitis | Management of aphthous ulcers**

- **By mouth using oromucosal spray**
  - Child: Apply up to 12 sprays twice daily as required, to be applied tooth, gingival, or ulcer surfaces
  - Adult: Apply up to 12 sprays twice daily as required, to be applied tooth, gingival, or ulcer surfaces

**Bladder irrigation and catheter patency solutions**

- **By intravesical instillation**
  - Adult: (consult product literature)

**UNLICENSED USE**

Corsodyl® not licensed for use in children under 12 years (unless on the advice of a healthcare professional).

**SIDE-EFFECTS**

Anaphylaxis | hypersensitivity | mucosal irritation | parotid gland swelling | reversible brown staining of composite restorations | reversible brown staining of silicate compositions | reversible brown staining of teeth | taste disturbance | tongue discolouration

**SIDE-EFFECTS, FURTHER INFORMATION**

If desquamation occurs with mucosal irritation, discontinue treatment or dilute mouthwash with an equal volume of water.

**PATIENT AND CARER ADVICE**

Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing product.

**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulary**

Corsodyl® dental gel may be prescribed as Chlorhexidine Gluconate Gel; Corsodyl® mouthwash may be prescribed as Chlorhexidine Mouthwash; Corsodyl® oral spray may be prescribed as Chlorhexidine Oral Spray.
Hydrogen peroxide

**INDICATIONS AND DOSE**

**Oral hygiene (with hydrogen peroxide 6%)**

- **BY MOUTH USING MOUTHWASH**
  - Child: Rinse or gargle 15 mL 2–3 times a day for 2–3 minutes, to be diluted in half a tumblerful of warm water
  - Adult: Rinse or gargle 15 mL 2–3 times a day for 2–3 minutes, to be diluted in half a tumblerful of warm water

**PEROXYL®**

**Oral hygiene**

- **BY MOUTH USING MOUTHWASH**
  - Child 6–17 years: Rinse or gargle 10 mL 3 times a day for about 1 minute, for maximum 7 days, to be used after meals and at bedtime
  - Adult: Rinse or gargle 10 mL up to 4 times a day for about 1 minute, to be used after meals and at bedtime

**SIDE-EFFECTS**

Hypertrophy of papillae of tongue on prolonged use

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Hydrogen Peroxide Mouthwash, BP consists of hydrogen peroxide 6% solution (= approx. 20 volume) BP.

**HANDLING AND STORAGE**

Hydrogen peroxide bleaches fabric.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary

Hydrogen Peroxide Mouthwash may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Mouthwash**

- **Peroxyl®** (Colgate-Palmolive (UK) Ltd)
  - **Hydrogen peroxide 15 mg per 1 ml**
    - Peroxyl 1.5% mouthwash sugar-free | 300 mL **£2.94**

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**Chlorhexidine with chlorobutanol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1064.

**INDICATIONS AND DOSE**

**Oral hygiene and plaque inhibition**

- **BY MOUTH USING MOUTHWASH**
  - Child 6–17 years: Rinse or gargle 10–15 mL 2–3 times a day, to be diluted with lukewarm water in measuring cup provided
  - Adult: Rinse or gargle 10–15 mL 2–3 times a day, to be diluted with lukewarm water in measuring cup provided

**Denture disinfection**

- Adult: Soak previously cleansed dentures in mouthwash (diluted with 2 volumes of water) for 60 minutes

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of mouthwash may include mint.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

No licensed medicines identified.

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**Hexetidine**

**INDICATIONS AND DOSE**

**Oral hygiene**

- **BY MOUTH USING MOUTHWASH**
  - Child 6–17 years: Rinse or gargle 15 mL 2–3 times a day, to be used undiluted
  - Adult: Rinse or gargle 15 mL 2–3 times a day, to be used undiluted

**SIDE-EFFECTS**

- Very rare Taste disturbance • transient anaesthesia
- Frequency not known Local irritation

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Mouthwash**

- **Oraldene (McNeil Products Ltd)**
  - Hexetidine 1 mg per 1 ml
    - Oraldene Icemint 0.1% mouthwash sugar-free | 200 mL **£2.21 DT price = £2.21**
    - Oraldene 0.1% mouthwash peppermint sugar-free | 100 mL **£1.43 sugar-free | 200 mL **£2.21 DT price = £2.21**

**REFERENCES**

- Prepared extemporaneously
- BP

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**Hydrogen peroxide**

**INDICATIONS AND DOSE**

**Oral hygiene (with hydrogen peroxide 6%)**

- **BY MOUTH USING MOUTHWASH**
  - Child: Rinse or gargle 15 mL 2–3 times a day for 2–3 minutes, to be diluted in half a tumblerful of warm water
  - Adult: Rinse or gargle 15 mL 2–3 times a day for 2–3 minutes, to be diluted in half a tumblerful of warm water

**PEROXYL®**

**Oral hygiene**

- **BY MOUTH USING MOUTHWASH**
  - Child 6–17 years: Rinse or gargle 10 mL 3 times a day for about 1 minute, for maximum 7 days, to be used after meals and at bedtime
  - Adult: Rinse or gargle 10 mL up to 4 times a day for about 1 minute, to be used after meals and at bedtime

**SIDE-EFFECTS**

Hypertrophy of papillae of tongue on prolonged use

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Hydrogen Peroxide Mouthwash, BP consists of hydrogen peroxide 6% solution (= approx. 20 volume) BP.

**HANDLING AND STORAGE**

Hydrogen peroxide bleaches fabric.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary

Hydrogen Peroxide Mouthwash may be prescribed.
**Sodium bicarbonate with sodium chloride**

- **INDICATIONS AND DOSE**
  - **Oral hygiene**
    - BY MOUTH USING MOUTHWASH
    - Adult: (consult product literature)

- **DIRECTIONS FOR ADMINISTRATION**
  For mouthwash, extemporaneous preparations should be prepared according to the following formula: sodium chloride 1.5 g, sodium bicarbonate 1 g, concentrated peppermint emulsion 2.5 mL, double-strength chloroform water 50 mL, water to 100 mL. To be diluted with an equal volume of warm water prior to administration.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Flavours of mouthwash may include peppermint.

- **PROFESSION SPECIFIC INFORMATION**
  Dental practitioners' formulary
  Compound sodium chloride mouthwash may be prescribed.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Flavors available from special-order manufacturers include: mouthwash

**Sodium chloride**

- **INDICATIONS AND DOSE**
  - **Oral hygiene**
    - BY MOUTH USING MOUTHWASH
    - Child: Rinse or gargle as required
    - Adult: Rinse or gargle as required

- **DIRECTIONS FOR ADMINISTRATION**
  Extemporaneous mouthwash preparations should be prepared according to the following formula: sodium chloride 1.5 g, sodium bicarbonate 1 g, concentrated peppermint emulsion 2.5 mL, double-strength chloroform water 50 mL, water to 100 mL. To be diluted with an equal volume of warm water.

- **PRESCRIBING AND DISPENSING INFORMATION**
  No mouthwash preparations available—when prepared extemporaneously, the BP states Sodium Chloride Mouthwash, Compound, BP consists of sodium bicarbonate 1%, sodium chloride 1.5% in a suitable vehicle with peppermint flavour.

- **PROFESSION SPECIFIC INFORMATION**
  Dental practitioners' formulary
  Compound Sodium Chloride Mouthwash may be prescribed.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. No Licensed medicines identified

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### 2.1 Dental caries

**Fluoride**

Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect.

When the fluoride content of drinking water is less than 700 micrograms per litre (0.7 parts per million), daily administration of fluoride tablets or drops provides suitable supplementation. Systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply. Infants need not receive fluoride supplements until the age of 6 months.

Dentifrices which incorporate sodium fluoride or monofluorophosphate are also a convenient source of fluoride.

Individuals who are either particularly caries prone or medically compromised may be given additional protection by use of fluoride rinses or by application of fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied regularly under professional supervision; extreme caution is necessary to prevent children from swallowing any excess. Less concentrated gels are available for home use. Varnishes are also available and are particularly valuable for young or disabled children since they adhere to the teeth and set in the presence of moisture.

**VITAMINS AND TRACE ELEMENTS**

**Sodium fluoride**

- **INDICATIONS AND DOSE**
  - **Prophylaxis of dental caries for water content less than 300 micrograms/litre (0.3 parts per million) of fluoride ion**
    - BY MOUTH USING TABLETS
    - Child 6 months–2 years: 250 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 3–5 years: 500 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 6–17 years: 1 mg daily, doses expressed as fluoride ion (F⁻)
    - Adult: 1 mg daily, doses expressed as fluoride ion (F⁻)
  - **Prophylaxis of dental caries for water content between 300 and 700 micrograms/litre (0.3–0.7 parts per million) of fluoride ion**
    - BY MOUTH USING TABLETS
    - Child 6 months–2 years: 250 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 3–5 years: 500 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 6–17 years: 1 mg daily, doses expressed as fluoride ion (F⁻)
    - Adult: 500 micrograms daily, doses expressed as fluoride ion (F⁻)
  - **Prophylaxis of dental caries for water content above 700 micrograms/litre (0.7 parts per million) of fluoride ion**
    - Child 6 months–17 years: Supplements not advised
    - Adult: Supplements not advised
  - **Prophylaxis of dental caries for individuals who are caries prone or medically compromised**
    - BY MOUTH USING PASTE
    - Child 10–17 years: Apply 1 centimetre twice daily, to be applied using a toothbrush
    - Adult: Apply 1 centimetre twice daily, to be applied using a toothbrush
  - **COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE**
    - **Prophylaxis of dental caries**
      - BY MOUTH USING PASTE
      - Child 10–17 years: Apply 2 centimetres 3 times a day, to be applied after meals using a toothbrush
      - Adult: Apply 2 centimetres 3 times a day, to be applied after meals using a toothbrush
EN-DE-KAY® FLUORINSE
Prophylaxis of dental carries for individuals who are caries prone or medically compromised
▶ BY MOUTH USING MOUTHWASH
▶ Adult: 5 drops daily, dilute 5 drops to 10 mL of water, alternatively 20 drops once weekly, dilute 20 drops to 10 mL.
DOSE EQUIVALENCE AND CONVERSION
▶ Sodium fluoride 2.2 mg provides approx. 1 mg fluoride ion.
▶ These doses reflect the recommendations of the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry (Br Dent J 1997; 182: 6–7).

● CONTRA-INDICATIONS Not for areas where drinking water is fluoridated
● SIDE-EFFECTS
▶ Uncommon Occasional white flecks on teeth with recommended doses
▶ Rare Yellowish-brown discoloration if recommended doses are exceeded
● DIRECTIONS FOR ADMINISTRATION
▶ With oral use Tablets should be sucked or dissolved in the mouth and taken preferably in the evening.
▶ With oral (topical) use For mouthwash, rinse mouth for 1 minute and then spit out.
COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE Brush teeth for 1 minute before spitting out.
COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE Brush teeth for 3 minutes before spitting out.
● PRESCRIBING AND DISPENSING INFORMATION Flavours of oral tablet formulations may include orange.
● PATIENT AND CARER ADVICE
Mouthwash Avoid eating, drinking, or rinsing mouth for 15 minutes after use.
COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE Patients or carers should be given advice on how to administer sodium fluoride toothpaste. Avoid drinking or rinsing mouth for 30 minutes after use.
COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE Patients or carers should be given advice on how to administer Sodium fluoride toothpaste.
● PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Tablets may be prescribed as Sodium Fluoride Tablets. Oral drops may be prescribed as Sodium Fluoride Oral Drops. Mouthwashes may be prescribed as Sodium Fluoride Mouthwash 0.05% or Sodium Fluoride Mouthwash 2%.
COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE May be prescribed as Sodium Fluoride Toothpaste 0.619%.
COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE May be prescribed as Sodium Fluoride Toothpaste 1.1%.
Dental information Fluoride mouthwash, oral drops, tablets and toothpaste are prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).
There are also arrangements for health authorities to supply fluoride tablets in the course of pre-school dental schemes, and they may also be supplied in school dental schemes.
Fluoride gels are not prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet
▶ Endekay (Manx Healthcare Ltd)
Sodium fluoride 1.1 mg Endekay Fluotabs 3–6 Years 1.1 mg tablets | 200 tablet | £2.38 DT price = £2.38
Sodium fluoride 2.2 mg Endekay Fluotabs 6+ Years 2.2 mg tablets | 200 tablet | £2.38 DT price = £2.38
Chewable tablet
▶ Fluor-a-day (Dental Health Products Ltd)
Sodium fluoride 1.1 mg Fluor-a-day 1.1 mg chewable tablets sugar-free | 200 tablet | £2.79 DT price = £2.79
Sodium fluoride 2.2 mg Fluor-a-day 2.2 mg chewable tablets sugar-free | 200 tablet | £2.79 DT price = £2.79
Oral drops
▶ Endekay (Manx Healthcare Ltd)
Sodium fluoride 3.7 mg per 1 ml Endekay Fluodrops 0.37% drops paediatric sugar-free | 60 ml | £2.38 DT price = £2.38
Paste
▶ Colgate Duraphat (Colgate-Palmolive (UK) Ltd)
Fluoride (as Sodium fluoride) 2.8 mg per 1 gm Colgate Duraphat 2800 ppm fluoride toothpaste sugar-free | 75 ml | £3.26 DT price = £3.26
Fluoride (as Sodium fluoride) 5 mg per 1 gm Colgate Duraphat 5000 ppm fluoride toothpaste sugar-free | 51 gm | £6.50 DT price = £6.50
Mouthwash
▶ Sodium fluoride (Non-proprietary)
Sodium fluoride 500 microgram per 1 mL Sodium fluoride 0.05% mouthwash sugar-free sugar-free | 250 ml | £3.51 no price available
Sodium fluoride 5000 microgram per 1 mL Sodium fluoride 0.5% daily dentine rinse alcohol-free sugar-free | 250 ml | £3.51 no price available
Colgate FluorGard (Colgate-Palmolive (UK) Ltd)
Sodium fluoride 500 microgram per 1 mL Colgate FluorGard 0.05% daily dentine rinse alcohol free sugar-free | 400 mL | £2.99
Colgate FluorGard 0.05% daily dentine rinse sugar-free | 400 mL | £2.99
Endekay (Manx Healthcare Ltd)
Sodium fluoride 500 microgram per 1 mL Endekay 0.05% daily fluoride mouthrinse sugar-free | 250 mL | £1.51 DT price = £1.51
Sodium fluoride 2 mg per 1 mL Endekay 0.5% daily fluoride mouthrinse sugar-free | 200 mL | £1.14

3 Oral ulceration and inflammation

Ulceration and inflammation
Ulceration of the oral mucosa may be caused by trauma (physical or chemical), recurrent aphthae, infections, carcinoma, dermatological disorders, nutritional deficiencies, gastro-intestinal disease, haematopoietic disorders, and drug therapy (see also Chemotherapy induced mucositis and myelosuppression under Cytotoxic drugs p. 797). It is important to establish the diagnosis in each case as the majority of these lesions require specific management in addition to local treatment. Local treatment aims to protect the ulcerated area, to relieve pain, to reduce inflammation, or to control secondary infection. Patients with an unexplained mouth ulcer of more than 3 weeks’ duration require urgent referral to hospital to exclude oral cancer.

Simple mouthwashes
A saline mouthwash may relieve the pain of traumatic ulceration. The mouthwash is made up with warm water and used at frequent intervals until the discomfort and swelling subsides.
Antiseptic mouthwashes
Secondary bacterial infection may be a feature of any mucosal ulceration; it can increase discomfort and delay healing. Use of a chlorhexidine mouthwash p. 1064 is often beneficial and may accelerate healing of recurrent aphthae.

Corticosteroids
Topical corticosteroid therapy may be used for some forms of oral ulceration. In the case of aphthous ulcers it is most effective if applied in the ‘prodromal’ phase.

Thrush or other types of candidiasis are recognised complications of corticosteroid treatment.

Hydrocortisone oromucosal tablets p. 1070 are allowed to dissolve next to an ulcer and are useful in recurrent aphthae and erosive lichenoid lesions. Beclometasone dipropionate tablets p. 1052 dissolved in water can be used as a mouthwash to treat oral ulceration [unlicensed indication]. Systemic corticosteroid therapy (see under Corticosteroids, inflammatory disorders p. 1011), is reserved for severe conditions such as pemphigus vulgaris.

Local analgesics
Local analgesics have a limited role in the management of oral ulceration. When applied topically their action is of a relatively short duration so that analgesia cannot be prolonged. For this purpose lidocaine hydrochloride 5% ointment, below, or lozenges containing a local anaesthetic are applied to the ulcer. Lidocaine hydrochloride 10% solution as spray can be applied thinly to the ulcer [unlicensed indication] using a cotton bud. When local anaesthetics are used in the mouth care must be taken not to produce anaesthesia of the pharynx before meals as this might lead to choking.

Preparations on sale to the public: many mouth ulcer preparations, throat lozenges, and throat sprays on sale to the public contain a local anaesthetic. To identify the active ingredients in such preparations, consult the product literature of the manufacturer—this might lead to choking.

Avoid anaesthesia of the pharynx before meals—risk of choking. Some preparations, such as those containing lidocaine or flurbiprofen, are allowed to be used in the mouth without the need for dilution. If a preparation contains two or more active ingredients, it may not be possible to estimate their relative effect. Consult the product literature when using such preparations.

Mouthwashes and other preparations for oropharyngeal use p. 1064 for mouthwashes used for oral hygiene and plaque inhibition.

ANAESTHETICS, LOCAL

Lidocaine hydrochloride
(Lignocaine hydrochloride)

- **INDICATIONS AND DOSE**

  - **Dental practice**
    - BY BUCCAL ADMINISTRATION USING OINTMENT
    - Adult: Rub gently into dry gum
  - **Relief of pain in oral lesions**
    - TO THE LESION USING OINTMENT
    - Adult: Apply as required, rub sparingly and gently on affected areas

  **LARYNGOJET®**

  - **Anaesthesia of mucous membranes of oropharynx, trachea, or respiratory tract**
    - TO MUCOUS MEMBRANES
    - Adult: Up to 20 doses
  - **Dental practice**
    - TO MUCOUS MEMBRANES
    - Adult: 1–5 doses
  - **Maxillary sinus puncture**
    - TO MUCOUS MEMBRANES
    - Adult: 3 doses
  - **Relief of pain in oral lesions**
    - TO THE LESION
    - Adult: Apply thinly to the ulcer using a cotton bud

- **UNLICENSED USE** Spray not licensed for the relief of pain in oral lesions.

- **CAUTIONS** Avoid anaesthesia of the pharynx before meals—risk of choking, can damage plastic cuffs of endotracheal tubes

- **INTERACTIONS** → Appendix 1 (lidocaine). Interactions less likely when lidocaine used topically.

- **SIDE-EFFECTS** A single application of a topical lidocaine preparation does not generally cause systemic side-effects.

- **ALLERGY AND CROSS-SENSITIVITY**

  - Hypersensitivity and cross-sensitivity
  - Reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Crosses the placenta but not known to be harmful in animal studies—use if benefit outweighs risk. When used as a local anaesthetic, large doses can cause fetal bradycardia; if given during delivery can also cause neonatal respiratory depression, hypotonia, or bradycardia after paracervical or epidural block.

- **BREAST FEEDING** Present in milk but amount too small to be harmful.

- **HEPATIC IMPAIRMENT** Caution—increased risk of side-effects.
**Renal Impairment**  Possible accumulation of lidocaine and active metabolite; caution in severe impairment.

**Profession Specific Information**

- **Dental Practitioners’ Formulary**
  - Lidocaine ointment 5% may be prescribed. Spray may be prescribed as Lidocaine Spray 10%
  - **Xylocaine®** May be prescribed as lidocaine spray 10%

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug.

- **Spray**
  - Benzydamine hydrochloride (Non-proprietary)
  - Benzydamine hydrochloride 1.5 mg per 1 ml Benzydamine 0.15% oromucosal spray sugar-free sugar-free | 30 ml | £4.64 DT price | £4.15
  - Difflam (Meda Pharmaceuticals Ltd)
  - Benzydamine hydrochloride 1.5 mg per 1 ml Difflam 0.15% spray sugar-free | 30 ml | £4.24 DT price | £4.15

- **Mouthwash**
  - Benzydamine hydrochloride (Non-proprietary)
  - Benzydamine hydrochloride 1.5 mg per 1 ml Benzydamine 0.15% mouthwash sugar-free sugar-free | 300 ml | £7.14 DT price | £6.24
  - Difflam (Meda Pharmaceuticals Ltd)
  - Benzydamine hydrochloride 1.5 mg per 1 ml Difflam Oral Rinse 0.15% solution sugar-free | 300 ml | £6.50 DT price | £6.24
  - Difflam 0.15% Sore Throat Rinse sugar-free | 200 ml | £4.64

**Analgesics**  >  **Non-Steroidal Anti-Inflammatory Drugs**

**Benzydamine Hydrochloride**

- **Indications and Dose**
  - **Painful Inflammatory Conditions of Oropharynx**
    - **To the lesion using mouthwash**
      - Child 13-17 years: Rinse or gargle 15 mL every 1.5–3 hours as required usually for not more than 7 days, dilute with an equal volume of water if stinging occurs
      - Adult: Rinse or gargle 15 mL every 1.5–3 hours as required usually for not more than 7 days, dilute with an equal volume of water if stinging occurs
    - **To the lesion using oromucosal spray**
      - Child 1 month–5 years (body-weight 4–7 kg): 1 spray every 1.5–3 hours, to be administered onto the affected area
      - Child 1 month–5 years (body-weight 8–11 kg): 2 sprays every 1.5–3 hours, to be administered onto the affected area
      - Child 1 month–5 years (body-weight 12–15 kg): 3 sprays every 1.5–3 hours, to be administered onto the affected area
      - Child 1 month–5 years (body-weight 16 kg and above): 4 sprays every 1.5–3 hours, to be administered onto the affected area
      - Child 6–11 years: 4 sprays every 1.5–3 hours, to be administered onto the affected area
      - Child 12–17 years: 4–8 sprays every 1.5–3 hours, to be administered onto the affected area
      - Adult: 4–8 sprays every 1.5–3 hours, to be administered onto the affected area

- **Side-effects**
  - Rare  Hypersensitivity reactions
  - Frequency not known  Occasional numbness or stinging

**Profession Specific Information**

- **Dental Practitioners’ Formulary**
  - Benzydamine oromucosal spray 0.15% may be prescribed. Benzydamine mouthwash may be prescribed as Benzydamine mouthwash 0.15%.

**Medicinal Forms**

**Flurbiprofen**

- **Indications and Dose**
  - Relief of sore throat
    - **By mouth using lozenges**
      - Child 12-17 years: 1 lozenge every 3–6 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day
      - Adult: 1 lozenge every 3–6 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day

- **Interactions**  >  Appendix 1 (NSAIDs).

- **Side-effects**  Mouth ulcers (move lozenge around mouth) - taste disturbance

- **Allergy and Cross-sensitivity**  Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**Corticosteroids**

**Beclometasone Dipropionate**  (Beclometasone dipropionate)

- **Indications and Dose**
  - Management of oral ulceration
    - **By buccal administration**
      - Adult: 50–100 micrograms twice daily, use inhaler device to spray dose on to the oral mucosa

- **Unlicensed Use**  Use of inhaler unlicensed in oral ulceration.

**Medicinal Forms**

For preparations, see inhaled beclometasone, p. 244
Betamethasone

- **INDICATIONS AND DOSE**

  **Oral ulceration**
  - Child 12-17 years: 500 micrograms 4 times a day, to be dissolved in 20 mL water and rinsed around the mouth; not to be swallowed
  - Adult: 500 micrograms 4 times a day, to be dissolved in 20 mL water and rinsed around the mouth; not to be swallowed

- **UNLICENSED USE**
  - In children Betamethasone soluble tablets not licensed for use as mouthwash or in oral ulceration.

- **SIDE- EFFECTS**
  - Candidal infection • exacerbation of local infection

- **PATIENT AND CARER ADVICE**
  - Patient counselling is advised for betamethasone soluble tablets (administration).

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Betamethasone Soluble Tablets 500 micrograms may be prescribed for oral ulceration.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Soluble tablet**
    - **CAUTIONARY AND ADVISORY LABELS 10, 13, 21 (not for use as mouthwash for oral ulceration)**
    - Betamethasone (Non-proprietary)
      - Betamethasone (as Betamethasone sodium phosphate)
      - 500 microgram Betamethasone 500microgram soluble tablets sugar free-sugar-free | 100 tablet  | £42.60 DT price = £42.57

Hydrocortisone

- **INDICATIONS AND DOSE**

  **Oral and perioral lesions**
  - Child 1 month–11 years: Only on medical advice
  - Child 12-17 years: 1 lozenge 4 times a day, allowed to dissolve slowly in the mouth in contact with the ulcer
  - Adult: 1 lozenge 4 times a day, allowed to dissolve slowly in the mouth in contact with the ulcer

- **UNLICENSED USE**
  - Hydrocortisone mucoadhesive buccal tablets licensed for use in children (under 12 years—on medical advice only).

- **SIDE-EFFECTS**
  - Untreated local infection

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Mucoadhesive buccal tablets may be prescribed as Hydrocortisone Oromucosal Tablets.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Muco-adhesive buccal tablet**
    - Hydrocortisone (Non-proprietary)
      - Hydrocortisone (as Hydrocortisone sodium succinate)
      - 2.5 mg Hydrocortisone 2.5mg muco-adhesive buccal tablets sugar free-sugar-free | 20 tablet | £6.83 DT price = £6.29

Choline salicylate

- **INDICATIONS AND DOSE**

  **Mild oral and perioral lesions**
  - To the lesion
  - Child 16-17 years: Apply 0.5 inch, with gentle massage, not more often than every 3 hours
  - Adult: Apply 0.5 inch, with gentle massage, not more often than every 3 hours

- **CONTRA-INDICATIONS**
  - Children under 16 years

- **FURTHER INFORMATION**
  - **Reye’s syndrome**
    - The CHM has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye’s syndrome.
  - **CAUTIONS**
    - Frequent application, especially in children, may give rise to salicylate poisoning - not to be applied to dentures—leave at least 30 minutes before re-insertion of dentures

- **SIDE-EFFECTS**
  - Transient local burning sensation

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Choline Salicylate Dental Gel, BP consists of choline salicylate 8.7% in a flavoured gel basis.

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Choline Salicylate Dental Gel may be prescribed.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Oromucosal gel**
    - Bonjela (Reckitt Benckiser Healthcare (UK) Ltd)
      - Choline salicylate 87 mg per 1 gram Bonjela Cool Mint gel sugar-free | 15 gram GSP £3.07 DT price = £2.58
      - Bonjela Original gel sugar-free | 15 gram GSP £2.58 DT price = £2.58

Salicylic acid with rhubarb extract

- **INDICATIONS AND DOSE**

  **Mild oral and perioral lesions**
  - To the lesion
  - Child 16-17 years: Apply 3–4 times a day maximum duration 7 days
  - Adult: Apply 3–4 times a day maximum duration 7 days

- **CONTRA-INDICATIONS**
  - Children under 16 years

- **FURTHER INFORMATION**
  - **Reye’s syndrome**
    - The CHM has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye’s syndrome.
  - **CAUTIONS**
    - Frequent application, especially in children, may give rise to salicylate poisoning - not to be applied to dentures—leave at least 30 minutes before re-insertion of dentures

- **SIDE-EFFECTS**
  - Temporary discoloration of oral mucosa - temporary discolouration of teeth - transient local burning sensation

- **PATIENT AND CARER ADVICE**
  - May cause temporary discoloration of teeth and oral mucosa.
**Suggested duration of treatment**

In severe infection, initial parenteral therapy with phenoxymethylpenicillin p. 495. If penicillin-allergic, clarithromycin p. 496 (or azithromycin p. 495 or erythromycin p. 497).

**Antibacterial therapy for pericoronitis**

Antibacterial required only in presence of systemic features of infection, or of trismus, or persistent swelling despite local treatment.

- Metronidazole p. 499, or alternatively, amoxicillin p. 506
- **Suggested duration of treatment** 3 days or until symptoms resolve.

**Antibacterial therapy for gingivitis: acute necrotising ulcerative**

Antibacterial required only if systemic features of infection.

- Metronidazole, or alternatively, amoxicillin
- **Suggested duration of treatment** 3 days or until symptoms resolve.

**Antibacterial therapy for periapical or periodontal abscess**

Antibacterial required only in severe disease with cellulitis or if systemic features of infection.

- Amoxicillin, or alternatively, metronidazole
- **Suggested duration of treatment** 5 days.

**Antibacterial therapy for periodontitis**

Antibacterial used as an adjunct to debridement in severe disease or disease unresponsive to local treatment alone.

- Metronidazole, or alternatively in adults and children over 12 years, doxycycline below

**Antibacterial therapy for throat infections**

Most throat infections are caused by viruses and many do not require antibiotic therapy. Consider antibacterial, if history of valvular heart disease, if marked systemic upset, if peritonsillar cellulitis or abscess, or if at increased risk from acute infection (e.g. in immunosuppression, cystic fibrosis); prescribe antibacterial for beta-haemolytic streptococcal pharyngitis.

- Phenoxymethylpenicillin p. 505
  - In severe infection, initial parenteral therapy with benzylpenicillin sodium p. 504, then oral therapy with phenoxymethylpenicillin or amoxicillin (or ampicillin p. 507). Avoid amoxicillin if possibility of glandular fever.
  - **Suggested duration of treatment** 10 days.
- If penicillin-allergic, clarithromycin p. 496 (or azithromycin p. 495 or erythromycin p. 497)
- **Suggested duration of treatment** 10 days

**Doxycycline**

- **INDICATIONS AND DOSE**
  - Treatment of recurrent aphthous ulceration
    - **BY MOUTH USING SOLUBLE TABLETS**
      - Child 12-17 years: 100 mg 4 times a day usually for 3 days, dispersible tablet can be stirred into a small amount of water then rinsed around the mouth for 2–3 minutes, it should preferably not be swallowed
      - Adult: 100 mg 4 times a day usually for 3 days, dispersible tablet can be stirred into a small amount of water then rinsed around the mouth for 2–3 minutes, it should preferably not be swallowed
  - **UNLICENSED USE** Not licensed for use in children under 12 years. Not licensed for severe recurrent aphthous ulceration.
  - **CAUTIONS** Alcohol dependence
  - **INTERACTIONS** The metabolism of doxycycline may be influenced by antiepileptics.
  - **SIDE-EFFECTS** Anorexia · anxiety · dry mouth · flushing · tinnitus
  - **RENAL IMPAIRMENT** Use with caution (avoid excessive doses).
  - **PATIENT AND CARER ADVICE** Counselling on administration advised. Photosensitivity Patients should be advised to avoid exposure to sunlight or sun lamps.
  - **PROFESSION SPECIFIC INFORMATION**
    - Dental practitioners’ formulary
    - Dispersible tablets may be prescribed as Dispersible Doxycycline Tablets.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Dispersible tablet**

- **CAUTIONARY AND ADVISORY LABELS** 6, 9, 11, 13
  - **Vibramycin-D (Pfizer Ltd)**
    - Doxycycline (as Doxycycline monohydrate) 100 mg
    - 100mg dispersible tablets sugar-free | 8 tablet £4.91 DT price = £4.91

**5 Oropharyngeal fungal infections**

**Oropharyngeal fungal infections**

**Overview**

Fungal infections of the mouth are usually caused by *Candida* spp. (candidiasis or candidosis). Different types of oropharyngeal candidiasis are managed as follows:

**Thrush**

Acute pseudomembranous candidiasis (thrush), is usually an acute infection but it may persist for months in patients receiving inhaled corticosteroids, cytotoxics or broad-spectrum antibacterials. Thrush also occurs in patients with serious systemic disease associated with reduced immunity such as leukaemia, other malignancies, and HIV infection. Any predisposing condition should be managed appropriately. When thrush is associated with corticosteroid inhalers, rinsing the mouth with water (or cleaning a child’s teeth) immediately after using the inhaler may avoid the problem. Treatment with nystatin p. 1073 or
Miconazole below may be needed. Fluconazole p. 548 is effective for unresponsive infections or if a topical antifungal drug cannot be used or if the patient has dry mouth. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

**Acute erythematous candidiasis**
Acute erythematous (atrophic) candidiasis is a relatively uncommon condition associated with corticosteroid and broad-spectrum antibacterial use and with HIV disease. It is usually treated with fluconazole.

**Denture stomatitis**
Patients with denture stomatitis (chronic atrophic candidiasis), should cleanse their dentures thoroughly and leave them out as often as possible during the treatment period. To prevent recurrence of the problem, dentures should not normally be worn at night. New dentures may be required if these measures fail despite good compliance. Miconazole oral gel can be applied to the fitting surface of the denture before insertion (for short periods only). Denture stomatitis is not always associated with candidiasis and other factors such as mechanical or chemical irritation, bacterial infection, or rarely allergy to the dental base material, may be the cause.

**Chronic hyperplastic candidiasis**
Chronic hyperplastic candidiasis (candidal leukoplakia) carries an increased risk of malignancy; biopsy is essential—this type of candidiasis may be associated with varying degrees of dysplasia, with oral cancer present in a high proportion of cases. Chronic hyperplastic candidiasis is treated with a systemic antifungal such as fluconazole to eliminate candidal overlay. Patients should avoid the use of tobacco.

**Angular cheilitis**
Angular cheilitis (angular stomatitis) is characterised by soreness, erythema and fissuring at the angles of the mouth. It is commonly associated with denture stomatitis but may represent a nutritional deficiency or it may be related to oro-facial granulomatosis or HIV infection. Both yeasts (Candida spp.) and bacteria (Staphylococcus aureus and beta-haemolytic streptococci) are commonly involved as interacting, infective factors. A reduction in facial height related to ageing and tooth loss with maceration in the deep occlusive folds that may subsequently arise, predisposes to such infection. While the underlying cause is being identified and treated, it is often helpful to apply miconazole cream or fusidic acid ointment p. 527; if the angular cheilitis is unresponsive to treatment, hydrocortisone with miconazole cream or ointment p. 1107 can be used.

**Immunocompromised patients**
See advice on prevention of fungal infections in Immunocompromised patients under Antifungals, systemic use p. 544.

**Drugs used in oropharyngeal candidiasis**
Nystatin is not absorbed from the gastro-intestinal tract and is applied locally (as a suspension) to the mouth for treating local fungal infections. Miconazole is applied locally (as an oral gel) in the mouth but it is absorbed to the extent that potential interactions need to be considered. Miconazole also has some activity against Gram-positive bacteria including streptococci and staphylococci. Fluconazole is given by mouth for infections that do not respond to topical therapy or when topical therapy cannot be used. It is reliably absorbed and effective. Itraconazole p. 550 can be used for fluconazole-resistant infections. If candidal infection fails to respond to 1 to 2 weeks of treatment with antifungal drugs the patient should be sent for investigation to eliminate the possibility of underlying disease. Persistent infection may also be caused by re-infection from the genito-urinary or gastro-intestinal tract. Infection can be eliminated from these sources by appropriate anticandidal therapy; the patient’s partner may also require treatment to prevent reinfection.

Antiseptic mouthwashes are used in the prevention of oral candidiasis in immunocompromised patients and in the treatment of denture stomatitis.

**ANTIFUNGALS ➔ IMIDAZOLE ANTIFUNGALS**

### Miconazole

- **INDICATIONS AND DOSE**
  - **PREVENTION AND TREATMENT OF ORAL CANDIDIASIS**
    - By mouth using oral gel
      - Child 2–17 years: 2.5 mL 4 times a day treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)
      - Adult: 2.5 mL 4 times a day treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)
  - **PREVENTION AND TREATMENT OF INTESTINAL CANDIDIASIS**
    - By mouth using oral gel
      - Child 4 months–17 years: 5 mg/kg 4 times a day (max. per dose 250 mg 4 times a day) treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared
      - Adult: 5 mg/kg 4 times a day (max. per dose 250 mg 4 times a day) treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared

- **SIDE-EFFECTS**
  - Very rare
  - Common or very common

- **INTERACTIONS**
  - Appendix 1 (antifungals, imidazole).

- **CAUTIONS**
  - Avoid in acute porphyrias p. 930

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Flavours of oral gel may include orange.

- **UNLICENSED USE**
  - Not licensed for use in children under 4 months of age or during first 5–6 months of life of an infant born pre-term.

- **CONTRA-INDICATIONS**
  - Infants with impaired swallowing reflex

- **PREGNANCY**
  - Manufacturer advises avoid if possible—toxicity at high doses in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises caution—no information available.

- **HEPATIC IMPAIRMENT**
  - Avoid.

- **DIRECTIONS FOR ADMINISTRATION**
  - Oral gel should be held after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer miconazole oromucosal gel.

- **PROFESSION SPECIFIC INFORMATION**
  - **Dental practitioners’ formulary**
    - Miconazole Oromucosal Gel may be prescribed.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - 15-g tube of oral gel can be sold to the public.
6 Oropharyngeal viral infections

Oropharyngeal viral infections

Management

Viral infections are the most common cause of a sore throat. They do not benefit from anti-infective treatment.

The management of primary herpetic gingivostomatitis is a soft diet, adequate fluid intake, and analgesics as required, including local use of benzydamine hydrochloride p. 1069. The use of chlorhexidine mouthwash p. 1064 will control plaque accumulation if toothbrushing is painful and will also help to control secondary infection in general.

In the case of severe herpetic stomatitis, a systemic antiviral such as aciclovir p. 585 is required. Valaciclovir p. 587 and famciclovir p. 587 are suitable alternatives for oral lesions associated with herpes zoster. Aciclovir and valaciclovir are also used for the prevention of frequently recurring herpes simplex lesions of the mouth, particularly when implicated in the initiation of erythema multiforme.
Chapter 13

Skin

Skin conditions, management

Vehicles

The British Association of Dermatologists list of preferred unlicensed dermatological preparations (specials) is available at www.bad.org.uk/specials.

Both vehicle and active ingredients are important in the treatment of skin conditions; the vehicle alone may have more than a mere placebo effect. The vehicle affects the degree of hydration of the skin, has a mild anti-inflammatory effect, and aids the penetration of active drug.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin (including the scalp) or nails.

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application.

Creams are emulsions of oil and water and are generally well absorbed into the skin. They may contain an antimicrobial preservative unless the active ingredient or basis is intrinsically bactericidal and fungicidal. Generally, creams are cosmetically more acceptable than ointments because they are less greasy and easier to apply.

Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; they generally have a high water content. Gels are particularly suitable for application to the face and scalp.

Lotions have a cooling effect and may be preferred to ointments or creams for application over a hairy area. Lotions in alcoholic basis can sting if used on broken skin. Shake lotions (such as calamine lotion) contain insoluble powders which leave a deposit on the skin surface.

Ointments are greasy preparations which are normally anhydrous and insoluble in water, and are more occlusive than creams. They are particularly suitable for chronic, dry lesions. The most commonly used ointment bases consist of soft paraffin or a combination of soft, liquid, and hard paraffin. Some ointment bases have both hydrophilic and lipophilic properties; they may have occlusive properties on the skin surface, encourage hydration, and also be miscible with water; they often have a mild anti-inflammatory effect. Water-soluble ointments contain macrogols which are freely soluble in water and are therefore readily washed off; they have a limited but useful role where ready removal is desirable.

Pastes are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in an ointment. They are used for circumscribed lesions such as those which occur in lichen simplex, chronic eczema, or psoriasis. They are less occlusive than ointments and can be used to protect inflamed, lichenified, or excoriated skin.

Dusting powders are used only rarely. They reduce friction between opposing skin surfaces. Dusting powders should not be applied to moist areas because they can cake and abrade the skin. Talc is a lubricant but it does not absorb moisture; it can cause respiratory irritation. Starch is less lubricant but absorbs water.

Dilution

The BP directs that creams and ointments should not normally be diluted but that should dilution be necessary care should be taken, in particular, to prevent microbial contamination. The appropriate diluent should be used and heating should be avoided during mixing; excessive dilution may affect the stability of some creams. Diluted creams should normally be used within 2 weeks of preparation.

Suitable quantities for prescribing

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Creams and Ointments</th>
<th>Lotions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>15–30 g</td>
<td>100 ml</td>
</tr>
<tr>
<td>Both hands</td>
<td>25–50 g</td>
<td>200 ml</td>
</tr>
<tr>
<td>Scalp</td>
<td>50–100 g</td>
<td>200 ml</td>
</tr>
<tr>
<td>Both arms or both legs</td>
<td>100–200 g</td>
<td>200 ml</td>
</tr>
<tr>
<td>Trunk</td>
<td>400 g</td>
<td>500 ml</td>
</tr>
<tr>
<td>Groins and genitalia</td>
<td>15–25 g</td>
<td>100 ml</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for twice daily application for 1 week. The recommendations do not apply to corticosteroid preparations. For suitable quantities of corticosteroid preparations, see relevant table.
Excipients and sensitisation

Excipients in topical products rarely cause problems. If a patch test indicates allergy to an excipient, products containing the substance should be avoided. The following excipients in topical preparations are associated, rarely, with sensitisation; the presence of these excipients is indicated in the entries for topical products.

- Beeswax
- Benzyl alcohol
- Butylated hydroxyanisole
- Butylated hydroxytoluene
- Cetostearyl alcohol (including cetyl and stearyl alcohol)
- Chlorocresol
- Edetic acid (EDTA)
- Ethylenediamine
- Fragrances
- Hydroxybenzoates (parabens)
- Imidurea
- Isopropyl palmitate
- N-(3-Chloroallyl)hexaminium chloride (quaternium 15)
- Polysorbates
- Propylene glycol
- Sodium metabisulphite
- Sorbic acid
- Wool fat and related substances including lanolin (purified versions of wool fat have reduced the problem)

1 Dry and scaling skin disorders

Emollient and barrier preparations

Borderline substances

The preparations marked ‘ACBS’ are regarded as drugs when prescribed in accordance with the advice of the Advisory Committee on Borderline Substances for the clinical conditions listed. Prescriptions issued in accordance with this advice and endorsed ‘ACBS’ will normally not be investigated.

Emollients

Emollients soothe, smooth and hydrate the skin and are indicated for all dry or scaling disorders. Their effects are short lived and they should be applied frequently even after improvement occurs. They are useful in dry and eczematous disorders, and to a lesser extent in psoriasis. The choice of an appropriate emollient will depend on the severity of the condition, patient preference, and the site of application. Some ingredients rarely cause sensitisation and this should be suspected if an eczematous reaction occurs. The use of aqueous cream as a leave-on emollient may increase the risk of skin reactions, particularly in eczema.

Preparations such as aqueous cream and emulsifying ointment can be used as soap substitutes for hand washing and in the bath; the preparation is rubbed on the skin before rinsing off completely. The addition of a bath oil may also be regular—preferably daily—because emollients soak into fabric and can become a fire hazard.

Barrier preparations

Barrier preparations often contain water-repellent substances such as dimeticone. They are used on the skin around stomas, bedsores, and pressure areas in the elderly where the skin is intact. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. Barrier preparations are not a substitute for adequate nursing care.

Nappy rash

The first line of treatment is to ensure that nappies are changed frequently and that tightly fitting water-proof pants are avoided. The rash may clear when left exposed to the air and a barrier preparation, applied with each nappy change, can be helpful. A mild corticosteroid such as hydrocortisone may be used if inflammation is causing discomfort, but it should be avoided in neonates. The barrier preparation should be applied after the corticosteroid preparation to prevent further damage. Preparations containing hydrocortisone should be applied for no more than a week; the hydrocortisone should be discontinued as soon as the inflammation subsides. The occlusive effect of nappies and waterproof pants may increase absorption of corticosteroids. If the rash is associated with candidal infection, a topical antifungal such as clotrimazole cream may be used. Topical antibacterial preparations can be used if bacterial infection is present; treatment with an oral antibacterial may occasionally be required in severe or recurrent infection. Hydrocortisone may be used in combination with antimicrobial preparations if there is considerable inflammation, erosion, and infection.

DERMATOLOGICAL DRUGS > BARRIER PREPARATIONS

Barrier creams and ointments

- INDICATIONS AND DOSE
  - For use as a barrier preparation
    - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Cream

EXCIPIENTS: May contain Beeswax, butylated hydroxyanisole, butylated hydroxytoluene, cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, fragrances, hydroxybenzoates (parabens), propylene glycol, wool fat and related substances including lanolin.

- Conotrane (LEO Pharma)
  - Benzalkonium chloride 1 mg per 1 gram, Dimeticone 220 mg per 1 gram Conotrane cream | 100 gram $2.90 DT price = $0.88 |
  - 500 gram $5.17 $3.51

Dry and scaling skin disorders 1075
Skin

DERMATOLOGICAL DRUGS

Emollient bath and shower products, antimicrobial-containing

31-Aug-2016

- Drapoline (Omega Pharma Ltd)
  Benzalkonium chloride 100 microgram per 1 gram, Cetrimide 2 mg per 1 gram Drapoline cream | 100 gram £1.76 | 200 gram £2.98 | 350 gram £4.28
- Siopel (Derma UK Ltd)
  Cetrimide 3 mg per 1 gram, Dimeticone 1000 100 mg per 1 gram Siopel cream | 50 gram £0.65
- Sudocrem (Forest Laboratories UK Ltd)
  Benzyl cinnamate 1.5 mg per 1 gram, Benzyl alcohol 3.9 mg per 1 gram, Benzyl benzoate 10.1 mg per 1 gram, Wool fat hydrous 40 mg per 1 gram, Zinc oxide 152.5 mg per 1 gram Sudocrem antiseptic healing cream | 60 gram £1.45 | 125 gram £2.15 | 250 gram £3.67 | 400 gram £5.25

Ointment
EXCIPIENTS: May contain Wool fat and related substances including lanolin
- Barrier creams and ointments (Non-proprietary)
  Cetostearyl alcohol 20 mg per 1 gram, Zinc oxide 75 mg per 1 gram, Beeswax white 100 mg per 1 gram, Arachis oil 305 mg per 1 gram, Castor oil 500 mg per 1 gram Zinc and Castor oil ointment | 100 gram £1.41 | 500 gram £4.99 | 55.34 DT price = £5.34
  Zinc and Castor oil cream | 100 gram £1.41
- Brands may include Metamium
  Sprilon (J M Loveridge Ltd)
  Dimeticone 10.4 mg per 1 gram, Zinc oxide 125 mg per 1 gram Sprilon aerosol spray | 115 gram £8.90 DT price = £8.90

DERMAL®
200 SHOWER EMOLLIENT

Dry and pruritic skin conditions including eczema and dermatitis
- TO THE SKIN
  Child: To be applied to the skin or used as a soap substitute
  Adult: To be applied to the skin or used as a soap substitute

DERMAL®
600® BATH EMOLLIENT

Dry and pruritic skin conditions including eczema and dermatitis
- TO THE SKIN
  Child 1-23 months: 5–10 mL/bath, not to be used undiluted
  Child 2-17 years: 15–30 mL/bath, not to be used undiluted
  Adult: Up to 30 mL/bath, not to be used undiluted

DERMAL®
WASH EMULSION

Dry and pruritic skin conditions including eczema and dermatitis
- TO THE SKIN
  Child: To be applied to the skin or used as a soap substitute
  Adult: To be applied to the skin or used as a soap substitute

EMULSIDERM®

Dry skin conditions including eczema and ichthyosis
- TO THE SKIN
  Child 1-23 months: 5–10 mL/bath, alternatively, to be rubbed into dry skin until absorbed
  Child 2-17 years: 7–30 mL/bath, alternatively, to be rubbed into dry skin until absorbed
  Adult: 7–30 mL/bath, alternatively, to be rubbed into dry skin until absorbed

OLLATUM® PLUS

Topical treatment of eczema, including eczema at risk from infection
- TO THE SKIN
  Child 6-11 months: 1 mL/bath, not to be used undiluted
  Child 1-17 years: 1–2 capfuls/bath, not to be used undiluted
  Adult: 1–2 capfuls/bath, not to be used undiluted

IMPORTANT SAFETY INFORMATION

These preparations make skin and surfaces slippery—particular care is needed when bathing.

MHRA/CHM UPDATE (APRIL 2016): FIRE RISK WITH PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING
See Emollient and barrier preparations p. 1075.

DIRECTIONS FOR ADMINISTRATION

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubes should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

PRESCRIBING AND DISPENSING INFORMATION

Preparations containing an antibacterial should be avoided unless infection is present or is a frequent complication.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Liquid

CAUTIONARY AND ADVISORY LABELS 15
EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)
- Dermal 200 (Dermal Laboratories Ltd)
  Benzalkonium chloride 1 mg per 1 gram, Chlorhexidine hydrochloride 1 mg per 1 gram, Isopropyl myristate 25 mg per 1 gram, Liquid paraffin 25 mg per 1 gram Dermal 200 shower emollient | 200 mL £3.55
- Dermal Wash (Dermal Laboratories Ltd)
  Benzalkonium chloride 1 mg per 1 gram, Chlorhexidine hydrochloride 1 mg per 1 gram, Isopropyl myristate 25 mg per 1 gram, Liquid paraffin 25 mg per 1 gram Dermal Wash cutaneous emulsion | 200 mL £3.55

Bath additive

CAUTIONARY AND ADVISORY LABELS 15
EXCIPIENTS: May contain Acetylated lanolin alcohols, isopropyl palmitate, polysorbates
- Dermal 600 (Dermal Laboratories Ltd)
  Benzalkonium chloride 5 mg per 1 gram, Isopropyl myristate 250 mg per 1 gram, Liquid paraffin 250 mg per 1 gram Dermal 600 bath emollient | 600 mL £7.55
- Emulsiderm (Dermal Laboratories Ltd)
  Benzalkonium chloride 5 mg per 1 gram, Isopropyl myristate 250 mg per 1 gram, Liquid paraffin light 525 mg per 1 gram Emulsiderm bath additive | 500 mL £6.98
Emollient bath and shower products, colloidal oatmeal-containing

**INDICATIONS AND DOSE**

**Endogenous and exogenous eczema | Xeroderma | Ichthyosis**

- **TO THE SKIN**
  - Child 2–17 years: 20–30 mL/bath, alternatively apply to wet skin and rinse
  - Adult: 20–30 mL/bath, alternatively apply to wet skin and rinse

**Pruritus of the elderly associated with dry skin**

- **TO THE SKIN**
  - Elderly: 20–30 mL/bath, alternatively apply to wet skin and rinse

**IMPORTANT SAFETY INFORMATION**

These preparations make skin and surfaces slippery—particular care is needed when bathing.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

**EXCIPIENTS:** May contain Beeswax, fragrances

- Aveeno (Johnson & Johnson Ltd)
  - Aveeno bath oil | 250 mL (ACBS) £4.49

Emollient bath and shower products, paraffin-containing

**INDICATIONS AND DOSE**

**AQUAMAX® WASH**

**Dry skin conditions**

- **TO THE SKIN**
  - Child: To be applied to wet or dry skin and rinse
  - Adult: To be applied to wet or dry skin and rinse

**CETRABEN® BATH**

**Dry skin conditions, including eczema**

- **TO THE SKIN**
  - Child 1 month–11 years: 0.5–1 capful/bath, alternatively, to be applied to wet skin and rinse
  - Child 12–17 years: 1–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
  - Adult: 1–2 capfuls/bath, alternatively, to be applied to wet skin and rinse

**DERMALO®**

**Dermatitis | Dry skin conditions, including ichthyosis**

- **TO THE SKIN**
  - Child 1 month–11 years: 5–10 mL/bath, alternatively, to be applied to wet skin and rinse
  - Child 12–17 years: 15–20 mL/bath, alternatively, to be applied to wet skin and rinse
  - Adult: 15–20 mL/bath, alternatively, to be applied to wet skin and rinse

**Pruritus of the elderly**

- **TO THE SKIN**
  - Elderly: 15–20 mL/bath

**DOUBLEBASE® EMOLLIENT BATH ADDITIVE**

**Dry skin conditions including dermatitis and ichthyosis**

- **TO THE SKIN**
  - Child 1 month–11 years: 5–10 mL/bath
  - Child 12–17 years: 15–20 mL/bath
  - Adult: 15–20 mL/bath

**Pruritus of the elderly**

- **TO THE SKIN**
  - Elderly: 15–20 mL/bath

**DOUBLEBASE® EMOLLIENT SHOWER GEL**

**Dry, chapped, or itchy skin conditions**

- **TO THE SKIN**
  - Child: To be applied to wet or dry skin and rinse, or apply to dry skin after showering
  - Adult: To be applied to wet or dry skin and rinse, or apply to dry skin after showering

**E45® BATH OIL**

**Endogenous and exogenous eczema, xeroderma, and ichthyosis**

- **TO THE SKIN**
  - Child 1 month–11 years: 5–10 mL/bath, alternatively, to be applied to wet skin and rinse
  - Child 12–17 years: 15 mL/bath, alternatively, to be applied to wet skin and rinse
  - Adult: 15 mL/bath, alternatively, to be applied to wet skin and rinse

**Pruritus of the elderly associated with dry skin**

- **TO THE SKIN**
  - Elderly: 15 mL/bath, alternatively, to be applied to wet skin and rinse

**E45® WASH CREAM**

**Endogenous and exogenous eczema, xeroderma, and ichthyosis**

- **TO THE SKIN**
  - Child: To be used as a soap substitute
  - Adult: To be used as a soap substitute

**Pruritus of the elderly associated with dry skin**

- **TO THE SKIN**
  - Elderly: To be used as a soap substitute

**HYDROMOL® BATH AND SHOWER EMOLLIENT**

**Dry skin conditions | Eczema | Ichthyosis**

- **TO THE SKIN**
  - Child 1 month–11 years: 0.5–2 capfuls/bath, alternatively apply to wet skin and rinse
  - Child 12–17 years: 1–3 capfuls/bath, alternatively apply to wet skin and rinse
  - Adult: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

**Pruritus of the elderly**

- **TO THE SKIN**
  - Elderly: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

**LPL 63.4®**

**Dry skin conditions**

- **TO THE SKIN**
  - Child 1 month–11 years: 0.5–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
  - Child 12–17 years: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse
  - Adult: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

continued →
**OILATUM**<sup>®</sup> EMOLLIENT BATH ADDITIVE

Dry skin conditions including dermatitis and ichthyosis

- **TO THE SKIN**
  - Child 1 month–11 years: Apply 0.5–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
  - Child 12–17 years: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse
  - Adult: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

**Pruritus of the elderly**

- **TO THE SKIN**
  - Elderly: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

**OILATUM**<sup>®</sup> JUNIOR BATH ADDITIVE

Dry skin conditions including dermatitis and ichthyosis

- **TO THE SKIN**
  - Child 1 month–11 years: 0.5–2 capfuls/bath, alternatively, apply to wet skin and rinse
  - Child 12–17 years: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse
  - Adult: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse

**Pruritus of the elderly**

- **TO THE SKIN**
  - Elderly: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse

**QV**<sup>®</sup> BATH OIL

Dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus

- **TO THE SKIN**
  - Child 1–11 months: 5 mL/bath, alternatively, to be applied to wet skin and rinse
  - Child 1–7 years: 10 mL/bath, alternatively, to be applied to wet skin and rinse
  - Adult: 10 mL/bath, alternatively, to be applied to wet skin and rinse

**QV**<sup>®</sup> GENTLE WASH

Dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus

- **TO THE SKIN**
  - Child: To be used as a soap substitute
  - Adult: To be used as a soap substitute

**ZEROLATUM**<sup>®</sup>

Dry skin conditions | Dermatitis | Ichthyosis

- **TO THE SKIN**
  - Child 1 month–11 years: 5–10 mL/bath
  - Child 12–17 years: 15–20 mL/bath
  - Adult: 15–20 mL/bath

**Pruritus of the elderly**

- **TO THE SKIN**
  - Elderly: 15–20 mL/bath

**IMPORTANT SAFETY INFORMATION**

These preparations make the skin and surfaces slippery—particular care is needed when bathing.

MHRA/CHM UPDATE (APRIL 2016): FIRE RISK WITH PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING

See Emollient and barrier preparations p. 1075.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)

- **Aqueous cream**
  - Phenoxyethanol 10 mg per 1 gram, Liquid paraffin 60 mg per 1 gram, Emulsifying wax 90 mg per 1 gram, White soft paraffin 150 mg per 1 gram, Purified water 690 mg per 1 gram

  **Aqueous cream | 100 gram (GSL) £1.81 DT price = £0.91 | 500 gram (GSL) £6.35 DT price = £4.55**

**Gel**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)

- **Doublebase** (Dermal Laboratories Ltd)
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram

  **Doublebase Daylione gel | 100 gram (GSL) £2.65 DT price = £2.65 | 500 gram (GSL) £6.29 DT price = £5.83**

- **Doublebase emollient wash gel | 200 gram (GSL) £5.21**

**Bath additive**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Acetylaced lanolin alcohols, cetostearyl alcohol (including cetyl) and stearyl alcohol, fragrances, isopropyl palmitate

- **Cetran®** (Genus Pharmaceuticals Ltd)
  - Liquid paraffin light 828 mg per 1 gram

  **Cetran emollient 82.8% bath additive | 500 mL (GSL) £5.75**

- **Dermol** (Dermal Laboratories Ltd)
  - Acetylated wool alcohols 50 mg per 1 gram, Liquid paraffin 650 mg per 1 gram

  **Dermol bath emollient | 500 mL (GSL) £3.44**

- **Doublebase emollient bath** (Dermal Laboratories Ltd)
  - Liquid paraffin 650 mg per 1 gram

  **Doublebase emollient bath additive | 500 mL (GSL) £5.45**

- **E45 emollient bath** (Forum Health Products Ltd)
  - E45 emollient bath oil | 250 mL (ACBS) £3.23 | 500 mL (ACBS) £5.18

- **Hydromol** (Alliance Pharmaceuticals Ltd)
  - Isopropyl myristate 130 mg per 1 mL, Liquid paraffin light 378 mg per 1 mL

  **Hydromol Bath & Shower emollient | 350 mL (GSL) £3.88 | 500 mL (GSL) £4.42 | 1000 mL (GSL) £8.80**

- **LPL** (Hussey Europe Ltd)
  - Liquid paraffin light 634 mg per 1 mL

  **LPL 63.4 bath additive and emollient | 500 mL £3.10 DT price = £4.57**

- **Oillatum** (GlasoSmithKline Consumer Healthcare)
  - Liquid paraffin light 634 mg per 1 mL

  **Oillatum Bath Formula | 150 mL (GSL) £2.84 DT price = £2.84 | 300 mL (GSL) £4.88 DT price = £4.88**

  **Oillatum Emollient | 250 mL (GSL) £2.75 DT price = £2.75 | 500 mL (GSL) £4.57 DT price = £4.57**

- **Oillatum junior** (GlasoSmithKline Consumer Healthcare)
  - Liquid paraffin light 634 mg per 1 mL

  **Oillatum Junior bath additive | 150 mL (GSL) £2.84 DT price = £2.84 | 250 mL (GSL) £4.05 DT price = £4.05 | 300 mL (GSL) £4.88 DT price = £4.88 | 500 mL (GSL) £5.89 DT price = £5.89**

- **QV** (Crawford Healthcare Ltd)
  - Liquid paraffin light 850.9 mg per 1 gram

  **QV 85.09% bath oil | 250 mL £2.91 | 500 mL £4.76**

- **Zerolatum** (Thornton & Ross Ltd)
  - Acetylated wool alcohols 50 mg per 1 gram, Liquid paraffin 650 mg per 1 gram

  **Zerolatum Emollient bath additive | 500 mL £4.79**

**Wash**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), polysorbates

- **Aquamax** (Intrapharm Laboratories Ltd)
  - Aquamax wash | 250 mL £2.92

- **E45 emollient wash** (Forum Health Products Ltd)
  - E45 emollient wash cream | 250 mL (ACBS) £3.23

- **QV Gentle** (Crawford Healthcare Ltd)
  - QV Gentle wash | 250 mL £3.17 | 500 mL £5.29
Emollient bath and shower products, soya-bean oil-containing

- **INDICATIONS AND DOSE**
  
  **BALNEUM® BATH OIL**
  
  Dry skin conditions including those associated with dermatitis and eczema
  
  - TO THE SKIN
  
  - Child 1-23 months: 5 mL/bath, not to be used undiluted
  
  - Child 2-17 years: 20–60 mL/bath, not to be used undiluted
  
  - Adult: 20 mL/bath, not to be used undiluted
  
  **BALNEUM® PLUS BATH OIL**
  
  Dry skin conditions including those associated with dermatitis and eczema where pruritus also experienced
  
  - TO THE SKIN
  
  - Child 1-23 months: 5 mL/bath, alternatively, to be applied to wet skin and rinse
  
  - Child 2-17 years: 10–20 mL/bath, alternatively, to be applied to wet skin and rinse
  
  - Adult: 20 mL/bath, alternatively, to be applied to wet skin and rinse
  
  **ZERONEUM®**
  
  Dry skin conditions including eczema
  
  - TO THE SKIN
  
  - Child 1 month-11 years: 5 mL/bath
  
  - Child 12-17 years: 20 mL/bath
  
  - Adult: 20 mL/bath
  
  **IMPORTANT SAFETY INFORMATION**
  
  These preparations make skin and surfaces slippery—particular care is needed when bathing.

- **DIRECTIONS FOR ADMINISTRATION**
  
  Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Bath additive**
  
  **EXCIPIENTS:** May contain Butylated hydroxytoluene, fragrances, propylene glycol
  
  - Balneum (Amirall Ltd)
  
  - Lauromacrogols 150 mg per 1 gram, Soya oil 829.5 mg per 1 gram Balneum Plus bath oil | 500 ml [GSL] £6.66
  
  - Soya oil 847.5 mg per 1 gram Balneum 84.75% bath oil | 200 ml [GSL] £2.48 | 500 ml [GSL] £5.38 | 1000 ml [GSL] £10.39
  
  - Zeroneum (Thornton & Ross Ltd)
  
  - Soya oil 833.5 mg per 1 gram Zeroneum 83.35% bath additive | 500 ml [GSL] £4.48

Emollient creams and ointments, antimicrobial-containing

- **INDICATIONS AND DOSE**
  
  **PSORIDERM® EMULSION**
  
  Psoriasis
  
  - TO THE SKIN
  
  - Adult: Up to 30 mL/bath, use 30 mL in adult-size bath, soak for 5 minutes
  
  **IMPORTANT SAFETY INFORMATION**
  
  These preparations make skin and surfaces slippery—particular care is needed when bathing.

- **DIRECTIONS FOR ADMINISTRATION**
  
  Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Bath additive**
  
  **EXCIPIENTS:** May contain Isopropyl palmitate, polysorbates
  
  - Psoriderm (Dermal Laboratories Ltd)
  
  - Coal tar distilled 400 mg per 1 ml Psoriderm Emulsion 40% bath additive | 200 ml [P] £2.74

Emollient bath and shower products, tar-containing

- **INDICATIONS AND DOSE**
  
  **POLYTAR EMOLIENT®**
  
  Psoriasis, eczema, atopic and pruritic dermatoses
  
  - TO THE SKIN
  
  - Adult: 2–4 capfuls/bath, add 15–30 mL to an adult-size bath; soak for 20 minutes
  
  **IMPORTANT SAFETY INFORMATION**
  
  These preparations make skin and surfaces slippery—particular care is needed when bathing.

- **DIRECTIONS FOR ADMINISTRATION**
  
  Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

- **PRESCRIBING AND DISPENSING INFORMATION**
  
  Preparations containing an antibacterial should be avoided unless infection is present or is a frequent complication.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Liquid**
  
  **CAUTIONARY AND ADVISORY LABELS** 15
  
  **EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)
  
  - Dermal 500 (Dermal Laboratories Ltd)
  
  - Benzalkonium chloride 1 mg per 1 gram, Chlorhexidine hydrochloride 1 mg per 1 gram, Isopropyl myristate 25 mg per 1 gram, Liquid paraffin 25 mg per 1 gram Dermal 500 lotion | 500 ml [P] £6.04
Emollient creams and ointments, colloidal oatmeal-containing

**INDICATIONS AND DOSE**

- **Endogenous and exogenous eczema**
- **Xeroderma**
- **Ichthyosis**

**DIRECTIONS FOR ADMINISTRATION**

Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream and lotion**

**EXCipients:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), isopropyl palmitate

- Dermol (Derma Lab Laboratories Ltd)
  - Benzalkonium chloride 1 mg per 1 gram, Chlorhexidine hydrochloride 1 mg per 1 gram, Isopropyl myristate 100 mg per 1 gram, Liquid paraffin 100 mg per 1 gram
  - Dermol cream 100 gram £2.86 | 500 gram £6.63
- Eczmol (Genus Pharmaceuticals Ltd)
  - Chlorhexidine gluconate 10 mg per 1 gram
  - Eczmol 1% cream | 250 ml G50 £1.70

**Emollient creams and ointments, paraffin-containing**

**INDICATIONS AND DOSE**

- **Dry skin conditions**
- **Eczema**
- **Psoriasis**
- **Ichthyosis**
- **Pruritus**

**DIRECTIONS FOR ADMINISTRATION**

Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.
Emollients, urea-containing

Empollients

**DRUG ACTION** Urea is a keratin softener and hydrating agent used in the treatment of dry, scaling conditions (including ichthyosis) and may be useful in elderly patients.

**INDICATIONS AND DOSE**

**AQUADRATÉ®**

**Dry, scaling, and itching skin**

- **TO THE SKIN**
- **Child:** Apply twice daily, to be applied thinly
- **Adult:** Apply twice daily

**BALNEUM® CREAM**

**Dry skin conditions**

- **TO THE SKIN**
- **Child:** Apply twice daily
- **Adult:** Apply twice daily

**CALMURID®**

**Dry, scaling, and itching skin**

- **TO THE SKIN**
- **Child:** Apply twice daily, apply a thick layer for 3–5 minutes, massage into area, and remove excess. Can be diluted with aqueous cream (life of diluted cream is 14 days). Half-strength cream can be used for 1 week if stinging occurs
- **Adult:** Apply twice daily, apply a thick layer for 3–5 minutes, massage into area, and remove excess. Can be diluted with aqueous cream (life of diluted cream is 14 days). Half-strength cream can be used for 1 week if stinging occurs

**DERMATONICS ONCE HEEL BALM®**

**Dry skin on soles of feet**

- **TO THE SKIN**
- **Child:** 12–17 years: Apply once daily
- **Adult:** Apply once daily

**E4S® ITCH RELIEF CREAM**

**Dry, scaling, and itching skin**

- **TO THE SKIN**
- **Child:** Apply twice daily
- **Adult:** Apply twice daily

**EUROCRÉME® INTENSIVE CREAM**

**Dry skin conditions including eczema, ichthyosis, xeroderma, and hyperkeratosis**

- **TO THE SKIN**
- **Child:** Apply twice daily, to be applied thinly and rubbed into area
- **Adult:** Apply twice daily, to be applied sparingly and rubbed into area

**EUROCRÉME® INTENSIVE LOTION**

**Dry skin conditions including eczema, ichthyosis, xeroderma, and hyperkeratosis**

- **TO THE SKIN**
- **Child:** Apply twice daily, to be applied sparingly and rubbed into area
- **Adult:** Apply twice daily, to be applied sparingly and rubbed into area
**HYDROMOL® INTENSIVE**

Dry, scaling, and itching skin

- **TO THE SKIN**
- Child: Apply twice daily, to be applied thinly
- Adult: Apply twice daily, to be applied thinly

**IMUDERM® EMMOLIENT**

Dry skin conditions including eczema, psoriasis or dermatitis

- **TO THE SKIN**
- Adult: Apply to skin or use as a soap substitute

**NUTRAPLUS®**

Dry, scaling, and itching skin

- **TO THE SKIN**
- Child: Apply 2–3 times a day
- Adult: Apply 2–3 times a day

- **DIRECTIONS FOR ADMINISTRATION** Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Liquid**
  
  **EXCIPIENTS:** May contain Benzyl alcohol, isopropyl palmitate
  - **Eucerin (Beiersdorf UK Ltd)**
    - Urea 100 mg per 1 g

  **Cream**
  
  **EXCIPIENTS:** May contain Benzy alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), isopropyl palmitate, polyborates, propylene glycol, wool fat and related substances including lanolin
  - **Aquafade (Alliance Pharmaceuticals Ltd)**
    - Urea 100 mg per 1 g
  - **Balneum (Almirall Ltd)**
    - Laurusmargoloids 30 mg per 1 g, Urea 50 mg per 1 g
    - Balneum Plus cream
  - **Calmurd (Kalderma UK Ltd)**
    - Lactic acid 50 mg per 1 g, Urea 100 mg per 1 g
  - **Eucerin (Beiersdorf UK Ltd)**
    - Urea 100 mg per 1 g
  - **Hydromol Intensive (Alliance Pharmaceuticals Ltd)**
    - Urea 100 mg per 1 g
  - **Nutraplus (Kalderma UK Ltd)**
    - Urea 100 mg per 1 g

  **Balm**
  
  **EXCIPIENTS:** May contain Beeswax, benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, lanolin
  - **ImuDERM (Clinisupplies Ltd)**
    - ImuDERM emollient
  - **Dermatronics once (Dermatronics Ltd)**
    - Dermatronics once Heel Balm
  - **Flexitol (Thorton & Ross Ltd)**
    - Flexitol Heel Balm

**2 Infections of the skin**

**Skin infections**

**Antibacterial preparations**

**Cellulitis,** a rapidly spreading deeply seated inflammation of the skin and subcutaneous tissue, requires systemic antibacterial treatment. Lower leg infections or infections spreading around wounds are almost always cellulitis. *Erysipelas,* a superficial infection with clearly defined edges (and often affecting the face), is also treated with a systemic antibacterial.

In the community, acute *impetigo* on small areas of the skin may be treated by short-term topical application of fusidic acid p. 1089; mupirocin p. 1086 should be used only to treat meticillin-resistant *Staphylococcus aureus*. If the impetigo is extensive or longstanding, an oral antibacterial such as fluclaxacin p. 511 (or clarithromycin p. 496 in penicillin allergy) should be used. Mild antiseptics can be used to soften crusts.

Although many antibacterial drugs are available in topical preparations, some are potentially hazardous and frequently their use is not necessary if adequate hygienic measures can be taken. Moreover, not all skin conditions that are oozing, crusted, or characterised by pustules are actually infected. Topical antibacterials should be avoided on *leg ulcers* unless used in short courses for defined infections; treatment of bacterial colonisation is generally inappropriate.

To minimise the development of resistant organisms it is advisable to limit the choice of antibacterials applied topically to those not used systemically. Unfortunately some of these, for example neomycin sulfate p. 1084, may cause sensitisation, and there is cross-sensitivity with other aminoglycoside antibiotics, such as gentamicin p. 479. *If large areas of skin* are being treated, ototoxicity may also be a hazard with aminoglycoside antibiotics (and also with polymyxins p. 1085), particularly in children, in the elderly, and in those with renal impairment. *Resistant organisms* are more common in hospitals, and whenever possible swabs should be taken for bacteriological examination before beginning treatment.

Mupirocin is not related to any other antibacterial in use; it is effective for skin infections, particularly those due to Gram-positive organisms but it is not indicated for pseudomonal infection. Although *Staphylococcus aureus* strains with low-level resistance to mupirocin are emerging, it is generally useful in infections resistant to other antibacterials. To avoid the development of resistance, mupirocin or fusidic acid should not be used for longer than 10 days and local microbiology advice should be sought before using it in hospital. In the presence of mupirocin-resistant MRSA infection, a topical antiseptic such as povidone-iodine p. 1032, chlorhexidine p. 1064, or alcohol can be used; their use should be discussed with the local microbiologist.

Retapamulin p. 1086 can be used for impetigo and other superficial bacterial skin infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* that are resistant to first-line topical antibacterials. However, it is not effective against MRSA.

Tedizolid p. 528 is licensed for the treatment of acute bacterial skin and skin structure infections. Silver sulfadiazine p. 1085 is used in the treatment of infected burns.

**Antibacterial preparations also used systemically**

Fusidic acid is a narrow-spectrum antibacterial used for staphylococcal infections. Fusidic acid has a role in the treatment of impetigo.
An ointment containing fusidic acid is used in the fissures of angular cheilitis when associated with staphylococcal infection. See Oropharyngeal fungal infections p. 1071 for further information on angular cheilitis.

Metronidazole p. 1084 is used topically for rosacea and to reduce the odour associated with anaerobic infections; oral metronidazole is used to treat wounds infected with anaerobic bacteria.

**Antifungal preparations**

Most localised fungal infections are treated with topical preparations. To prevent relapse, local antifungal treatment should be continued for 1–2 weeks after the disappearance of all signs of infection. Systemic therapy is necessary for scalp infection or if the skin infection is widespread, disseminated, or intractable; although topical therapy may be used to treat some nail infections, systemic therapy is more effective. Skin scrapings should be examined if systemic therapy is being considered or where there is doubt about the diagnosis.

**Dermatophytes**

Ringworm infection can affect the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), hand (tinea manuum), foot (tinea pedis, athlete’s foot), or nail (tinea unguium). Scalp infection requires systemic treatment; additional application of a topical antifungal, during the early stages of treatment, may reduce the risk of transmission. A topical antifungal can also be used to treat asymptomatic carriers of scalp ringworm. Most other local ringworm infections can be treated adequately with topical antifungal preparations (including shampoos). The imidazole antifungals clotrimazole p. 1087, econazolene nitrate p. 1087, ketoconazole p. 1087, and miconazole p. 1088 are all effective. Terbinafine cream p. 1089 is also effective but it is more expensive. Other topical antifungals include griseofulvin p. 1089 and the undecenoates. **Compound benzoic acid ointment** (Whitfield’s ointment) has been used for ringworm infections but it is cosmetically less acceptable than proprietary preparations. Topical preparations for athlete’s foot containing tolnaftate are on sale to the public.

Antifungal dusting powders are of little therapeutic value in the treatment of fungal skin infections and may cause skin irritation; they may have some role in preventing relapse. Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. However, topical application of amorolfine p. 1088 or tioconazole p. 1088 may be useful for treating early onychomycosis when involvement is limited to mild distal disease, or for superficial white onychomycosis, or where there are contra-indications to systemic therapy.

**Pityriasis versicolor**

Pityriasis (tinea) versicolor can be treated with ketoconazole shampoo. Alternatively, **selenium sulfide** shampoo [unlicensed indication] can be used as a lotion (diluting with a small amount of water can reduce irritation) and left on the affected area for 10 minutes before rinsing off; it should be applied once daily for 7 days, and the course repeated if necessary.

Topical imidazole antifungals such as clotrimazole, econazole nitrate, ketoconazole, and miconazole, or topical terbinafine are alternatives, but large quantities may be required.

If topical therapy fails, or if the infection is widespread, pityriasis versicolor is treated systemically with a triazole antifungal. Relapse is common, especially in the immunocompromised.

**Candidiasis**

Candidal skin infections can be treated with a topical imidazole antifungal, such as clotrimazole, econazole nitrate, ketoconazole, or miconazole; topical terbinafine is an alternative. Topical application of nystatin p. 1073 is also effective for candidiasis but it is ineffective against dermatophytes. Refractory candidiasis requires systemic treatment generally with a triazole such as fluconazole p. 548; systemic treatment with terbinafine is not appropriate for refractory candidiasis.

**Angular cheilitis**

Miconazole cream is used in the fissures of angular cheilitis when associated with Candida.

**Compound topical preparations**

Combination of an imidazole and a mild corticosteroid (such as hydrocortisone 1% p. 620) may be of value in the treatment of eczematous intertrigo and, in the first few days only, of a severely inflamed patch of ringworm.

Combination of a mild corticosteroid with either an imidazole or nystatin p. 1073 may be of use in the treatment of intertrigo associated with candida.

**Antiviral preparations**

Aciclovir cream p. 1092 is licensed for the treatment of initial and recurrent labial and genital herpes simplex infections; treatment should begin as early as possible. Systemic treatment is necessary for buccal or vaginal infections and for herpes zoster (shingles).

**Herpes labialis**

Aciclovir cream can be used for the treatment of initial and recurrent labial herpes simplex infections (cold sores). It is best applied at the earliest possible stage, usually when prodromal changes of sensation are felt in the lips and before vesicles appear. Penciclovir cream is also licensed for the treatment of herpes labialis; it needs to be applied more frequently than aciclovir cream.

Systemic treatment is necessary if cold sores recur frequently or for infections in the mouth.

**Parasiticidal preparations**

**Suitable quantities of parasiticidal preparations**

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Skin creams</th>
<th>Lotions</th>
<th>Cream rinses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp (head lice)</td>
<td>50–100 mL</td>
<td>50–100 mL</td>
<td></td>
</tr>
<tr>
<td>Body (scabies)</td>
<td>30–60 g</td>
<td>100 mL</td>
<td></td>
</tr>
<tr>
<td>Body (crab lice)</td>
<td>30–60 g</td>
<td>100 mL</td>
<td></td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for single application.

**Scabies**

Permethrin p. 1092 is used for the treatment of scabies (Sarcoptes scabiei); malathion p. 1092 can be used if permethrin is inappropriate.

Benzy1 benzoate p. 1091 is an irritant and should be avoided in children; it is less effective than malathion and permethrin.

Ivermectin p. 557 (available on a named patient basis from ‘special-order’ manufacturers or specialist importing companies) by mouth has been used, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone; further doses may be required.

**Application**

Although acaricides have traditionally been applied after a hot bath, this is not necessary and there is even evidence that a hot bath may increase absorption into the blood, removing them from their site of action on the skin.
All members of the affected household should be treated simultaneously. Treatment should be applied to the whole body including the scalp, neck, face, and ears. Particular attention should be paid to the webs of the fingers and toes and lotion brushed under the ends of nails. It is now recommended that malathion and permethrin should be applied twice, one week apart; in the case of benzyl benzoate in adults, up to 3 applications on consecutive days may be needed. It is important to warn users to reapply treatment to the hands if they are washed. Patients with hyperkeratotic scabies may require 2 or 3 applications of acaricide on consecutive days to ensure that enough penetrates the skin crusts to kill all the mites.

**Intox**
The itch and eczema of scabies persists for some weeks after the infestation has been eliminated and treatment for pruritus and eczema may be required. Application of crotamiton p. 1117 can be used to control itching after treatment with more effective acaricides. A topical corticosteroid may help to reduce itch and inflammation after scabies has been treated successfully; however, persistent symptoms suggest that scabies eradication was not successful. Oral administration of a sedating antihistamine at night may also be useful.

**Head lice**
Dimeticone p. 1091 is effective against head lice (Pediculus humanus capitis). It coats head lice and interferes with water balance in lice by preventing the excretion of water; it is less active against eggs and treatment should be repeated after 7 days. Malathion, an organophosphorous insecticide, is an alternative, but resistance has been reported. Benzyl benzoate is licensed for the treatment of head lice but it is less effective than other drugs and not recommended for use in children. Permethrin is active against head lice but the formulation and licensed methods of application of the current products make them unsuitable for the treatment of head lice.

Head lice infestation (pediculosis) should be treated using lotion or liquid formulations only if live lice are present. Shampoos are diluted too much in use to be effective. A contact time of 8–12 hours or overnight treatment is recommended for lotions and liquids; a 2-hour treatment is not sufficient to kill eggs.

In general, a course of treatment for head lice should be 2 applications of product 7 days apart to kill lice emerging from any eggs that survive the first application. All affected household members should be treated simultaneously.

**Wet combing methods**
Head lice can be mechanically removed by combing wet hair meticulously with a plastic detection comb (probably for at least 30 minutes each time) over the whole scalp at 4-day intervals for a minimum of 2 weeks, and continued until no lice are found on 3 consecutive sessions; hair conditioner or vegetable oil can be used to facilitate the process.

Several devices for the removal of head lice such as combs and topical solutions, are available and some are prescribable on the NHS.

The Drug Tariffs can be accessed online at:
- National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm
- Health and Personal Social Services for Northern Ireland Drug Tariff: www.hscbusines.hscni.net/services/2034.htm
- Scottish Drug Tariff: www.isdscotland.org/Health-topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

**Crab lice**
Permethrin and malathion are used to eliminate crab lice (Pthirus pubis). An aqueous preparation should be applied, allowed to dry naturally and washed off after 12 hours; a second treatment is needed after 7 days to kill lice emerging from surviving eggs. All surfaces of the body should be treated, including the scalp, neck, and face (paying particular attention to the eyebrows and other facial hair). A different insecticide should be used if a course of treatment fails.

### 2.1 Bacterial skin infections

**ANTIBACTERIALS ➔ AMINOGLYCOSIDES**

**Neomycin sulfate**

- **INDICATIONS AND DOSE**
  - **Bacterial skin infections**
    - **TO THE SKIN**
      - Child: Apply up to 3 times a day, for short-term use only
      - Adult: Apply up to 3 times a day, for short-term use only
    - **UNLICENSED USE**
      - In children Neomycin Cream BPC—no information available.
    - **CONTRA-INDICATIONS**
      - Neomatoses
    - **CAUTIONS**
      - If large areas of skin are being treated ototoxicity may be a hazard, particularly in children, the elderly, and in those with renal impairment.
    - **INTERACTIONS**
      - Sensitisation (cross sensitivity with other aminoglycosides may occur)
    - **RENAI IMPAIRMENT**
      - Ototoxicity may be a hazard if large areas of skin are treated.
    - **LESS SUITABLE FOR PRESCRIBING**
      - Neomycin sulfate cream is less suitable for prescribing.

**AMINOGLYCOSIDES ➔ NITROIMIDAZOLE DERIVATIVES**

**Metronidazole**

- **DRUG ACTION**
  - Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

- **INDICATIONS AND DOSE**
  - **ACEA®**
    - Acute inflammatory exacerbation of rosacea
      - **TO THE SKIN**
        - Adult: Apply twice daily for 8 weeks, to be applied thinly
    - **ANABACT®**
      - Malodor fungating tumours and malodor gravitational and decubitus ulcers
        - **TO THE SKIN**
          - Adult: Apply 1–2 times a day, to be applied to clean wound and covered with non-adherent dressing
    - **METROGEL®**
      - Acute inflammatory exacerbation of rosacea
        - **TO THE SKIN**
          - Adult: Apply twice daily for 8–9 weeks, to be applied thinly
      - Malodor fungating tumours
        - **TO THE SKIN**
          - Adult: Apply 1–2 times a day, to be applied to clean wound and covered with non-adherent dressing
ANTIBACTERIALS

Acute exacerbation of rosacea
- TO THE SKIN
- Adult: Apply twice daily for up to 8 weeks, to be applied thinly

CAUTIONS
Avoid exposure to strong sunlight or UV light

SIDE-EFFECTS
Skin irritation

MEDICINAL FORMS
There can be variation in the licensing in the UK of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, gel

Cream
EXCIPIENTS: May contain Benzyl alcohol, isopropyl palmitate, propylene glycol
- Rozex® Cream (Galderma (UK) Ltd)
- Metrogel® (Cambridge Healthcare Supplies Ltd)

Gel
EXCIPIENTS: May contain Benzyl alcohol, disodium edetate, hydroxybenzoates (parabens), propylene glycol
- Acea® (Ferndale Pharmaceuticals Ltd)
- Anabact® (Cambridge Healthcare Supplies Ltd)
- Metrogel® (Galderma (UK) Ltd)
- Metrosa® (M & A Pharmachem Ltd)
- Rozex® (Galderma (UK) Ltd)

Antibacterials > Sulfonamides

Silver sulfadiazine

INDICATIONS AND DOSE
Prophylaxis and treatment of infection in burn wounds
- TO THE SKIN
  - Child: Apply daily, may be applied more frequently if very exudative
  - Adult: Apply daily, may be applied more frequently if very exudative

For conservative management of finger-tip injuries
- TO THE SKIN
  - Child: Apply every 2–3 days, consult product literature for details
  - Adult: Apply every 2–3 days, consult product literature for details

Adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions
- TO THE SKIN
  - Adult: (consult product literature)

Adjunct to short-term treatment of infection in pressure sores
- TO THE SKIN
  - Adult: Apply once daily or on alternate days

As an adjunct to short-term treatment of infection in leg ulcers
- TO THE SKIN
  - Adult: Apply once daily or on alternate days, not recommended if ulcer is very exudative

UNLICENSED USE
- In children No age range specified by manufacturer.

CONTRA-INDICATIONS
Not recommended for neonates

CAUTIONS
- G6PD deficiency
- Severe blood and skin disorders: Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders or rashes develop.

INTERACTIONS
- Appendix 1 (sulfonamides)—if large amounts given. May inactivate enzymatic degrading agents—concomitant use may be inappropriate

SIDE-EFFECTS
Allergic reactions - argea (following treatment of large areas of skin or prolonged use) - burning - itching - leucopenia - rashes

POLYMYXINS

INDICATIONS AND DOSE
Bacterial skin infections
- TO THE SKIN
  - Adult: Apply twice daily, may be applied more frequently if required

CAUTIONS
If large areas of skin are being treated nephrotoxicity and neurotoxicity may be a hazard, particularly in children, in the elderly, and in those with renal impairment.

SIDE-EFFECTS
Sensitisation

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

No licensed medicines identified.

Bacterial skin infections

Silver sulfadiazine

INDICATIONS AND DOSE
Prophylaxis and treatment of infection in burn wounds
- TO THE SKIN
  - Child: Apply daily, may be applied more frequently if very exudative
  - Adult: Apply daily, may be applied more frequently if very exudative

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- TO THE SKIN
  - Adult: Apply once daily or on alternate days, not recommended if ulcer is very exudative

UNLICENSED USE
- In children No age range specified by manufacturer.

CONTRA-INDICATIONS
Not recommended for neonates

CAUTIONS
G6PD deficiency
CAUTIONS, FURTHER INFORMATION
- Large areas Plasma-sulfadiazine concentrations may approach therapeutic levels with side-effects and interactions as for sulfonamides if large areas of skin are treated.

INTERACTIONS
- Appendix 1 (sulfonamides)—if large amounts given. May inactivate enzymatic degrading agents—concomitant use may be inappropriate

SIDE-EFFECTS
Allergic reactions - argyria (following treatment of large areas of skin or prolonged use) - burning - itching - leucopenia - rashes

SIDE-EFFECTS, FURTHER INFORMATION
- Severe blood and skin disorders: Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders or rashes develop.

Leucopenia developing 2–3 days after starting treatment of burns patients is reported usually to be self-limiting and silver sulfadiazine need not usually be discontinued provided blood counts are monitored carefully to ensure return to normality within a few days.

ALLERGY AND CROSS-SENSITIVITY
Contra-indicated in patients with sensitivity to sulfonamides.
Mupirocin ointment is licensed for use in the following conditions:

- **Skin infections**, particularly those caused by Gram-positive organisms (except pseudomonal infection)

**INDICATIONS AND DOSE**

- **To the skin**
  - **Child**: Apply up to 3 times a day for up to 10 days
  - **Adult**: Apply up to 3 times a day for up to 10 days

**SIDE-EFFECTS**
- Burning sensation, local reactions, pruritus, rash, urticaria

**PREGNANCY**
- Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**BREAST FEEDING**
- No information available.

**RENAI IMPAIRMENT**
- Manufacturer advises caution when mupirocin ointment used in moderate or severe impairment because it contains macrogols (polyethylene glycol).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- **Excipients**: May contain benzyl alcohol, cetyl alcohol, stearyl alcohol.
  - **Flamazine** (Smith & Nephew Healthcare Ltd)
    - **Sulfadiazine silver 10 mg per 1 gram Flamazine 1% cream**: 20 gram (PO) £2.91, 50 gram (PO) £3.85, 250 gram (PO) £10.32 2007 DT medicine price = £8.27

**Antibacterials**

### Bacitracin with polymyxin B

**Bacterial skin infections**
- **To the skin**
  - **Child**: Apply twice daily, can be applied more frequently if required
  - **Adult**: Apply twice daily, can be applied more frequently if required

**Unlicensed use**
- Licensed for use in children (age range not specified by manufacturer).

**Cautionary and Advisory Labels**

- **Nephrotoxicity**: Neutropenia
  - **Further information**: If large areas of skin are being treated nephrotoxicity and neutropenia may be a hazard, particularly in children with renal impairment.

**Side-effects**
- Contact sensitisation

**Renal impairment**
- Renal impairment increases the risk of nephrotoxicity and neutropenia.

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

- **Ointment**
  - **Polyfax** (Teva UK Ltd)
    - Bacitracin zinc 500 unit per 1 gram, Polymyxin B sulfate 10000 unit per 1 gram Polyfax ointment: 4 gram (PO) £1.26, 20 gram (PO) £4.62 2007 DT medicine price = £4.62

### Mupirocin

**Indications and dose**

- **Bacterial skin infections, particularly those caused by Gram-positive organisms (except pseudomonal infection)**
  - **To the skin**
    - **Child**: Apply up to 3 times a day for up to 10 days
    - **Adult**: Apply up to 3 times a day for up to 10 days

**Unlicensed use**
- Mupirocin ointment is licensed for use in children (age range not specified by manufacturer). Bactroban® cream not recommended for use in children under 1 year.

**Side-effects**
- Burning sensation, local reactions, pruritus, rash, urticaria

**Pregnancy**
- Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**Breast-feeding**
- No information available.

**Renal impairment**
- Manufacturer advises caution when mupirocin ointment in moderate or severe impairment because it contains macrogols (polyethylene glycol).

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - **Excipients**: May contain benzyl alcohol, cetyl alcohol, stearyl alcohol.
    - **Mupirocin (as Mupirocin calcium) 20 mg per 1 gram**: Bactroban 2% cream: 15 gram (PO) £5.26 2007 DT medicine price = £5.26

- **Ointment**
  - **Mupirocin (Non-proprietary)**
    - Mupirocin 20 mg per 1 gram: Mupirocin 2% ointment: 15 gram (PO) £14.25 2007 DT medicine price = £14.25
  - **Bactroban** (GlaxoSmithKline Ltd)
    - Mupirocin 20 mg per 1 gram: Bactroban 2% ointment: 15 gram (PO) £5.26

**Retapamulin**

**Indications and dose**

- **Superficial bacterial skin infection caused by Staphylococcus aureus and Streptococcus pyogenes (if resistant to first line topical antibacterials)**
  - **To the skin**
    - **Child**
      - 9 months–17 years: Apply twice daily for 5 days, to be applied thinly, maximum area of skin treated 2% of body surface area, review treatment if no response within 2–3 days
    - **Adult**
      - Apply twice daily for 5 days, to be applied thinly, maximum area of skin treated 100 cm² or lesion length 10 cm, review treatment if no response within 2–3 days

**Contra-indications**
- Contact with eyes, contact with mucous membranes

**Side-effects**
- Contact dermatitis, localised erythema, localised irritation, localised pain, pruritus

**National funding/access decisions**

- Scottish Medicines Consortium (SMC) Decisions

  - The Scottish Medicines Consortium has advised (March 2008) that Retapamulin (Altargo®) is not recommended for use within NHS Scotland for the treatment of superficial skin infections.

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

- **Ointment**
  - **Excipients**: May contain Butylated hydroxytoluene
    - **Altargo** (GlaxoSmithKline Ltd)
      - Retapamulin 10 mg per 1 gram: Altargo 10mg/g ointment: 5 gram (PO) £7.89
2.2 Fungal skin infections

**ANTIFUNGALS** > **IMIDAZOLE ANTIFUNGALS**

### Clotrimazole

- **INDICATIONS AND DOSE**
  - **Fungal skin infections**
    - TO THE SKIN
    - Child: Apply 2–3 times a day
    - Adult: Apply 2–3 times a day
  - **Fungal nail infections**
    - By transungual application
    - Child: Apply once daily, applied under occlusive dressing
    - Adult: Apply once daily, applied under occlusive dressing

- **CAUTIONS** Contact with eyes and mucous membranes should be avoided
- **SIDE-EFFECTS** Local irritation - erythema - hypersensitivity reactions - itching - mild burning sensation
  - **SIDE-EFFECTS, FURTHER INFORMATION** Treatment should be discontinued if side-effects are severe.
- **PREGNANCY** Minimal absorption from skin; not known to be harmful.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - **EXCIPIENTS:** May contain Butylated hydroxyanisole, fragrances
    - **Econazole nitrate** 10 mg per 1 gram
      - Pevaryl (Janssen-Cilag Ltd)
      - Econazole nitrate 10 mg per 1 gram
      - Pevaryl 1% cream | 30 gram £3.71

### Econazolone nitrate

- **INDICATIONS AND DOSE**
  - **Fungal skin infections**
    - TO THE SKIN
    - Child: Apply twice daily
    - Adult: Apply twice daily
  - **Fungal nail infections**
    - BY TRANSGUNGAL APPLICATION
    - Child: Apply once daily, applied under occlusive dressing
    - Adult: Apply once daily, applied under occlusive dressing

- **CAUTIONS** Avoid contact with eyes - avoid contact with mucous membranes
- **SIDE-EFFECTS** Burning sensation - erythema - hypersensitivity reactions - itching - occasional local irritation
  - **SIDE-EFFECTS, FURTHER INFORMATION** Treatment should be discontinued if side-effects are severe.
- **PREGNANCY** Minimal absorption from skin; not known to be harmful.

### Ketoconazole

- **INDICATIONS AND DOSE**
  - **Tinea pedis**
    - TO THE SKIN USING CREAM
      - Adult: Apply twice daily
  - **Fungal skin infection (not Tinea pedis)**
    - TO THE SKIN USING CREAM
      - Adult: Apply 1–2 times a day
  - **Treatment of seborrhoeic dermatitis and dandruff**
    - TO THE SKIN USING SHAMPOO
      - Child 12–17 years: Apply twice weekly for 2–4 weeks, leave preparation on for 3–5 minutes before rinsing
      - Adult: Apply twice weekly for 2–4 weeks, leave preparation on for 3–5 minutes before rinsing
  - **Prophylaxis of seborrhoeic dermatitis and dandruff**
    - TO THE SKIN USING SHAMPOO
      - Child 12–17 years: Apply every 1–2 weeks, leave preparation on for 3–5 minutes before rinsing
      - Adult: Apply every 1–2 weeks, leave preparation on for 3–5 minutes before rinsing
  - **Treatment of pityriasis versicolor**
    - TO THE SKIN USING SHAMPOO
      - Child 12–17 years: Apply once daily for maximum 5 days, leave preparation on for 3–5 minutes before rinsing
      - Adult: Apply once daily for maximum 5 days, leave preparation on for 3–5 minutes before rinsing
  - **Prophylaxis of pityriasis versicolor**
    - TO THE SKIN USING SHAMPOO
      - Child 12–17 years: Apply once daily for up to 3 days before sun exposure, leave preparation on for 3–5 minutes before rinsing
      - Adult: Apply once daily for up to 3 days before sun exposure, leave preparation on for 3–5 minutes before rinsing

- **CAUTIONS** Avoid contact with eyes - avoid contact with mucous membranes
- **INTERACTIONS** Appendix 1 (antifungals, imidazole).
- **SIDE-EFFECTS** Erythema - hypersensitivity reactions - itching - mild burning sensation - occasional local irritation
  - **SIDE-EFFECTS, FURTHER INFORMATION** Treatment should be discontinued if side-effects are severe.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NHS restrictions** Ketoconazole cream is not prescribable on the NHS except for seborrhoeic dermatitis and pityriasis versicolor and endorsed ‘SLS’.
- **EXCEPTIONS TO LEGAL CATEGORY**
  - With topical use for Fungal skin infections in adults: A 15-g tube is available for sale to the public for the treatment of tinea pedis, tinea cruris, and candidal intertrigo.
  - With topical use for Seborrhoeic dermatitis and dandruff: Can be sold to the public for the prevention and treatment of dandruff and seborrhoeic dermatitis of the scalp as a shampoo formulation containing ketoconazole maximum 2%, in a pack containing maximum 120 mL and labelled to show a maximum frequency of application of once every 3 days.
**Miconazole**

**INDICATIONS AND DOSE**

**Fungal skin infections**

- **TO THE SKIN**
  - Child: Apply twice daily for 10 days, or until lesion is resolved
  - Adult: Apply twice daily for 10 days, or until lesion is resolved

**Fungal nail infections**

- **TO THE SKIN**
  - Child: Apply 1–2 times a day
  - Adult: Apply 1–2 times a day

**UNLICENSED USE**

Licensed for use in children (age range not specified by manufacturer).

**CAUTIONS**

Avoid in acute porphyrias and contact with eyes and mucous membranes.

**INTERACTIONS**

Appendix 1 (antifungals, imidazole).

**SIDE-EFFECTS**

- Frequency not known: Burning sensation, erythema, hypersensitivity reactions, itching, occasional local irritation, rash

**SIDE-EFFECTS, FURTHER INFORMATION**

Treatment should be discontinued if side effects are severe.

**PREGNANCY**

Absorbed from the skin in small amounts; manufacturer advises caution.

**BREAST FEEDING**

Manufacturer advises caution—no information available.

**PROFESSIONAL INFORMATION**

Dental practitioners’ formulary

**NATIONAL FUNDING/ACCESS DECISIONS**

NHS restrictions: Miconazole nitrate 2% powder may not be prescribable on the NHS.

**MEDITINAL FORMS**

- **Cream**
  - **EXCIPIENTS:** May contain cetostearyl alcohol, propylene glycol, and stearyl alcohol.
  - **Daktarin Gold**: (McNeil Products Ltd), Miconazole nitrate 20 mg per gram 15 gram, price £3.16
  - **Daktarin Intensive**: (McNeil Products Ltd), Miconazole nitrate 20 mg per gram 15 gram, price £3.16
  - **Nizoral**: (Janssen-Cilag Ltd), Miconazole nitrate 20 mg per gram 30 gram, price £4.24

- **Shampoo**
  - **EXCIPIENTS:** May contain imidurea.
  - **Ketoconazole (Non-proprietary)**
    - Miconazole nitrate 20 mg per gram 120 ml, price £2.74
  - **Dandranozol (Transdermal Ltd)**
    - Dandralo Anti-dandruff 2% shampoo, 60 ml, price £3.24
  - **Nizoral** (Janssen-Cilag Ltd, McNeil Products Ltd), Miconazole nitrate 20 mg per gram 120 ml, price £3.59

**Tioconazole**

**INDICATIONS AND DOSE**

**Fungal nail infections**

- **BY TRANSUNGUAL APPLICATION**
  - Child: Apply twice daily usually for up to 6 months (may be extended to 12 months), apply to nails and surrounding skin
  - Adult: Apply twice daily usually for up to 6 months (may be extended to 12 months), apply to nails and surrounding skin

**UNLICENSED USE**

Licensed for use in children (age range not specified by manufacturer).

**CAUTIONS**

Contact with eyes and mucous membranes should be avoided • use with caution if child likely to suck affected digits (in children)

**SIDE-EFFECTS**

- Burning sensation, dry skin, erythema, exfoliation, hypersensitivity reactions, itching, local oedema, nail discoloration, nail pain, occasional local irritation, periungual inflammation, rash

**SIDE-EFFECTS, FURTHER INFORMATION**

Treatment should be discontinued if side effects are severe.

**PREGNANCY**

Manufacturer advises caution.

**MEDITINAL FORMS**

- **Paint**
  - **Tioconazole** (Non-proprietary)
    - Tioconazole 283 mg per 1 ml, price £27.38
  - **Trosyl**: (Pfizer Ltd)
    - Tioconazole 283 mg per 1 ml, price £28.72

**ANTIFUNGALS > OTHER**

**Amorolfin**

**INDICATIONS AND DOSE**

**Fungal nail infections**

- **BY TRANSUNGUAL APPLICATION**
  - Child 12–17 years: Apply 1–2 times a week for 6 months to treat fingernails and for toenails 9–12 months (review at intervals of 3 months), apply to infected nails after filing and cleansing, allow to dry for approximately 3 minutes
  - Adult: Apply 1–2 times a week for 6 months to treat fingernails and for toenails 9–12 months (review at intervals of 3 months), apply to infected nails after filing and cleansing, allowing to dry for approximately 3 minutes
### Terbinafine

**INDICATIONS AND DOSE**

**Tinea pedis**
- **To the skin using cream**
  - Adult: Apply 1–2 times a day for up to 1 week, to be applied thinly
  - By mouth using tablets
  - Adult: 250 mg once daily for 2–6 weeks

**Tinea corporis**
- **To the skin using cream**
  - Adult: Apply 1–2 times a day for up to 1–2 weeks, to be applied thinly, review treatment after 2 weeks
  - By mouth using tablets
  - Adult: 250 mg once daily for 4 weeks

**Tinea cruris**
- **To the skin using cream**
  - Adult: Apply 1–2 times a day for up to 1–2 weeks, to be applied thinly, review treatment after 2 weeks
  - By mouth using tablets
  - Adult: 250 mg once daily for 2–4 weeks

**Dermatophyte infections of the nails**
- **By mouth using tablets**
  - Adult: 250 mg once daily for 6 weeks-3 months (occasionally longer in toenail infections)

**Cutaneous candidiasis**/Pythiosis versicolor
- **To the skin using cream**
  - Adult: Apply 1–2 times a day for 2 weeks, to be applied thinly, review treatment after 2 weeks

**CAUTIONS**
- With oral use Autoimmune disease (risk of lupus-erythematosus-like effect) • psoriasis (risk of exacerbation)
- With topical use Contact with eyes and mucous membranes should be avoided

**INTERACTIONS**
- With oral use
  - Appendices 1 (terbinafine).

**SIDE-EFFECTS**
- Common or very common
  - With oral use Abdominal discomfort • anorexia • arthralgia • diarrhoea • dyspepsia • headache • myalgia • nausea • rash • urticaria
- Uncommon
  - With oral use Taste disturbance
- Rare
  - With oral use Cholestatic • dizziness • hepatitis • hypoaesthesia • jaundice • liver toxicity • malaise • paraesthesia
- Very rare
  - With oral use Alopecia • blood disorders • lupus erythematosus-like effect • neutropenia • photosensitivity • serious skin reactions • Stevens-Johnson syndrome • thrombocytopenia • toxic epidermal necrolysis
- Frequency not known
  - With oral use Disturbances in smell • exacerbation of psoriasis • hearing disturbances • influenza-like symptoms • pancreatitis • rhabdomyolysis • vasculitis
- With topical use Erythema • hypersensitivity reactions • itching • mild burning sensation • occasional local irritation

**MEDICINAL FORMS**

- **Spray**

  **Spray cautionary and advisory labels 15**
  - Excipients: May contain Benzyl alcohol
  - Grisofulvin 10 mg per 1 gram Grisol AF 1% spray 20 ml £3.35

**Griseofulvin**

**INDICATIONS AND DOSE**

**Tinea pedis**
- **To the skin using cream**
  - Adult: Apply 400 micrograms once daily, apply to an area approximately 13 cm²; increased if necessary to 1.2 mg once daily for maximum treatment duration of 4 weeks, allow each spray to dry between application

**CAUTIONS**
- Avoid contact with eyes and mucous membranes

**INTERACTIONS**
- Appendix 1 (griseofulvin).

**SIDE-EFFECTS**
- Burning sensation • erythema • hypersensitivity reactions • itching • occasional local irritation

**MEDICINAL FORMS**

- **Spray**

  **Spray cautionary and advisory labels 15**
  - Excipients: May contain Benzyl alcohol
  - Grisofulvin 10 mg per 1 gram Grisol AF 1% spray | 20 ml £3.35
**PREGNANCY**
- With topical use: Manufacturer advises use only if potential benefit outweighs risk—animal studies suggest no adverse effects.
- With oral use: Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING**
- With topical use: Manufacturer advises avoid—present in milk. Less than 5% of the dose is absorbed after topical application of terbinafine; avoid application to mother's breast.
- With oral use: Avoid—present in milk.

**HEPATIC IMPAIRMENT**
- With oral use: Monitor hepatic function before treatment and then every 4–6 weeks during treatment—discontinue if abnormalities in liver function tests.

**RENAL IMPAIRMENT**
- With oral use: Use half normal dose if eGFR less than 30 mL/minute/1.73 m² and no suitable alternative available.

**SIDE-EFFECTS**
- Pain, burning and redness at the site of application, mild skin irritation and occasional local burning sensation.
- Hypersensitivity reactions—erythema, pruritus, local irritation.
- Pain and burning sensations may occur when broken skin is contacted.
- Treatment should be discontinued if side-effects are severe.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- **EXCIPIENTS**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), Fragrances
  - **Undecenoic acid with zinc undecenoate (Non-proprietary)**
    - Undecenoic acid 50 mg per 1 gram, Zinc undecenoate 200 mg per 1 gram Mycota cream | 25 gram GSL £2.01
  - **Powder**
    - **EXCIPIENTS**: May contain Fragrances
      - **Undecenoic acid with zinc undecenoate (Non-proprietary)**
        - Undecenoic acid 20 mg per 1 gram, Zinc undecenoate 200 mg per 1 gram Mycota powder | 70 gram GSL £2.71

**OTHER**

**Chlorhexidine with nystatin**

**INDICATIONS AND DOSE**
- Skin infections due to **Candida** spp.
  - **TO THE SKIN**
    - Child: Apply 2–3 times a day, continuing for 7 days after lesions have healed
    - Adult: Apply 2–3 times a day, continuing for 7 days after lesions have healed

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- **EXCIPIENTS**: May contain Benzyl alcohol, Cetostearyl alcohol (including cetyl and stearyl alcohol), polyols, and colourings.

**Antiseptics and Disinfectants**

**Undecenoates**

**Undecenoic acid with zinc undecenoate**

**INDICATIONS AND DOSE**
- Treatment of athletes foot
  - **TO THE SKIN**
    - Child: Apply twice daily, continue use for 7 days after lesions have healed
  - Adult: Apply once daily

**UNLICENSED USE**
- **Mycota** licensed for use in children (age range not specified by manufacturer).

**CAUTIONS**
- Avoid broken skin—contact with eyes should be avoided—contact with mucous membranes should be avoided.

**SIDE-EFFECTS**
- Erythema, hypersensitivity reactions—itching, local irritation, mild burning sensation.

**SIDE-EFFECTS, FURTHER INFORMATION**
- Treatment should be discontinued if side-effects are severe.
BENZOATES

Benzoic acid with salicylic acid

- **INDICATIONS AND DOSE**
  - **Ringworm** (tinea)
    - **TO THE SKIN**
    - Child: Apply twice daily
    - Adult: Apply twice daily

- **UNLICENSED USE** Licensed for use in children (age range not specified by manufacturer).

- **CAUTIONS** Avoid broken or inflamed skin - avoid contact with eyes - avoid contact with mucous membranes

- **SIDE-EFFECTS** Erythema - hypersensitivity reactions - itching - mild burning sensation - occasional local irritation

- **PRESCRIBING AND DISPENSING INFORMATION** Benzoic Acid Ointment, Compound, BP has also been referred to as Whitfield’s ointment.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

SALICYLIC ACID AND DERIVATIVES

Boric acid with salicylic acid and tannic acid

- **INDICATIONS AND DOSE**
  - **Fungal nail infection, particularly tinea**
    - **BY TRANSGENIC APPLICATION**
    - Child 5–17 years: Apply twice daily, and after washing
    - Adult: Apply twice daily, and after washing

- **CAUTIONS** Avoid broken or inflamed skin - contact with eyes and mucous membranes should be avoided - use with caution in children likely to suck affected digits

- **SIDE-EFFECTS** Burning sensation - erythema - hypersensitivity reactions - itching - occasional local irritation

- **PRESCRIBING AND DISPENSING INFORMATION** Treatment should be discontinued if side effects are severe.

- **PREGNANCY** Avoid.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

2.3 Parasitic skin infections

PARASITICIDES

Benzyl benzoate

- **INDICATIONS AND DOSE**
  - **Scabies**
    - **TO THE SKIN**
    - Child: Apply once weekly for 2 doses, rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)
    - Adult: Apply once weekly for 2 doses, rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)

- **CAUTIONS** Avoid contact with eyes - children under 6 months, medical supervision required

- **SIDE-EFFECTS** Skin irritation

- **PATIENT AND CARER ADVICE** Patients should be told to keep hair away from fire and flames during treatment.

- **UNLICENSED USE** Not licensed for use in children under 6 months except under medical supervision.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

Dimeticone

- **INDICATIONS AND DOSE**
  - **Head lice**
    - **TO THE SKIN**
    - Child: Apply once weekly for 2 doses, rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)
    - Adult: Apply once weekly for 2 doses, rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)

- **UNLICENSED USE** Not licensed for use in children under 6 months except under medical supervision.

- **CAUTIONS** Avoid contact with eyes - children under 6 months, medical supervision required

- **SIDE-EFFECTS** Skin irritation

- **PATIENT AND CARER ADVICE** Patients should be told to keep hair away from fire and flames during treatment.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

- **Hedrin** (Thornton & Ross Ltd)
  - Dimeticone 40 mg per 1 gram
    - Hedrin 4% lotion | 50 ml £2.98
    - DT price = £2.98
    - 150 ml £6.92
    - DT price = £6.92

**Cutaneous spray solution**

- **Hedrin** (Thornton & Ross Ltd)
  - Dimeticone 40 mg per 1 gram
    - Hedrin 4% spray | 120 ml £7.13
Malathion

**INDICATIONS AND DOSE**

**Head lice**
- **TO THE SKIN**
  - Child: Apply once weekly for 2 doses, rub preparation over dry hair and scalp, allow to dry naturally, remove by washing after 12 hours
  - Adult: Apply once weekly for 2 doses, rub preparation over dry hair and scalp, allow to dry naturally, remove by washing after 12 hours

**Crab lice**
- **TO THE SKIN**
  - Child: Apply once weekly for 2 doses, apply preparation over whole body, allow to dry naturally, wash off after 12 hours or overnight
  - Adult: Apply once weekly for 2 doses, apply preparation over whole body, allow to dry naturally, wash off after 12 hours or overnight

**Scabies**
- **TO THE SKIN**
  - Child: Apply once weekly for 2 doses, apply preparation over whole body, wash off after 24 hours, if hands are washed with soap within 24 hours, they should be retreated
  - Adult: Apply once weekly for 2 doses, apply preparation over whole body, wash off after 24 hours, if hands are washed with soap within 24 hours, they should be retreated

**UNLICENSED USE**
- Not licensed for use in children under 6 months except under medical supervision.
- **CAUTIONS**
  - Alcoholic lotions not recommended for head lice in children with severe eczema or asthma, or for scabies or crab lice - avoid contact with eyes - children under 6 months, medical supervision required - do not use lotion more than once a week for 3 consecutive weeks - do not use on broken or secondarily infected skin
- **SIDE-EFFECTS**
  - Chemical burns - hypersensitivity reactions - skin irritation
- **PRESCRIBING AND DISPENSING INFORMATION**
  - For scabies, manufacturer recommends application to the body but not exclude head and neck. However, application should be extended to the scalp, neck, face, and ears. It is not recommended for head lice in children under 18 years. Creme Rinse (head lice) not licensed for use in children under 6 months except under medical supervision.

**PERMITRIN**

**INDICATIONS AND DOSE**

**Scabies**
- **TO THE SKIN**
  - Child: Apply once weekly for 2 doses, apply preparation over whole body, allow to dry naturally, wash off after 8–12 hours. If hands are washed with soap within 8 hours of application, they should be treated again with cream
  - Adult: Apply once weekly for 2 doses, apply preparation over whole body, allow to dry naturally, wash off after 8–12 hours. If hands are washed with soap within 8 hours of application, they should be treated again with cream

**UNLICENSED USE**
- Dermal Cream (scabies), not licensed for use in children under 2 months; not licensed for treatment of crab lice in children under 18 years. Creme Rinse (head lice) not licensed for use in children under 6 months except under medical supervision.
- **CAUTIONS**
  - Avoid contact with eyes - children aged 2 months–2 years, medical supervision required for dermal cream (scabies) - children under 6 months, medical supervision required for creme rinse (head lice) - do not use on broken or secondarily infected skin
- **SIDE-EFFECTS**
  - Rare: Oedema - rashes
  - Frequency not known: Erythema - pruritus - stinging
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Manufacturer recommends application to the body but to exclude head and neck. However, application should be extended to the scalp, neck, face, and ears.
  - Larger patients may require up to two 30-g packs for adequate treatment.
- **LESS SUITABLE FOR PRESCRIBING**
  - Lyclear® Creme Rinse is less suitable for prescribing.

**MEDICINAL FORMS**

**Liquid**
- There can be variation in the licensing of different medicines containing the same drug.
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)
    - Lyclear (Omega Pharma Ltd)
      - Permethrin 10 mg per 1 gram Lyclear 1% creme rinse 59 ml £3.55 DT price = £3.55
      - 118 ml £6.46 DT price = £6.46

**Cream**
- CAUTIONARY AND ADVISORY LABELS 10 (Dermal cream only)
  - EXCIPIENTS: May contain Butylated hydroxytoluene, wool fat and related substances including lanolin
    - Permethrin (Non-proprietary)
      - Permethrin 50 mg per 1 gram Permethrin 5% cream 30 gram £7.46 DT price = £7.46
    - Lyclear (Omega Pharma Ltd)
      - Permethrin 50 mg per 1 gram Lyclear 5% dermal cream 30 gram £5.71 DT price = £7.46

2.4 Viral skin infections

**ANTIVIRALS**

**ACICLOVIR**

**INDICATIONS AND DOSE**

**Herpes simplex infection (local treatment)**
- **TO THE SKIN**
  - Child: Apply 5 times a day for 5–10 days, to be applied to lesions approximately every 4 hours, starting at first sign of attack
  - Adult: Apply 5 times a day for 5–10 days, to be applied to lesions approximately every 4 hours, starting at first sign of attack

**UNLICENSED USE**
- Cream licensed for use in children (age range not specified by manufacturer).
3.1 Eczema and psoriasis

Eczema

Types and management

Eczema (dermatitis) has several causes, which may influence treatment. The main types of eczema are irritant, allergic contact, atopic, venous and disseoid; different types may co-exist. Lichenification, due to scratching and rubbing, may complicate any chronic eczema. Atopic eczema is the most common type and it usually involves dry skin as well as infection and lichenification.

Management of eczema involves the removal or treatment of contributory factors including occupational and domestic irritants. Known or suspected contact allergens should be avoided. Rarely, ingredients in topical medicinal products may sensitise the skin; the BNF lists active ingredients together with excipients that have been associated with skin sensitisation.

Skin dryness and the consequent irritant eczema requires emollients applied regularly (at least twice daily) and liberally to the affected area; this can be supplemented with bath or shower emollients. The use of emollients should continue even if the eczema improves or if other treatment is being used.

Topical corticosteroids are also required in the management of eczema; the potency of the corticosteroid should be appropriate to the severity and site of the condition. Mild corticosteroids are generally used on the face and on flexures; potent corticosteroids are generally required for use on adults with discoid or lichenified eczema or with eczema on the scalp, limbs, and trunk. Treatment should be reviewed regularly, especially if a potent corticosteroid is required. In patients with frequent flares (2–3 per month), a topical corticosteroid can be applied on 2 consecutive days each week to prevent further flares.

Bandages (including those containing ichthammol with zinc oxide p. 1108) are sometimes applied over topical corticosteroids or emollients to treat eczema of the limbs. Dry-wrap dressings can be used to provide a physical barrier to help prevent scratching and improve retention of emollients. See Wound management products and elasticated garments for details of elasticated visco stockinette tubular bandages and garments, and silk clothing.


Infection

Bacterial infection (commonly with Staphylococcus aureus and occasionally with Streptococcus pyogenes) can exacerbate eczema and requires treatment with topical or systemic antibacterial drugs. Antibacterial drugs should be used in short courses (typically 1 week) to reduce the risk of drug resistance or skin sensitisation. Associated eczema is treated simultaneously with a topical corticosteroid which can be combined with a topical antiminocular.

Eczema involving widespread or recurrent infection requires the use of a systemic antibacterial that is active against the infecting organism. Products that combine an antiseptic with an emollient application and with a bath emollient can also be used; antiseptic shampoos can be used on the scalp.

Interginginuous eczema commonly involves candida and bacteria; it is best treated with a mild or moderately potent topical corticosteroid and a suitable antimicrobial drug. Widespread herpes simplex infection may complicate atopic eczema and treatment with a systemic antiviral drug is indicated.

Management of other features of eczema

Lichenification, which results from repeated scratching is treated initially with a potent corticosteroid. Bandages containing ichthammol paste p. 1410 (to reduce pruritus) and other substances such as zinc oxide can be applied over the corticosteroid or emollient. Coal tar and ichthammol can be useful in some cases of chronic eczema.

A non-sedating antihistamine may be of some value in relieving severe itching or urticaria associated with eczema. A sedating antihistamine can be used if itching causes sleep disturbance.

Exudative (‘weeping’) eczema requires a potent corticosteroid initially; infection may also be present and require specific treatment. Potassium permanganate solution (1 in 10,000) p. 1128 can be used in exudating eczema for its antiseptic and astringent effects; treatment should be stopped when exudation stops.

Severe refractory eczema

Severe refractory eczema is best managed under specialist supervision; it may require phototherapy or drugs that act on the immune system. Alitretinoin p. 1113 is licensed for the treatment of severe chronic hand eczema refractory to potent topical corticosteroids; patients with hyperkeratotic features are more likely to respond to alitretinoin than those with pompholyx.

Seborrhoeic dermatitis

Seborrhoeic dermatitis (seborrhoeic eczema) is associated with species of the yeast Malassezia and affects the scalp, paranasal areas, and eyebrows. Shampoos active against the yeast (including those containing ketoconazole p. 624 and coal tar) and combinations of mild corticosteroids with suitable antimicrobials are used.
Eczema and psoriasis, drugs affecting the immune response

Overview

Drugs affecting the immune response are used for eczema or psoriasis. Systemic drugs acting on the immune system are used under specialist supervision.

Pimecrolimus p. 1111 by topical application is licensed for mild to moderate atopic eczema. Tacrolimus p. 1112 is licensed for topical use in moderate to severe atopic eczema. Both are drugs whose long-term safety is still being evaluated and they should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Treatment of atopic eczema with topical pimecrolimus or topical tacrolimus should be initiated only by prescribers experienced in managing the condition. Topical tacrolimus and pimecrolimus have a role in the treatment of psoriasis.

A short course of a systemic corticosteroid can be given for eczema flares that have not improved despite appropriate topical treatment.

Ciclosporin p. 766 by mouth can be used for severe psoriasis and for severe eczema. Azathioprine p. 765 or mycophenolate mofetil p. 773 are used for severe refractory eczema [unlicensed indication].

Methotrexate p. 817 can be used for severe psoriasis, the dose being adjusted according to severity of the condition and haematological and biochemical measurements. Folic acid p. 898 should be given to reduce the possibility of side-effects associated with methotrexate. Folic acid can be given once weekly [unlicensed indication], on a different day from the methotrexate; alternative regimens of folic acid may be used in some settings.

Etanercept p. 973, adalimumab p. 969, and infliximab p. 976 inhibit the activity of tumour necrosis factor (TNF-α). They are used for severe plaque psoriasis either refractory to at least 2 standard systemic treatments and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications; while either etanercept or adalimumab is considered to be the first choice in stable disease, infliximab or adalimumab may be useful when rapid disease control is required. Secukinumab p. 966 inhibits the activity of interleukin-17A. It is used for moderate to severe plaque psoriasis in patients who are candidates for systemic therapy. Secukinumab is also licensed for psoriatic arthritis and ankylosing spondylitis. Ustekinumab p. 967 (a monoclonal antibody that inhibits interleukins 12 and 23) can be used for severe plaque psoriasis that has not responded to at least 2 standard systemic treatments and photochemotherapy, or when these treatments cannot be used because of intolerance or contra-indications. Adalimumab is also licensed for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in patients who have had inadequate response to conventional systemic therapy. Adalimumab, etanercept, infliximab and ustekinumab are also licensed for psoriatic arthritis.

Emollients, in addition to their effects on dryness, scaling and cracking, may have an anti-proliferative effect in psoriasis, and may be the only treatment necessary for mild psoriasis. They are particularly useful in inflammatory psoriasis and in plaque psoriasis of palms and soles, in which irritant factors can perpetuate the condition. Emollients are useful adjuncts to other more specific treatment.

More specific topical treatment for chronic stable plaque psoriasis on extensor surfaces of trunk and limbs involves the use of vitamin D analogues, coal tar p. 1109, dithranol p. 1108, and the retinoid tazarotene p. 1114. However, they can irritate the skin and they are not suitable for the more inflammatory forms of psoriasis; their use should be suspended during an inflammatory phase of psoriasis. The efficacy and the irritancy of each substance varies between patients. If a substance irritates significantly, it should be stopped or the concentration reduced; if it is tolerated, its effects should be assessed after 4 to 6 weeks and treatment continued if it is effective.

Scalp psoriasis is usually scaly, and the scale may be thick and adherent; this will require softening with an emollient cream, ointment, or oil. A tar-based shampoo is first-line treatment for scalp psoriasis; a keratolytic, such as salicylic acid, should also be used if there is significant scaling, to allow other treatments to work.

Some preparations prescribed for psoriasis affecting the scalp, combine salicylic acid with coal tar or sulfur. The product should be applied generously, and an adequate quantity should be prescribed. It should be left on for at least an hour, often more conveniently overnight, before washing off. The use of scalp preparations containing a potent corticosteroid or a vitamin D analogue, either alone or in combination, can also be helpful.

Facial, flexural and genital psoriasis can be managed with short-term use of a mild or moderate potency topical corticosteroid (a mild potency topical corticosteroid is preferred for the initial treatment of facial psoriasis). Calcipotriol p. 1115 or tacalcitol p. 1115 can be used for longer-term treatment, or if the response to mild or moderate potency topical corticosteroids is inadequate; calcipotriol p. 1115 is more likely to cause irritation. Low strength tar preparations can also be used. Pimecrolimus p. 1111 or tacrolimus p. 1112 by topical application [unlicensed indication] can be used short-term, under specialist supervision, in patients whose condition has not responded adequately to other treatments, or who are intolerant of them.

Widespread unstable psoriasis of erythrodermic or generalised pustular type requires urgent specialist assessment. Initial topical treatment should be limited to using emollients frequently and generously; emollients should be prescribed in quantities of 1 kg or more. More localised acute or subacute inflammatory psoriasis with hot, spreading or itchy lesions, should be treated topically with emollients or with a corticosteroid of moderate potency.

Calcipotriol and tacalcitol are analogues of vitamin D that affect cell division and differentiation. Calcipotriol is an active form of vitamin D. Vitamin D and its analogues are used first-line for the long-term treatment of plaque psoriasis; they do not smell or stain and they may be more acceptable than tar or dithranol products. Of the vitamin D analogues, tacalcitol and calcipotriol are less likely to irritate.

Coal tar has anti-inflammatory properties that are useful in chronic plaque psoriasis; it also has antiscaling properties. Crude coal tar or morillonite BP is the most effective form, typically in a concentration of 1 to 10% in a soft paraffin base, but few outpatients tolerate the smell and mess.

Cleaner extracts of coal tar included in proprietary preparations, are more practicable for home use but they are less effective and improvement takes longer. Contact of coal tar products with normal skin is not normally harmful and they can be used for widespread small lesions; however,
irritation, contact allergy, and sterile folliculitis can occur. The milder tar extracts can be used on the face and flexures. Tar baths and tar shampoos are also helpful.

Dithranol is effective for chronic plaque psoriasis. Its major disadvantages are irritation (for which individual susceptibility varies) and staining of skin and of clothing. Dithranol is not generally suitable for widespread small lesions nor should it be used in the flexures or on the face. Proprietary preparations are more suitable for home use; they are usually washed off after 5 to 60 minutes (‘short contact’). Specialist nurses may apply intensive treatment with dithranol paste which is covered by stockinette dressings and usually retained overnight. Dithranol should be discontinued if even a low concentration causes acute inflammation; continued use can result in the psoriasis becoming unstable.

Tazarotene, a retinoid, has a similar efficacy to vitamin D and its analogues, but is associated with a greater incidence of irritation. Although irritation is common, it is minimised by applying tazarotene sparingly to the plaques and avoiding normal skin; application to the face and in flexures should also be avoided. Tazarotene does not stain and is odourless. A topical corticosteroid is not generally suitable for long-term use or as the sole treatment of extensive chronic plaque psoriasis; any early improvement is not usually maintained and there is a risk of the condition deteriorating or of precipitating an unstable form of psoriasis (e.g. erythrodermic psoriasis or generalised pustular psoriasis) on withdrawal. Topical use of potent corticosteroids on widespread psoriasis can also lead to systemic as well as local side-effects. However, topical corticosteroids used short-term may be appropriate to treat systemic or very potent topical corticosteroids should be used only under specialist supervision. Combining the use of a corticosteroid with another specific topical treatment may be beneficial in chronic plaque psoriasis; the drugs may be used separately at different times of the day or used together in a single formulation. Eczema co-existing with psoriasis may be treated with a corticosteroid or coal tar, or both.

Phototherapy
Phototherapy is available in specialist centres under the supervision of a dermatologist. Ultraviolet B (UVB) radiation is usually effective for chronic stable psoriasis and for guttate psoriasis. It may be considered for patients with moderately severe psoriasis in whom topical treatment has failed, but it may irritate inflammatory psoriasis.

Photochemotherapy combining long-wave ultraviolet A radiation with a psoralen (PUVA) is available in specialist centres under the supervision of a dermatologist. The psoralen, which enhances the effect of irradiation, is administered either by mouth or topically. PUVA is effective in most forms of psoriasis, including localised palmoplantar pustular psoriasis. Early adverse effects include phototoxicity and pruritus. Higher cumulative doses exaggerate skin ageing, increase the risk of dysplastic and neoplastic skin lesions, especially squamous cancer, and pose a theoretical risk of cataracts.

Phototherapy combined with coal tar, dithranol, tazarotene, topical vitamin D or vitamin D analogues, or oral acitretin, allows reduction of the cumulative dose of phototherapy required to treat psoriasis.

Systemic treatment
Systemic treatment is required for severe, resistant, unstable or complicated forms of psoriasis, and it should be initiated only under specialist supervision. Systemic drugs for psoriasis include acitretin and drugs that affect the immune response (such as ciclosporin p. 766 and methotrexate p. 817).

Systemic corticosteroids should be used only rarely in psoriasis because rebound deterioration may occur on reducing the dose. Acitretin p. 1112, a metabolite of etretinate, is a retinoid (vitamin A derivative); it is prescribed by specialists. The main indication for acitretin is psoriasis, but it is also used in disorders of keratinisation such as severe Darier’s disease (keratosis follicularis), and some forms of ichthyosis. Although a minority of cases of psoriasis respond well to acitretin alone, it is only moderately effective in many cases and it is combined with other treatments. A therapeutic effect occurs after 2 to 4 weeks and the maximum benefit after 4 months. Consideration should be given to stopping acitretin if the response is inadequate after 4 months at the optimum dose. The manufacturers of acitretin do not recommend continuous treatment for longer than 6 months. However, some patients may benefit from longer treatment, provided that the lowest effective dose is used, patients are monitored carefully for adverse effects, and the need for treatment is reviewed regularly.

Apart from teratogenicity, which remains a risk for 3 years after stopping, acitretin is the least toxic systemic treatment for psoriasis; in women with a potential for child-bearing, the possibility of pregnancy must be excluded before treatment and effective contraception must be used during treatment and for at least 3 years afterwards (oral progestogen-only contraceptives not considered effective).

Topical treatment
The vitamin D and analogues, calcipotriol p. 1115, calcitriol p. 1115, and tacalcitol p. 1115 are used for the management of plaque psoriasis. They should be avoided by those with calcium metabolism disorders, and used with caution in generalised pustular or erythrodermic exfoliative psoriasis (enhanced risk of hypercalcaemia).

Corticosteroids
Corticosteroids

Topical corticosteroids

Overview
Topical corticosteroids are used for the treatment of inflammatory conditions of the skin (other than those arising from an infection), in particular eczema, contact dermatitis, insect stings, and eczema of scabies. Corticosteroids suppress the inflammatory reaction during use; they are not curative and on discontinuation a rebound exacerbation of the condition may occur. They are generally used to relieve symptoms and suppress signs of the disorder when other measures such as emollients are ineffective.

Topical corticosteroids are not recommended in the routine treatment of urticaria; treatment should only be initiated and supervised by a specialist. They should not be used indiscriminately in pruritus (where they will only benefit if inflammation is causing the itch) and are not recommended for acne vulgaris.

Systemic or very potent topical corticosteroids should be avoided or given only under specialist supervision in psoriasis because, although they may suppress the psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal (sometimes precipitating severe pustular psoriasis). See the role of topical corticosteroids in the treatment of psoriasis.

In general, the most potent topical corticosteroids should be reserved for recalcitrant dermatoses such as chronic discoid lupus erythematosus, lichen simplex chronicus, hypertrophic lichen planus, and palmoplantar pustulosis. Potent corticosteroids should generally be avoided on the face and skin flexures, but specialists occasionally prescribe them for use on these areas in certain circumstances.
When topical treatment has failed, intralesional corticosteroid injections may be used. These are more effective than the very potent topical corticosteroid preparations and should be reserved for severe cases where there are localised lesions such as keloid scars, hypertrophic lichen planus, or localised alopecia areata.

**Perioral lesions**

Hydrocortisone cream 1% p. 1102 can be used for up to 7 days to treat uninfected inflammatory lesions on the lips. Hydrocortisone with miconazole cream or ointment p. 1107 is useful where infection by susceptible organisms and inflammation co-exist, particularly for initial treatment (up to 7 days) e.g. in angular cheilitis. Organisms susceptible to miconazole include *Candida* spp. and many Gram-positive bacteria including streptococci and staphylococci.

**Choice of formulation**

Water-miscible corticosteroid creams are suitable for moist or weeping lesions whereas ointments are generally chosen for dry, lichenified or scaly lesions or where a more occlusive effect is required. Lotions may be useful when minimal application to a large or hair-bearing area is required or for the treatment of exudative lesions. Occlusive polythene or hydrocolloid dressings increase absorption, but also increase the risk of side effects; they are therefore used only under supervision on a short-term basis for areas of very thick skin (such as the palms and soles). The inclusion of urea or salicylic acid also increases the penetration of the corticosteroid.

In the BNF publications topical corticosteroids for the skin are categorised as 'mild', 'moderately potent', 'potent' or 'very potent'; the least potent preparation which is effective should be chosen but dilution should be avoided whenever possible.

**Absorption through the skin**

Mild and moderately potent topical corticosteroids are associated with few side-effects but care is required in the use of potent and very potent corticosteroids. Absorption through the skin can rarely cause adrenal suppression and even Cushing’s syndrome, depending on the area of the body being treated and the duration of treatment. Absorption is greatest where the skin is thin or raw, and from intertriginous areas; it is increased by occlusion.

### Suitable quantities of corticosteroid preparations to be prescribed for specific areas of the body

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Creams and Ointments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face and neck</td>
<td>15 to 30 g</td>
</tr>
<tr>
<td>Both hands</td>
<td>15 to 30 g</td>
</tr>
<tr>
<td>Scalp</td>
<td>15 to 30 g</td>
</tr>
<tr>
<td>Both arms</td>
<td>30 to 60 g</td>
</tr>
<tr>
<td>Both legs</td>
<td>100 g</td>
</tr>
<tr>
<td>Trunk</td>
<td>100 g</td>
</tr>
<tr>
<td>Groins and genitalia</td>
<td>15 to 30 g</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for a single daily application for 2 weeks

### Compound preparations

The advantages of including other substances (such as antibacterials or antifungals) with corticosteroids in topical preparations are uncertain, but such combinations may have a place where inflammatory skin conditions are associated with bacterial or fungal infection, such as infected eczema. In these cases the antimicrobial drug should be chosen according to the sensitivity of the infecting organism and used regularly for a short period (typically twice daily for 1 week). Longer use increases the likelihood of resistance and of sensitisation.

The keratolytic effect of salicylic acid p. 1137 facilitates the absorption of topical corticosteroids; however, excessive and prolonged use of topical preparations containing salicylic acid may cause salicylism.

**Topical corticosteroid preparation potencies**

Potency of a topical corticosteroid preparation is a result of the formulation as well as the corticosteroid. Therefore, proprietary names are shown.

**Mild**

- Hydrocortisone 0.1–2.5%
- Dicortin
- Mildison
- Synalar 1 in 10 dilution

**Mild with antimicrobials**

- Canesten HC
- Daktacort
- Econacort
- Fucidin H
- Nystaform-HC
- Terra-Cortril
- Timodine

**Moderate**

- Betnovate-RD
- Eumovate
- Haelan
- Modrasone
- Synalar 1 in 4 Dilution
- Ultralanum Plain

**Moderate with antimicrobials**

- Trimovate

**Moderate with urea**

- Alphaderm

**Potent**

- Beclometasone dipropionate 0.025%
- Betamethasone valerate 0.1%
- Betacap
- Betesil
- Betamousse
- Betnovate
- Cultivate
- Diprosone
- Elocon
- Hydrocortisone butyrate
- Locoid
- Locoid Crelo
- Metosyn
- Mometasone furoate 0.1%
- Nerisone
- Synalar

**Potent with antimicrobials**

- Aureocort
- Betamethasone and clioquinol
- Betamethasone and neomycin
- Fucibet
- Lotriderm
- Synalar C
- Synalar N

**Potent with salicylic acid**

- Diprosalic

**Very potent**

- Clarelux
- Dermovate
- Etrivex
- Nerisone Forte

**Very potent with antimicrobials**

- Clopobetasol with neomycin and nystatin
Use in children
Children, especially infants, are particularly susceptible to side-effects. However, concern about the safety of topical corticosteroids in children should not result in the child being undertreated. The aim is to control the condition as well as possible; inadequate treatment will perpetuate the condition. A mild corticosteroid such as hydrocortisone 0.5% or 1% is useful for treating nappy rash and hydrocortisone 1% for atopic eczema in childhood. A moderately potent or potent corticosteroid may be appropriate for severe atopic eczema on the limbs, for 1–2 weeks only, switching to a less potent preparation as the condition improves. In an acute flare-up of atopic eczema, it may be appropriate to use more potent formulations of topical corticosteroids for a short period to regain control of the condition. A very potent corticosteroid should be initiated under the supervision of a specialist. Carers of young children should be advised that treatment should not necessarily be reserved to ‘treat only the worst areas’ and they may need to be advised that patient information leaflets may contain inappropriate advice for the patient’s condition.

Corticosteroids (topical)

- **CONTRA-INDICATIONS** Acne · perioral dermatitis · potent corticosteroids in widespread plaque psoriasis · rosacea (in adults) · untreated bacterial, fungal or viral skin lesions
- **CAUTIONS** Avoid prolonged use (particularly on the face) · cautions applicable to systemic corticosteroids may also apply if absorption occurs following topical and local use · dermatoses of infancy, including nappy rash (extreme caution required—treatment should be limited to 5–7 days) · infection · keep away from eyes · use potent or very potent topical corticosteroids under specialist supervision (in children) · use potent or very potent topical corticosteroids under specialist supervision in psoriasis (can result in rebound relapse, development of generalised pustular psoriasis, and local and systemic toxicity) (in adults)
- **SIDE-EFFECTS**
  - Rare · Adrenal suppression · Cushing’s syndrome
  - Frequency not known · Acne · contact dermatitis · hypertrichosis · irreversible striae atrophicae · irreversible telangiectasia · mild depigmentation (may be reversible) · perioral dermatitis · side-effects applicable to systemic corticosteroids may also apply if absorption occurs following topical and local use · spread and worsening of untreated infection · thinning of the skin (may be restored over a period after stopping treatment but the original structure may never return) · worsening of acne · worsening of rosacea

**SIDE-EFFECTS, FURTHER INFORMATION**
In order to minimise the side-effects of a topical corticosteroid, it is important to apply it thinly to affected areas only, no more frequently than twice daily, and to use the least potent formulation which is fully effective.

- **DIRECTIONS FOR ADMINISTRATION** Topical corticosteroid preparations should be applied no more frequently than twice daily; once daily is often sufficient. Topical corticosteroids should be spread thinly on the skin but in sufficient quantity to cover the affected areas. The length of cream or ointment expelled from a tube may be used to specify the quantity to be applied to a given area of skin. This length can be measured in terms of a fingertip unit (the distance from the tip of the adult index finger to the first crease). One fingertip unit (approximately 500 mg from a tube with a standard 5 mm diameter nozzle) is sufficient to cover an area that is twice that of the flat adult handprint (palm and fingers). Mixing topical preparations on the skin should be avoided where possible; several minutes should elapse between application of different preparations.
  - In children ‘Wet-wrap bandaging’ increases absorption into the skin, but should be initiated only by a dermatologist and application supervised by a healthcare professional trained in the technique.

**PRESCRIBING AND DISPENSING INFORMATION** The potency of each topical corticosteroid should be included on the label with the directions for use. The label should be attached to the container (for example, the tube) rather than the outer packaging.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer corticosteroid creams and ointments. If a patient is using topical corticosteroids of different potencies, the patient should be told when to use each corticosteroid. Patients and their carers should be reassured that side effects such as skin thinning and systemic effects rarely occur when topical corticosteroids are used appropriately.

Alclometasone dipropionate

- **INDICATIONS AND DOSE**
  - **Inflammatory skin disorders such as eczemas**
    - **TO THE SKIN**
      - Child: Apply 1–2 times a day, to be applied thinly
      - Adult: Apply 1–2 times a day, to be applied thinly

- **POTENCY**
  - Alclometasone dipropionate cream 0.05%: moderate

- **UNLICENSED USE** Licensed for use in children (age range not specified by manufacturer).

- **PATIENT AND CARER ADVICE** Patients or carers should be counselled on the application of alclometasone dipropionate cream.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

**CAUTIONARY AND ADVISORY LABELS** 28

**EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, propylene glycol

- **Alclometasone dipropionate (Non-proprietary)**
  - Alclometasone dipropionate 500 microgram per 1 gram Boots Dermcare Eczema & Dermatitis Flare-Up 0.05% cream 15 gram no price available

Beclometasone dipropionate

(Beclomethasone dipropionate)

- **INDICATIONS AND DOSE**
  - **Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis**
    - **TO THE SKIN**
      - Child: Apply 1–2 times a day, thin layer to be applied
      - Adult: Apply 1–2 times a day, thin layer to be applied

- **POTENCY**
  - Beclometasone dipropionate cream and ointment 0.025%: potent.

- **UNLICENSED USE** Not licensed for use in children under 1 year.
Betamethasone

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
- **Child:** Apply 1–2 times a day, to be applied thinly
- **Adult:** Apply 1–2 times a day, to be applied thinly

**POTENCY**

Betamethasone valerate 0.025% cream and ointment: moderate.
Betamethasone valerate 0.1% cream, lotion, ointment, and scalp application: potent.
Betamethasone valerate 0.12% foam: potent.
Betamethasone dipropionate 0.05% cream, lotion, and ointment: potent.

**UNLICENSED USE**

Betacap®, Betnovate® and Betnovate-RD® are not licensed for use in children under 1 year. Bettamousse® is not licensed for use in children under 6 years.

**CAUTIONS**

Use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression

**PATIENT AND CARER ADVICE**

Patient counselling is advised for betamethasone cream, ointment, scalp application and foam (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

**Cream**

**CAUTIONARY AND ADVISORY LABELS** 28

- **Betnovate**
  - Beclometasone dipropionate (Non-proprietary)
  - Beclometasone dipropionate 250 microgram per gram
    - 1 gram Beclometasone 0.025% cream | 30 gram POM £68.00 DT price = £68.00

**Ointment**

**CAUTIONARY AND ADVISORY LABELS** 28

- **Beclometasone dipropionate (Non-proprietary)
  - Beclometasone dipropionate 250 microgram per gram
    - 1 gram Beclometasone 0.025% ointment | 30 gram POM £68.00 DT price = £68.00

**Betnovate** (GlaxoSmithKline Ltd)

Betamethasone (as Betamethasone valerate) 1 mg per gram
Betamethasone valerate 0.1% cream | 500 microgram per 1 gram
Betamethasone valerate 0.1% cream | 15 gram POM £3.00 | 30 gram POM £5.99 DT price = £3.33 | 100 gram POM £11.99 DT price = £11.10

- **Audavate** (Audit McKenzie (Pharma Division) Ltd)
  - Betamethasone (as Betamethasone valerate) 250 microgram per gram
    - 1 gram Audavate RD 0.025% cream | 100 gram POM £2.52 DT price = £3.15

- **Bettamousse** (Focus Pharmaceuticals Ltd)
  - Betamethasone (as Betamethasone valerate) 1 mg per gram
    - 1 gram Betnovate 0.1% cream | 30 gram POM £1.43 DT price = £3.33 | 100 gram POM £4.05 DT price = £11.10

- **Diprosone** (Merck Sharp & Dohme Ltd)
  - Betamethasone (as Betamethasone dipropionate)
  - 500 microgram per 1 gram Diprosone 0.05% cream | 30 gram POM £2.16 DT price = £2.16 | 100 gram POM £6.12 DT price = £6.12


**Calcipotriol with betamethasone**

The properties listed below are those particular to the combination only. For the properties of the components please consider, calcipotriol p. 1115, betamethasone above.

**INDICATIONS AND DOSE**

**DOVOBET® GEL**

**Scalp psoriasis**

- **TO THE SKIN**
  - Adult: Apply 1–4 g once daily usual duration of therapy 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, shampoo off after leaving on scalp overnight or during day, when different preparations containing calcipotriol used together, maximum total calcipotriol 5 mg in any one week
Mild to moderate plaque psoriasis

- **TO THE SKIN**
- Adult: Apply once daily for 8 weeks; if necessary, treatment may be continued beyond 8 weeks or repeated, on the advice of a specialist, to apply maximum 30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day

**DOVOBET® OINTMENT**

Stable plaque psoriasis

- **TO THE SKIN**
- Adult: Apply once daily for 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, to apply to a maximum 30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

**CAUTIONARY AND ADVISORY LABELS 28**

EXCIPIENTS: May contain Butylated hydroxytoluene

- **Dovobet (LEO Pharma)**
  - Calcipotriol (as Calcipotriol hydrate) 50 microgram per 1 gram, Betamethasone (as Betamethasone dipropionate) 500 microgram per 1 gram Dovobet ointment | 30 gram | £3.56
  - Calcipotriol (as Calcipotriol monohydrate) 50 microgram per 1 gram, Betamethasone (as Betamethasone dipropionate) 500 microgram per 1 gram Dovobet gel Applicator | 60 gram | £3.72
  - Dovobet gel | 60 gram | £6.21

**Gel**

**CAUTIONARY AND ADVISORY LABELS 28**

EXCIPIENTS: May contain Butylated hydroxytoluene

- **Dovobet (LEO Pharma)**
  - Calcipotriol (as Calcipotriol monohydrate) 50 microgram per 1 gram, Betamethasone (as Betamethasone dipropionate) 500 microgram per 1 gram Dovobet ointment | 30 gram | £3.56
  - Dovobet gel | 60 gram | £6.21

**Clobetasol propionate**

**INDICATIONS AND DOSE**

Short-term treatment only of severe resistant inflammatory skin disorders such as recalcitrant eczemas unresponsive to less potent corticosteroids

<table>
<thead>
<tr>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TO THE SKIN</strong></td>
</tr>
<tr>
<td>Child: Apply 1–2 times a day for up to 4 weeks, to be applied thinly</td>
</tr>
<tr>
<td>Adult: Apply 1–2 times a day for up to 4 weeks, to be applied thinly, maximum 50 g of 0.05% preparation per week</td>
</tr>
</tbody>
</table>

**ETRIVEX®**

**Moderate scalp psoriasis**

<table>
<thead>
<tr>
<th><strong>TO THE SKIN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult: Apply once daily maximum duration of treatment 4 weeks, to be applied thinly then rinsed off after 15 minutes; frequency of application should be reduced after clinical improvement</td>
</tr>
</tbody>
</table>

**POTENCY**

Clobetasol propionate 0.05% cream, foam, ointment, scalp application, and shampoo: very potent.

**UNLICENSED USE**

- **Dermovate®** not licensed for use in children under 1 year.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer clobetasol propionate foam, liquid (scalp application), cream, ointment and shampoo.

Scalp application Patients or carers should be advised to apply foam directly to scalp lesions (foam begins to subside immediately on contact with skin).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment, paste

- **Foam**
  - **CAUTIONARY AND ADVISORY LABELS 15, 28**
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol
  - **Clarelux (Pierre Fabre Dermo-Cosmetique)**
    - Clobetasol propionate 500 microgram per 1 gram Clarelux 500 micrograms/g foam | 10 gram | £11.06

- **Cream**
  - **CAUTIONARY AND ADVISORY LABELS 28**
  - EXCIPIENTS: May contain Beeswax, cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, propylene glycol
  - **Dermovate (GlaxoSmithKline UK Ltd)**
    - Clobetasol propionate 0.05% cream | 30 gram | £3.07 DT price = £3.07 | 100 ml | £10.42 DT price = £10.42
  - **ClobaDerm (Auden McKenzie (Pharma Division) Ltd)**
    - Clobetasol propionate 500 microgram per 1 gram ClobaDerm 0.05% cream | 30 gram | £2.69 DT price = £2.69 | 100 gram | £6.32 DT price = £7.90
    - **Dermovate (GlaxoSmithKline UK Ltd)**
      - Clobetasol propionate 500 microgram per 1 gram Dermovate 0.05% cream | 30 gram | £2.69 DT price = £2.69 | 100 gram | £7.90 DT price = £7.90
  - **Scalp application**
    - **CAUTIONARY AND ADVISORY LABELS 28**
    - EXCIPIENTS: May contain Propylene glycol
    - **Clobetasol propionate (Non-proprietary)**
      - Clobetasol propionate 500 microgram per 1 gram Clobetasol 0.05% ointment | 30 gram | £2.69 DT price = £2.69 | 100 gram | £7.90 DT price = £7.90
    - **Dermovate (GlaxoSmithKline UK Ltd)**
      - Clobetasol propionate 500 microgram per 1 gram Dermovate 0.05% ointment | 30 gram | £2.69 DT price = £2.69 | 100 gram | £7.90 DT price = £7.90

- **SHAMPOO**
  - **CAUTIONARY AND ADVISORY LABELS 28**
  - **Etrivex (Galderma (UK) Ltd)**
    - Clobetasol propionate 500 microgram per 1 gram Etrivex 500 micrograms/g shampoo | 125 ml | £10.29 DT price = £10.29

**Combinations available:** **Clobetasol propionate with neomycin sulfate and nystatin**, p. 1105

**Clobetasone butyrate**

**INDICATIONS AND DOSE**

Eczemas and dermatitis of all types | Maintenance between courses of more potent corticosteroids

<table>
<thead>
<tr>
<th><strong>TO THE SKIN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Child: 1–2 times a day, to be applied thinly</td>
</tr>
<tr>
<td>Adult: 1–2 times a day, to be applied thinly</td>
</tr>
</tbody>
</table>

**POTENCY**

Clobetasone butyrate 0.05% cream and ointment: moderate.

**UNLICENSED USE**

- Licensed for use in children (age range not specified by manufacturer).
1100 Inflammatory skin conditions

- **PATIENT AND CARER ADVICE** Patients or carers should be advised on the application of clobetasone butyrate containing preparations.

- **EXCEPTIONS TO LEGAL CATEGORY** Cream can be sold to the public for short-term symptomatic treatment and control of patches of eczema and dermatitis (but not seborrhoeic dermatitis) in adults and children over 12 years provided pack does not contain more than 15 g.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

- **CAUTIONARY AND ADVISORY LABELS 28**
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol
  - **Eumovate** (GlaxoSmithKline Consumer Healthcare, GlaxoSmithKline UK Ltd)
    - Clobetasone butyrate 500 microgram per 1 gram Eumovate
  - Eumovate 0.05% cream | 30 gram £1.86 DT price = £1.86  
  - 100 gram £5.44 DT price = £5.44

**Ointment**

- **CAUTIONARY AND ADVISORY LABELS 28**
  - **Clobavate** (Teva UK Ltd)
    - Clobetasone butyrate 500 microgram per 1 gram Clobavate
    - Clobavate 4 microgram per 1 square cm tape
    - Clobavate 12 microgram per 1 square cm tape
  - **Eumovate** (GlaxoSmithKline UK Ltd)
    - Clobetasone butyrate 500 microgram per 1 gram Eumovate
    - Eumovate 0.05% ointment | 30 gram £1.86 DT price = £1.86  
    - 100 gram £5.44 DT price = £5.44

**Combinations available:**

- **Clobetasone butyrate with nystatin and oxytetracycline**, p. 1105

### Fludroxy cortisol

(Flurandrenolone)

- **INDICATIONS AND DOSE**
  - **Inflammatory skin disorders such as eczemas**
    - **TO THE SKIN**
      - Child: Apply 1–2 times a day, to be applied thinly
      - Adult: Apply 1–2 times a day, to be applied thinly
  - **HAELAN® TAPE**
    - **Chronic localised recalcitrant dermatoses (but not acute or weeping)**
      - **TO THE SKIN**
      - Child: Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily
      - Adult: Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily
  - **POTENCY**
    - Fludroxy cortisol 0.0125% cream and ointment: moderate

- **UNLICENSED USE** Licensed for use in children (age range not specified by manufacturer).

- **PATIENT AND CARER ADVICE** Patients or carers should be counselled on application of fludroxy cortisol cream and ointment.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

- **CAUTIONARY AND ADVISORY LABELS 28**
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol
  - **Fludroxycortide (Non-proprietary)**
    - Fludroxy cortisol 125 microgram per 1 gram
      - Fludroxy cortisol 0.0125% cream | 60 gram £5.99
  - **Haelan (Typharm Ltd)**
    - Fludroxy cortisol 125 microgram per 1 gram
      - Haelan 0.0125% cream | 60 gram £3.26

**Ointment**

- **CAUTIONARY AND ADVISORY LABELS 28**
  - EXCIPIENTS: May contain Beeswax, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
  - **Fludroxy cortisol (Non-proprietary)**
    - Fludroxy cortisol 125 microgram per 1 gram
      - Fludroxy cortisol 0.0125% ointment | 60 gram £5.99
  - **Haelan (Typharm Ltd)**
    - Fludroxy cortisol 125 microgram per 1 gram
      - Haelan 0.0125% ointment | 60 gram £3.26

**Impregnated dressing**

- **Fludroxy cortisol (Non-proprietary)**
  - Fludroxy cortisol 4 microgram per 1 square cm
    - Fludroxy cortisol 4 micrograms/square cm tape 7.5 cm |
      - 20 cm £12.49 DT price = £8.19
      - 40 cm £19.99
      - 80 cm £28.66

### Diflucortolone valerate

- **INDICATIONS AND DOSE**
  - **Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (using 0.3% diflucortolone valerate)**
    - **Short-term treatment of severe exacerbations (using 0.3% diflucortolone valerate)**
      - **Psoriasis (using 0.3% diflucortolone valerate)**
        - **TO THE SKIN**
          - Child 4–17 years: Apply 1–2 times a day for up to 2 weeks, reducing strength as condition responds, to be applied thinly; maximum 60 g per week
          - Adult: Apply 1–2 times a day for up to 2 weeks, reducing strength as condition responds, to be applied thinly; maximum 60 g per week
  - **Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (using 0.1% diflucortolone valerate)**
    - **Psoriasis (using 0.1% diflucortolone valerate)**
      - **TO THE SKIN**
        - Child: Apply 1–2 times a day for up to 4 weeks, to be applied thinly
        - Adult: Apply 1–2 times a day for up to 4 weeks, to be applied thinly
  - **POTENCY**
    - Diflucortolone valerate 0.1% cream and ointment: potent.
    - Diflucortolone valerate 0.3% cream and ointment: very potent.

- **UNLICENSED USE** Nerisone® licensed for use in children (age range not specified by manufacturer); Nerisone Forte® not licensed for use in children under 4 years.

- **PRESCRIBING AND DISPENSING INFORMATION** Patients or carers should be advised on application of diflucortolone valerate containing preparations.
**Fluocinolone acetonide**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas

Psoriasis

- **TO THE SKIN**
  - Child 1–17 years: Apply 1–2 times a day, to be applied thinly, reduce strength as condition responds
  - Adult: Apply 1–2 times a day, to be applied thinly, reduce strength as condition responds

**POTENCY**

Fluocinolone acetonide 0.025% cream, gel, and ointment: potent.

Fluocinolone acetonide 0.00625% cream and ointment: moderate.

Fluocinolone acetonide 0.0025% cream: mild.

**UNLICENSED USE** Not licensed for use in children under 1 year.

**PRESCRIBING AND DISPENSING INFORMATION** Gel is useful for application to the scalp and other hairy areas.

**PATIENT AND CARER ADVICE** Patient counselling is advised for fluocinolone acetonide cream, gel and ointment (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polymers, propylene glycol

- **Synalar** (Derma UK Ltd)
  - Fluocinolone acetonide 25 microgram per 1 gram Synalar 1 in 10 Dilution 0.0025% cream | 50 gram £4.58 DT price = £4.58
  - Fluocinolone acetonide 62.5 microgram per 1 gram Synalar 1 in 4 Dilution 0.00625% cream | 50 gram £4.84 DT price = £4.84
  - Fluocinolone acetonide 250 microgram per 1 gram Synalar 0.025% cream | 30 gram £4.14 DT price = £4.14 | 100 gram £11.75 DT price = £11.75

**Ointment**

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Propylene glycol, wool fat and related substances including lanolin

- **Synalar** (Derma UK Ltd)
  - Fluocinolone acetonide 62.5 microgram per 1 gram Synalar 1 in 4 Dilution 0.00625% ointment | 50 gram £4.84 DT price = £4.84
  - Fluocinolone acetonide 250 microgram per 1 gram Synalar 0.025% ointment | 30 gram £4.14 DT price = £4.14 | 100 gram £11.75 DT price = £11.75

**Gel**

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Hydroxybenzoates (parabens), propylene glycol

- **Synalar** (Derma UK Ltd)
  - Fluocinolone acetonide 250 microgram per 1 gram Synalar 0.025% gel | 30 gram £5.56 DT price = £5.56 | 60 gram £10.02 DT price = £10.02

Combinations available: Fluocinolone acetonide with clioquinol, p. 1106 - Fluocinolone acetonide with neomycin, p. 1106

**Fluocinonide**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

Fluocinonide 0.05% cream and ointment: potent.

**UNLICENSED USE** Not licensed for use in children under 1 year.

**PATIENT AND CARER ADVICE** Patients or carers should be advised on the application of fluocinonide preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Cream**

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Propylene glycol

- **Metosyn FAPG** (Derma UK Ltd)
  - Fluocinonide 500 microgram per 1 gram Metosyn FAPG 0.05% cream | 25 gram £3.96 DT price = £3.96 | 100 gram £13.34 DT price = £13.34

**Ointment**

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Propylene glycol, wool fat and related substances including lanolin

- **Metosyn** (Derma UK Ltd)
  - Fluocinonide 500 microgram per 1 gram Metosyn 0.05% ointment | 25 gram £3.50 DT price = £3.50 | 100 gram £13.15 DT price = £13.15

**Flucortolone**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
  - Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

**POTENCY**

Flucortolone hexanoate 0.25% cream and ointment; flucortolone pivalate 0.25% cream and flucortolone 0.25% ointment: moderate.

**PRESCRIBING AND DISPENSING INFORMATION** Patients or carers should be counselled on the application of flucortolone preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

**Fluticasone**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as dermatitis and eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

Fluticasone cream 0.05%: potent.

Fluticasone ointment 0.005%: potent.

**UNLICENSED USE** Not licensed for use in children under 3 months.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on application of fluticasone creams and ointments.
Hydrocortisone

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

► TO THE SKIN
► Child: Apply 1–2 times a day, to be applied thinly
► Adult: Apply 1–2 times a day, to be applied thinly

**NAPPY RASH**
► TO THE SKIN
► Child: Apply 1–2 times a day for no longer than 1 week, discontinue as soon as the inflammation subsides

**POTENCY**
Hydrocortisone cream and ointment 0.5 to 2.5%: mild

**PRESCRIBING AND DISPENSING INFORMATION**
When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied. Although Dioderm® contains only 0.1% hydrocortisone, the formulation is designed to provide a clinical activity comparable to that of Hydrocortisone Cream 1% BP.

**PATIENT AND CARER ADVICE**
Patient counselling is advised for hydrocortisone cream and ointment (application).

**PROFESSIONAL INFORMATION**
Dental practitioners’ formulary
Hydrocortisone Cream 1% 15 g may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY**
Over-the-counter hydrocortisone preparations Skin creams and ointments containing hydrocortisone (alone or with other ingredients) can be sold to the public for the treatment of allergic contact dermatitis, irritant dermatitis, insect bite reactions and mild to moderate eczema in patients over 10 years, to be applied sparingly over the affected area 1–2 times daily for max. 1 week. Over-the-counter hydrocortisone preparations should not be sold without medical advice for children under 10 years or for pregnant women; they should not be sold for application to the face, anogenital region, broken or infected skin (including cold sores, acne, and athlete’s foot).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

**Cream**
CAUTIONARY AND ADVISORY LABELS 28
EXCipients: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), imidurea, propylene glycol

► Hydrocortisone (Non-proprietary)
Hydrocortisone 5 mg per 1 gram Hydrocortisone 0.5% cream | 15 gram (POT) | £3.00 DT price = £1.17 | 50 gram (POT) | £16.69–£49.90
Hydrocortisone 10 mg per 1 gram Hydrocortisone 1% cream | 15 gram (POT) | £1.64 DT price = £0.94 | 15 gram (POT) | £10.50 DT price = £0.94 | 30 gram (POT) | £23.48 DT price = £1.88 | 50 gram (POT) | £36.12 DT price = £3.13

Hydrocortisone butyrate

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

► TO THE SKIN
► Child 1–17 years: Apply 1–2 times a day, to be applied thinly
► Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**
Hydrocortisone butyrate 0.1% cream, liquid, and ointment: potent

**PATIENT AND CARER ADVICE**
Patients or carers should be given advice on how to administer hydrocortisone butyrate lotion, cream, ointment and scalp lotion.

Medicines for Children leaflet: Hydrocortisone (topical) for eczema [www.medicinesforchildren.org.uk/hydrocortisone-topical-for-eczema](http://www.medicinesforchildren.org.uk/hydrocortisone-topical-for-eczema)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Liquid**
CAUTIONARY AND ADVISORY LABELS 15(excluding Locoid Crelo topical emulsion), 28
EXCipients: May contain Butylated hydroxytoluene, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), propylene glycol

► Locoid (LEO Pharma)
Hydrocortisone butyrate 1 mg per 1 ml Locoid 0.1% scalp lotion | 100 ml (POT) | £6.83 DT price = £6.83
Hydrocortisone with urea

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102.

**INDICATIONS AND DOSE**

**Mild inflammatory skin disorders such as eczemas**
- **TO THE SKIN**
  - **Child:** To be applied thinly (consult product literature)
  - **Adult:** To be applied thinly (consult product literature)

**POTENCY**
Hydrocortisone 1% with urea cream: moderate

**PATIENT AND CARER ADVICE**
Patients or carers should be advised on application of hydrocortisone with urea cream.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoid Crelo (LEO Pharma)</td>
<td>£5.91</td>
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</table>

**Ointment**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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</thead>
<tbody>
<tr>
<td>Locoid Lipocream (LEO Pharma)</td>
<td>£4.93</td>
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</table>

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Liquid**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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</thead>
<tbody>
<tr>
<td>Elocon (Merck Sharp &amp; Dohme Ltd)</td>
<td>£4.36</td>
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</table>

**Mometasone furoate**

**Cream**

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<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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</thead>
<tbody>
<tr>
<td>Elocon (Merck Sharp &amp; Dohme Ltd)</td>
<td>£15.10</td>
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</table>

**Ointment**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elocon (Merck Sharp &amp; Dohme Ltd)</td>
<td>£6.23</td>
</tr>
</tbody>
</table>

**Corticosteroids > Corticosteroid Combinations with Anti-Infectives**

**Betamethasone with clioquinol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1098.

**INDICATIONS AND DOSE**

**Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis**
- **TO THE SKIN**
  - **Child:** (consult product literature)
  - **Adult:** (consult product literature)

**POTENCY**
Betamethasone (as valerate) 0.1% with clioquinol cream and ointment: potent.

**UNLICENSED USE**
Betamethasone and clioquinol preparations is not licensed for use in children under 1 year.

**PATIENT AND CARER ADVICE**
Stains clothing. Patients or carers should be counselled on application of betamethasone with clioquinol preparations.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone with clioquinol (Non-proprietary)</td>
<td>£28.88</td>
</tr>
</tbody>
</table>

**Locoid Crelo**

Hydrocortisone butyrate 1 mg per 1 gram Locoid Crelo 0.1% topical emulsion | 100 gram POM £5.91

**Cream**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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</thead>
<tbody>
<tr>
<td>Alphaderm (Alliance Pharmaceuticals Ltd)</td>
<td>£2.38</td>
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</table>

**Hydrocortisone butyrate 1 mg per 1 gram**

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<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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<tbody>
<tr>
<td>Alphaderm 1% cream</td>
<td>£2.38</td>
</tr>
<tr>
<td>1%/10% cream</td>
<td>£2.38</td>
</tr>
<tr>
<td>10% cream</td>
<td>£7.03</td>
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</table>

**Betamethasone with clioquinol (Non-proprietary)**

Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Clioquinol 30 mg per 1 gram Clioquinol 30 mg per 1 gram Betamethasone valerate 0.1% / Clioquinol 3% cream | £28.88 |

**Clioquinol 30 mg per 1 gram**

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<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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<tbody>
<tr>
<td>Clioquinol 3% cream</td>
<td>£28.88</td>
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</tbody>
</table>

**Locoid Lipocream**

Hydrocortisone butyrate 1 mg per 1 gram Locoid Lipocream 0.1% | 30 gram POM £1.69 | 100 gram POM £5.17

**Locoid Crelo**

Locoid Crelo 0.1% cream | 30 gram POM £4.93 | 100 gram POM £4.93

**Betamethasone furoate (Non-proprietary)**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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</thead>
<tbody>
<tr>
<td>Mometasone furoate 1 mg per 1 gram</td>
<td>£12.44</td>
</tr>
<tr>
<td>15 gram POM</td>
<td>£12.44</td>
</tr>
<tr>
<td>30 gram POM</td>
<td>£12.44</td>
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</table>

**Mometasone furoate (Non-proprietary)**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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<tbody>
<tr>
<td>Mometasone furoate 1 mg per 1 gram</td>
<td>£10.71</td>
</tr>
<tr>
<td>10 gram POM</td>
<td>£10.71</td>
</tr>
<tr>
<td>30 gram POM</td>
<td>£10.71</td>
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**Clioquinol 30 mg per 1 gram**

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<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clioquinol 30 mg per 1 gram</td>
<td>£5.90</td>
</tr>
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</table>

**Betamethasone with clioquinol (Non-proprietary)**

Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Clioquinol 30 mg per 1 gram Betamethasone valerate 0.1% / Clioquinol 3% cream | £28.88 |

**Clioquinol 3 mg per 1 gram**

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<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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</thead>
<tbody>
<tr>
<td>Clioquinol 3% cream</td>
<td>£9.38</td>
</tr>
</tbody>
</table>

**Hydrocortisone butyrate 1 mg per 1 gram**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone butyrate 1 mg per 1 gram</td>
<td>£1.60</td>
</tr>
<tr>
<td>30 gram POM</td>
<td>£1.60</td>
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**Betamethasone with clioquinol cream**

<table>
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<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
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<tbody>
<tr>
<td>Mometasone furoate 1 mg per 1 gram</td>
<td>£12.44</td>
</tr>
<tr>
<td>15 gram POM</td>
<td>£12.44</td>
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**Betamethasone with clioquinol**

**Ointment**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mometasone furoate 1 mg per 1 gram</td>
<td>£6.23</td>
</tr>
<tr>
<td>30 gram POM</td>
<td>£6.23</td>
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**Betamethasone with clioquinol**

**Ointment**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mometasone furoate 1 mg per 1 gram</td>
<td>£12.44</td>
</tr>
<tr>
<td>10 gram POM</td>
<td>£12.44</td>
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</table>

**Betamethasone with clioquinol**

**Ointment**

<table>
<thead>
<tr>
<th><strong>CN/POM</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mometasone furoate 1 mg per 1 gram</td>
<td>£12.44</td>
</tr>
<tr>
<td>10 gram POM</td>
<td>£12.44</td>
</tr>
</tbody>
</table>
Betamethasone with clotrimazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1098, clotrimazole p. 758.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- TO THE SKIN
- Child: (consult product literature)
- Adult: (consult product literature)

**POTENCY**
Betamethasone dipropionate 0.064% (=betamethasone 0.5%) with clotrimazole cream: potent.

**UNLICENSED USE** Lotriderm® not licensed for use in children under 12 years.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer betamethasone with clotrimazole cream.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - CAUTIONARY AND ADVISORY LABELS 28
  - EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol
    - Lotriderm (Merck Sharp & Dohme Ltd)
      - Betamethasone dipropionate 640 microgram per 1 gram, Clotrimazole 10 mg per 1 gram
      - Lotriderm cream | 30 gram [PoD] £6.34 DT price = £6.34

Betamethasone with fusidic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1098, fusidic acid p. 527.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- TO THE SKIN
- Child: (consult product literature)
- Adult: (consult product literature)

**POTENCY**
Betamethasone (as valerate) 0.1% with fusidic acid cream: potent.

**UNLICENSED USE** Fucibet® Lipid Cream is not licensed for use in children under 6 years.

**PATIENT AND CARER ADVICE** Patients or carers should be counselled on application of betamethasone with fusidic acid preparations.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - CAUTIONARY AND ADVISORY LABELS 28
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, hydroxybenzoates (parabens)
    - Fucibet Lipid Cream (LEO Pharma)
      - Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Fusidic acid 20 mg per 1 gram
      - Fucibet Lipid cream | 30 gram [PoD] £6.74 DT price = £6.38

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1098, neomycin sulfate p. 480.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- TO THE SKIN USING OINTMENT, OR TO THE SKIN USING CREAM
- Child 2-17 years: Apply 1–2 times a day, to be applied thinly
- Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**
Betamethasone (as valerate) 0.1% with neomycin cream and ointment: potent.

**UNLICENSED USE** Betamethasone and neomycin preparations not licensed for use in children under 2 years.

**PATIENT AND CARER ADVICE** Patient counselling is advised for betamethasone with neomycin cream and ointment (application).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - CAUTIONARY AND ADVISORY LABELS 28
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol
    - Betamethasone with neomycin (Non-proprietary)
      - Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram
        - Betamethasone valerate 0.1% / Neomycin 0.5% cream | 30 gram [PoD] £28.88 DT price = £17.74
        - 100 gram [PoD] £48.00 DT price = £59.14

- **Ointment**
  - CAUTIONARY AND ADVISORY LABELS 28
    - Betamethasone with neomycin (Non-proprietary)
      - Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram
        - Betamethasone valerate 0.1% / Neomycin 0.5% ointment | 30 gram [PoD] £28.88 DT price = £17.74
        - 100 gram [PoD] £48.00 DT price = £59.14

Betamethasone with salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1098, salicylic acid p. 1157.

**INDICATIONS AND DOSE**
DIPROSALIC® OINTMENT
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- TO THE SKIN
- Child: Apply 1–2 times a day, max. 60 g per week
- Adult: Apply 1–2 times a day, max. 60 g per week

**POTENCY**
For Dipsoralic® ointment: Betamethasone (as dipropionate) 0.05% with salicylic acid 3%: potent.
PATIENT AND CARER ADVICE
Patients or carers should be counselled on application of betamethasone and salicylic acid preparations.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Liquid
CAUTIONARY AND ADVISORY LABELS 28
EXCIPIENTS: May contain Disodium edetate

Diprosalic (Merck Sharp & Dohme Ltd)
Betamethasone (as Betamethasone dipropionate)
500 microgram per 1 ml, Salicylic acid 20 mg per 1 ml
Diprosalic 0.05%/2% scalp application | 100 ml | £10.10 DT price = £10.10

Ointment
CAUTIONARY AND ADVISORY LABELS 28

Diprosalic (Merck Sharp & Dohme Ltd)
Betamethasone (as Betamethasone dipropionate)
500 microgram per 1 gram, Salicylic acid 30 mg per 1 gram
Diprosalic 0.05%/3% ointment | 30 gram | £3.18 DT price = £3.18

PATIENT AND CARER ADVICE
Stains clothing. Patients or carers should be counselled on application of betamethasone and salicylic acid preparations.

POTENCY
For Diprosalic® scalp ointment: Betamethasone (as dipropionate) 0.05% with salicylic acid 2%: potent.

Chlortetracycline with triamcinolone

INDICATIONS AND DOSE
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (associated with infection) | Psoriasis (associated with infection)

TO THE SKIN

Adult: To be applied thinly (consult product literature)

POTENCY
Triamcinolone acetonide 0.1%, chlortetracycline hydrochloride 3% ointment: potent.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Ointment
CAUTIONARY AND ADVISORY LABELS 28
EXCIPIENTS: May contain Wool fat and related substances including lanolin

Aureocort (AMCo)
Triamcinolone acetonide 1 mg per 1 gram, Chlortetracycline hydrochloride 30.9 mg per 1 gram
Aureocort ointment | 15 gram | £3.51

PATIENT AND CARER ADVICE
Stains clothing. Patients or carers should be counselled on the application of chlortetracycline with triamcinolone products.

Clobetasol propionate with neomycin sulfate and nystatin
The properties listed below are those particular to the combination only. For the properties of the components please consider, clobetasol propionate p. 1099, neomycin sulfate p. 480.

INDICATIONS AND DOSE
Short-term treatment only of severe resistant inflammatory skin disorders such as recalcitrant eczemas associated with infection and unresponsive to less potent corticosteroids | Psoriasis associated with infection

TO THE SKIN

Adult: (consult product literature)

POTENCY
Clobetasol propionate 0.05% with neomycin sulfate and nystatin cream and ointment: very potent.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Cream
CAUTIONARY AND ADVISORY LABELS 28

Clobetasol propionate with neomycin sulfate and nystatin (Non-proprietary)
Clobetasol propionate 500 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram, Nystatin 100000 unit per 1 gram
Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units/g cream | 30 gram | £64.00 DT price = £64.00

Ointment
CAUTIONARY AND ADVISORY LABELS 28

Clobetasol propionate with neomycin sulfate and nystatin (Non-proprietary)
Clobetasol propionate 500 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram, Nystatin 100000 unit per 1 gram
Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units/g ointment | 30 gram | £64.00 DT price = £64.00

PATIENT AND CARER ADVICE
Patients or carers should be advised on application of clobetasol propionate, neomycin sulfate and nystatin containing preparations.

Clobetasone butyrate with nystatin and oxytetracycline
The properties listed below are those particular to the combination only. For the properties of the components please consider, clobetasone butyrate p. 1099, oxytetracycline p. 523.

INDICATIONS AND DOSE
Steroid-responsive dermatoses where candidal or bacterial infection is present

TO THE SKIN

Adult: (consult product literature)

POTENCY
Clobetasone butyrate 0.05% with nystatin and oxytetracycline cream: moderate.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Cream
CAUTIONARY AND ADVISORY LABELS 28
EXCIPIENTS: May contain Cellosolve alcohol (including cetyl and stearyl alcohol), chlorocresol, sodium metabisulfite

Trimovate (GlaxoSmithKline UK Ltd)
Clobetasone butyrate 500 microgram per 1 gram, Nystatin 100000 unit per 1 gram, Oxytetracycline (as Oxytetracycline calcium) 30 mg per 1 gram
Trimovate cream | 30 gram | £3.29

PATIENT AND CARER ADVICE
Stains clothing.

Skin
Fluocinolone acetonide with clioquinol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluorocinolone acetonide p. 1101.

- **INDICATIONS AND DOSE**
  - **Inflammatory skin disorders such as eczemas associated with infection**
    - **Psoriasis associated with infection**
    - **TO THE SKIN**
    - Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

- **PATIENT AND CARER ADVICE**: Patient counselling is advised for clioquinol with fluorocinolone acetonide cream and ointment (application). Ointment stains clothing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - CAUTIONARY AND ADVISORY LABELS: 28
    - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol
    - Synalar C (Derma UK Ltd)
      - Clioquinol 30 mg per 1 gram, Fluocinolone acetonide 250 microgram per 1 gram
      - Synalar C ointment | 15 gram £2.66
  - **Ointment**
    - CAUTIONARY AND ADVISORY LABELS: 28
    - EXCIPIENTS: May contain Propylene glycol, wool fat and related substances including lanolin
    - Synalar C (Derma UK Ltd)
      - Clioquinol 30 mg per 1 gram, Fluocinolone acetonide 250 microgram per 1 gram
      - Synalar C ointment | 15 gram £2.66

Fluocinolone acetonide with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluorocinolone acetonide p. 1101, neomycin sulfate p. 480.

- **INDICATIONS AND DOSE**
  - **Inflammatory skin disorders such as eczemas associated with infection**
  - **Psoriasis associated with infection**
  - **TO THE SKIN**
  - Child 1-17 years: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds
  - Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

- **PATIENT AND CARER ADVICE**: Patients or carers should be counselled on the application of fluorocinolone acetonide with neomycin preparations.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - CAUTIONARY AND ADVISORY LABELS: 28
    - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), polysorbates, propylene glycol
    - Synalar N (Derma UK Ltd)
      - Fluocinolone acetonide 250 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram
      - Synalar N cream | 30 gram £4.36

Hydrocortisone with benzalkonium chloride, dimeticon and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102.

- **INDICATIONS AND DOSE**
  - **Mild inflammatory skin disorders such as eczemas associated with infection**
  - **Psoriasis associated with infection**
  - **TO THE SKIN**
  - Child: Apply 3 times a day until lesion has healed, to be applied thinly
  - Adult: Apply 3 times a day until lesion has healed, to be applied thinly

- **PATIENT AND CARER ADVICE**: Patients or carers should be advised on application of benzalkonium with dimeticon and hydrocortisone and nystatin preparations.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - CAUTIONARY AND ADVISORY LABELS: 28
    - EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), sodium metabisulfite, sorbic acid
    - Timodine (Alliance Pharmaceuticals Ltd)
      - Benzalkonium chloride 1 mg per 1 gram, Hydrocortisone 5 mg per 1 gram, Nystatin 100000 unit per 1 gram
      - Timodine cream | 30 gram £3.37

Hydrocortisone with chlorhexidine hydrochloride and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102, chlorhexidine p. 1064.

- **INDICATIONS AND DOSE**
  - **Mild inflammatory skin disorders such as eczemas**
  - **Psoriasis associated with infection**
  - **TO THE SKIN**
  - Child: To be applied thinly (consult product literature)
  - Adult: To be applied thinly (consult product literature)

- **PATIENT AND CARER ADVICE**: Patients or carers should be given advice on application of chlorhexidine hydrochloride with hydrocortisone and nystatin preparations.
Hydrocortisone with fusidic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102, fusidic acid p. 527.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

- **TO THE SKIN**
  - Child: (consult product literature)
  - Adult: (consult product literature)

**POTENCY**

Hydrocortisone with fusidic acid cream: mild

Hydrocortisone with clotrimazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102, clotrimazole p. 758.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas (associated with fungal infection)

- **TO THE SKIN**
  - Child: (consult product literature)
  - Adult: (consult product literature)

**POTENCY**

Clotrimazole with hydrocortisone 1% cream: mild

**PATIENT AND CARER ADVICE**

Patients or carers should be advised on application of hydrocortisone with fusidic acid preparations.

**INTERACTIONS**

→ Appendix 1 (antifungals, imidazole).

**PATIENT AND CARER ADVICE**

Patients or carers should be advised on application of hydrocortisone with miconazole preparations.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners' formulary

May be prescribed as Miconazole and Hydrocortisone preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - Canesten HC (Bayer Plc)
    - Clotrimazole 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram Canesten HC cream | 30 gram | £2.42
  - Canesten Hydrocortisone (Bayer Plc)
    - Clotrimazole 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram Canesten Hydrocortisone cream | 15 gram | £3.11

- **Ointment**
  - Daktacort (McNeil Products Ltd, Janssen-Cilag Ltd)
    - Hydrocortisone 10 mg per 1 gram, Miconazole nitrate 20 mg per 1 gram Daktacort Hydrocortisone cream | 15 gram | £3.17
    - Daktacort 2%/1% cream | 30 gram | £2.49

Hydrocortisone with miconazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102, miconazole p. 760.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas associated with infections

- **TO THE SKIN**
  - Child: (consult product literature)
  - Adult: (consult product literature)

**POTENCY**

Hydrocortisone 1% with miconazole cream and ointment: mild

**INTERACTIONS**

→ Appendix 1 (antifungals, imidazole).

**PATIENT AND CARER ADVICE**

Patients or carers should be advised on application of hydrocortisone with miconazole preparations.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners' formulary

May be prescribed as Miconazole and Hydrocortisone preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - Canesten HC (Bayer Plc)
    - Clotrimazole 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram Canesten HC cream | 30 gram | £2.42
  - Canesten Hydrocortisone (Bayer Plc)
    - Clotrimazole 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram Canesten Hydrocortisone cream | 15 gram | £3.11

- **Ointment**
  - Daktacort (Janssen-Cilag Ltd)
    - Hydrocortisone 10 mg per 1 gram, Miconazole nitrate 20 mg per 1 gram Daktacort ointment | 30 gram | £2.50
Hydrocortisone with oxytetracycline

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1102, oxytetracycline p. 523.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

- **TO THE SKIN**
  - Child 12-17 years: (consult product literature)
  - Adult: (consult product literature)

**POTENCY**

Hydrocortisone 1% with oxytetracycline ointment: mild.

**CONTRA-INDICATIONS**

- Children under 12 years
- Pregnancy: Tetracyclines should not be given to pregnant women. Effects on skeletal development have been documented when tetracyclines have been used in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth.
- Breastfeeding: Tetracyclines should not be given to women who are breast-feeding (although absorption and therefore discoloration of teeth in the infant is probably usually prevented by chelation with calcium in milk).

**PATIENT AND CARER ADVICE**

Patients should be given advice on the application of hydrocortisone with oxytetracycline ointment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

- Terra-Cortril (Intrapharm Laboratories Ltd)
  - Hydrocortisone 10 mg per 1 gram, Oxytetracycline (as Oxytetracycline hydrochloride) 30 mg per 1 gram Terra-Cortril ointment | 30 gram [POM] £5.01 DT price = £5.01

**DERMATOLOGICAL DRUGS > ANTI-INFECTIVES**

Ichthammol

**INDICATIONS AND DOSE**

Chronic lichenified eczema

- **TO THE SKIN**
  - Child 1-7 years: Apply 1–3 times a day
  - Adult: Apply 1–3 times a day

**UNLICENSED USE**

- In children: No information available.

**SIDE-EFFECTS**

- Skin irritation

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, paste

**Liquid**

- Ichthammol (Non-proprietary)
  - Ichthammol 1 mg per 1 mg Ichthammol liquid | 100 gram [GSL] £11.42 DT price = £11.42 | 500 gram [GSL] £34.27

Ichthammol with zinc oxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, ichthammol above.

**INDICATIONS AND DOSE**

Chronic lichenified eczema

- **TO THE SKIN**
  - Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

**Impregnated dressing**

- Ichthopaste (Smith & Nephew Healthcare Ltd)
  - Ichthopaste bandage 7.5cm × 6m | 1 bandage £3.72

**Dermatological Drugs > Antracen Derivatives**

Dithranol

(Anthralin)

**INDICATIONS AND DOSE**

Subacute and chronic psoriasis

- **TO THE SKIN**
  - Adult: (consult product literature)

**DITHROCREAM®**

Subacute and chronic psoriasis

- **TO THE SKIN**
  - Adult: For application to skin or scalp, 0.1–0.5% cream suitable for overnight treatment, 1–2% cream for maximum 1 hour (consult product literature)

**MICANOL®**

Subacute and chronic psoriasis

- **TO THE SKIN**
  - Adult: Apply once daily, for application to skin or scalp, to be applied for up to 30 minutes, apply 1% cream, if necessary 3% cream can be used under medical supervision

**CONTRA-INDICATIONS**

- Acute and postural psoriasis - hypersensitivity
- **CAUTIONS**
  - Avoid sensitive areas of skin - avoid use near eyes
- **SIDE-EFFECTS**
  - Local burning sensation - local irritation - stains hair - stains skin
- **PREGNANCY**
  - No adverse effects reported.
- **BREAST FEEDING**
  - No adverse effects reported.
- **DIRECTIONS FOR ADMINISTRATION**
  - When applying dithranol, hands should be protected by gloves or they should be washed thoroughly afterwards. Dithranol should be applied to chronic extensor plaques only, carefully avoiding normal skin.
- **MICANOL®**
  - At the end of contact time, use plenty of lukewarm (not hot) water to rinse off cream; soap may be used after the cream has been rinsed off; use shampoo before applying cream to scalp and if necessary after cream has been rinsed off.

**PRESCRIBING AND DISPENSING INFORMATION**

Treatment should be started with a low concentration such as dithranol 0.1%, and the strength increased gradually every few days up to 3%, according to tolerance.

**PATIENT AND CARER ADVICE**

Dithranol can stain the skin, hair and fabrics.

**EXCEPTIONS TO LEGAL CATEGORY**

Prescription only medicine if dithranol content more than 1%, otherwise may be sold to the public.
DERMATOLOGICAL DRUGS > TARS

 Coal tar

• INDICATIONS AND DOSE

Psoriasis | Chronic atopic eczema
► TO THE SKIN USING PASTE
► Child: Apply 1–3 times a day, start application with low-strength preparations
► Adult: Apply 1–3 times a day, start application with low-strength preparations
► TO THE SKIN
► Child: 100 mL/bath, to be added to an adult sized bath; add proportionally less for a child’s bath. Use Coal Tar Solution BP
► Adult: 100 mL/bath, to be added to an adult sized bath. Use Coal Tar Solution BP

ALPHOSYL 2 IN 1® SHAMPOO
Psoriasis | Seborrhoeic dermatitis | Scaling | Itching
► TO THE SKIN
► Adult: Apply every 2–3 days

Dandruff
► TO THE SKIN
► Adult: Apply 1–2 times a week as required

EXOREX® LOTION
Psoriasis
► TO THE SKIN
► Adult: Apply 2–3 times a day, to be applied to skin or scalp; in elderly, lotion can be diluted with a few drops of water before applying

• CONTRA-INDICATIONS
Avoid broken or inflamed skin. Avoid eye area, avoid genital area, avoid mucosal areas, avoid rectal area, infection, sore, acute, or purulent psoriasis

• CAUTIONS
Application to face. Application to skin flexures

• SIDE-EFFECTS
Acne-like eruptions, photosensitivity, skin irritation

• PRESCRIBING AND DISPENSING INFORMATION
Coal Tar Solution BP contains coal tar 20%, Strong Coal Tar Solution BP contains coal tar 40%. May stain skin, hair and fabric.

• PATIENT AND CARER ADVICE
May stain skin, hair and fabric.

Coal tar with arachis oil extract of coal tar, cade oil, light liquid paraffin and tar

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1108, salicylic acid p. 1137.

DERMATOLOGICAL DRUGS > MEDICINAL FORMS

Dithranol with salicylic acid and zinc oxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, dithranol p. 1108, salicylic acid p. 1137.

• INDICATIONS AND DOSE

Subacute and chronic psoriasis
► TO THE SKIN
► Adult: (consult local protocol)

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, paste

MEDICINAL FORMS

Cream

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol

► Dithrocream (Dermal Laboratories Ltd)
Dithranol 10 mg per 1 gram Dithrocream 1% foam | 50 gram £5.77
Dithranol 5 mg per 1 gram Dithrocream 0.5% cream | 50 gram £4.66
Dithranol 10 mg per 1 gram Dithrocream HP 1% cream | 50 gram £6.42
Dithranol 20 mg per 1 gram Dithrocream 2% cream | 50 gram £6.77

► Micanol (Derma UK Ltd)
Dithranol 10 mg per 1 gram Micanol 1% cream | 50 gram £16.18
Dithranol 30 mg per 1 gram Micanol 3% cream | 50 gram £20.15

Combinations available: Coal tar with dithranol and salicylic acid, p. 1110

Coal tar

• INDICATIONS AND DOSE

Psoriasis | Eczema | Atopic dermatoses | Pruritic dermatoses
► TO THE SKIN
► Child: 2–4 capfuls/bath, alternatively 15–30 mL, to be added in an adult-size bath and soak for 20 minutes (proportionally less for a child’s bath)
► Adult: 2–4 capfuls/bath, alternatively 15–30 mL, to be added in an adult-size bath and soak for 20 minutes

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

EXOREX® LOTION
Psoriasis
► TO THE SKIN
► Adult: Apply 2–3 times a day, to be applied to skin or scalp; in elderly, lotion can be diluted with a few drops of water before applying

• CONTRA-INDICATIONS
Avoid broken or inflamed skin. Avoid eye area, avoid genital area, avoid mucosal areas, avoid rectal area, infection, sore, acute, or purulent psoriasis

• CAUTIONS
Application to face. Application to skin flexures

• SIDE-EFFECTS
Acne-like eruptions, photosensitivity, skin irritation

• PRESCRIBING AND DISPENSING INFORMATION
Coal Tar Solution BP contains coal tar 20%, Strong Coal Tar Solution BP contains coal tar 40%. Use suitable chemical protection gloves for extemporaneous preparation. May stain skin, hair and fabric.

• PATIENT AND CARER ADVICE
May stain skin, hair and fabric.

Coal tar with arachis oil extract of coal tar, cade oil, light liquid paraffin and tar

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar above.

DERMATOLOGICAL DRUGS > MEDICINAL FORMS

Coal tar

• INDICATIONS AND DOSE

Psoriasis | Chronic atopic eczema
► TO THE SKIN USING PASTE
► Child: Apply 1–3 times a day, start application with low-strength preparations
► Adult: Apply 1–3 times a day, start application with low-strength preparations
► TO THE SKIN
► Child: 100 mL/bath, to be added to an adult sized bath; add proportionally less for a child’s bath. Use Coal Tar Solution BP
► Adult: 100 mL/bath, to be added to an adult sized bath. Use Coal Tar Solution BP

ALPHOSYL 2 IN 1® SHAMPOO
Psoriasis | Seborrhoeic dermatitis | Scaling | Itching
► TO THE SKIN
► Adult: Apply every 2–3 days

Dandruff
► TO THE SKIN
► Adult: Apply 1–2 times a week as required
### Coal tar with calamine

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109.

- **INDICATIONS AND DOSE**
  - Psoriasis | Chronic atopic eczema (occasionally)
  - **TO THE SKIN**
  - **Adult:** Apply 1–2 times a day

- **IMPORTANT SAFETY INFORMATION**

  MHRA/CHM UPDATE (APRIL 2016): FIRE RISK WITH PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING

  See Emollient and barrier preparations p. 1075.

- **PRESCRIBING AND DISPENSING INFORMATION**

  When prepared extemporaneously, the BP states Calamine and Coal Tar Ointment BP, consists of calamine 12.5 g, strong coal tar solution 2.5 g, zinc oxide 12.5 g, hydrous wool fat 25 g, white soft paraffin 47.5 g.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  Forms available from special order manufacturers include: ointment.

### Coal tar with coconut oil and salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109, salicylic acid p. 1137.

- **INDICATIONS AND DOSE**
  - Scaly scalp disorders | Psoriasis | Seborrhoeic dermatitis | Dandruff | Cradle cap
  - **TO THE SKIN USING SHAMPOO**
  - **Child:** Apply daily as required
  - **Adult:** Apply daily as required

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  Forms available from special order manufacturers include: scalp lotion.

  - Capasal (Dermal Laboratories Ltd)
  - Salicylic acid 5 mg per 1 gram, Coal tar distilled 10 mg per 1 gram, Coconut oil 10 mg per 1 gram
  - Capasal Therapeutic shampoo | 250 ml £4.69

### Coal tar with dithranol and salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109, dithranol p. 1108, salicylic acid p. 1137.

- **INDICATIONS AND DOSE**
  - Subacute and chronic psoriasis
  - **TO THE SKIN**
  - **Child:** Apply up to twice daily
  - **Adult:** Apply up to twice daily

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment.

### Coal tar with salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109, salicylic acid p. 1137.

- **INDICATIONS AND DOSE**
  - Psoriasis | Chronic atopic eczema
  - **TO THE SKIN USING OINTMENT**
  - **Adult:** Apply 1–2 times a day

- **IMPORTANT SAFETY INFORMATION**

  MHRA/CHM UPDATE (APRIL 2016): FIRE RISK WITH PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING

  See Emollient and barrier preparations p. 1075.

- **PRESCRIBING AND DISPENSING INFORMATION**

  When prepared extemporaneously, the BP states Coal Tar and Salicylic Acid Ointment, BP consists of coal tar 2 g, salicylic acid 2 g, emulsifying wax 11.4 g, white soft paraffin 19 g, coconut oil 54 g, polysorbate ‘80’ 4 g, liquid paraffin 7.6 g.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment.
Coal tar with salicylic acid and precipitated sulfur

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109, salicylic acid p. 1137.

- INDICATIONS AND DOSE

COCOIS® OINTMENT
Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

▷ INITIALLY TO THE SKIN USING SCALP OINTMENT
▷ Child 6-11 years: Medical supervision required
▷ Child 12-17 years: Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour
▷ Adult: Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour

SEBCO® OINTMENT
Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

▷ TO THE SKIN USING SCALP OINTMENT
▷ Adult: Apply once weekly as required, alternatively apply daily for the first 3–7 days (if severe), shampoo off after 1 hour
▷ Child: Apply as required, alternatively apply daily for the first 3–7 days (if severe), shampoo off after 1 hour

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

IMMUNOSUPPRESSANTS ▶ CALCINEURIN INHIBITORS AND RELATED DRUGS

Pimecrolimus

- INDICATIONS AND DOSE

Short-term treatment of mild to moderate atopic eczema (including flares) when topical corticosteroids cannot be used (initiated by a specialist)

▷ TO THE SKIN
▷ Adult: Apply twice daily until symptoms resolve (stop treatment if eczema worsens or no response after 6 weeks)

Short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy (initiated by a specialist)

▷ TO THE SKIN
▷ Adult: Apply twice daily until symptoms resolve (maximum duration of treatment 4 weeks)

- UNLICENSED USE

Pimecrolimus is not licensed for short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy.

- CONTRA-INDICATIONS

Application to malignant or potentially malignant skin lesions - application under occlusion - congenital epidermal barrier defects - contact with eyes - contact with mucous membranes - generalised erythoderma - immunodeficiency - inflammation at treatment site

- CAUTIONS

Alcohol consumption (risk of facial flushing and skin irritation) - avoid other topical treatments except emollients at treatment site - UV light (avoid excessive exposure to sunlight and sunlamps)

- INTERACTIONS

Concomitant use with drugs that cause immunosuppression is contra-indicated (may be prescribed in exceptional circumstances by specialists).

- SIDE-EFFECTS

▷ Common or very common Burning sensation, erythema, folliculitis, pruritus, skin infections
▷ Uncommon Herpes simplex, herpes zoster, impetigo, molluscum contagiosum
▷ Rare Dryness, local reactions including pain, oedema, papilloma, paraesthesia, peeling, skin discoloration, worsening of eczema
▷ Frequency not known Skin malignancy

- PREGNANCY

Manufacturer advises avoid; toxicity in animal studies following systemic administration.

- BREAST FEEDING

Manufacturer advises caution; ensure infant does not come in contact with treated areas.

Coal tar with zinc oxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109.

- INDICATIONS AND DOSE

Psoriasis | Chronic atopic eczema

▷ TO THE SKIN
▷ Child: Apply 1–2 times a day
▷ Adult: Apply 1–2 times a day

- IMPORTANT SAFETY INFORMATION

MHRA/CHM UPDATE (APRIL 2016): FIRE RISK WITH PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING

See Emollient and barrier preparations p. 1075.

- PRESCRIBING AND DISPENSING INFORMATION

No preparations available—when prepared extemporaneously, the BP states Zinc and Coal Tar Paste, BP consists of zinc oxide 6%, coal tar 6%, emulsifying wax 5%, stearch 38%, yellow soft paraffin 45%.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, paste

Extract of coal tar with arachis oil

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1109.

- INDICATIONS AND DOSE

Scalp disorders | Psoriasis | Seborrhoea | Eczema | Pruritus | Dandruff

▷ TO THE SKIN
▷ Child: Apply 1–2 times a week, to the scalp
▷ Adult: Apply 1–2 times a week, to the scalp

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

- PREGNANCY

Manufacturer advises avoid; toxicity in animal studies following systemic administration.

- BREAST FEEDING

Manufacturer advises caution; ensure infant does not come in contact with treated areas.
Tacrolimus

**DRUG ACTION** Tacrolimus is a calcineurin inhibitor.

### INDICATIONS AND DOSE

**Short-term treatment of moderate to severe atopic eczema (including flares) in patients unresponsive to, or intolerant of conventional therapy (initiated by a specialist)**

- **TO THE SKIN**
  - Adult: Apply twice daily until lesion clears (consider other treatment if eczema worsens or no improvement after 2 weeks), initially 0.1% ointment to be applied thinly, reduce frequency to once daily or strength of ointment to 0.03% if condition allows

**Prevention of flares in patients with moderate to severe atopic eczema and 4 or more flares a year who have responded to initial treatment with topical tacrolimus (initiated by a specialist)**

- **TO THE SKIN**
  - Adult: Apply twice weekly, 0.1% ointment to be applied thinly, with an interval of 2–3 days between applications, use short-term treatment regimen during an acute flare; review need for preventative therapy after 1 year

**Short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy (initiated under specialist supervision)**

- **TO THE SKIN**
  - Adult: Apply twice daily until symptoms resolve, 0.1% ointment to be applied thinly, reduce to once daily or switch to 0.03% ointment if condition allows, maximum duration of treatment 4 weeks

### UNLICENSED USE

Short-term treatment of facial, flexural, or genital psoriasis is unlicensed.

### CONTRA-INDICATIONS

Application to malignant or potentially malignant skin lesions; application under occlusion; avoid contact with eyes; avoid contact with mucous membranes; congenital epidermal barrier defects; generalised erythema; immunodeficiency; infection at treatment site

### CAUTIONS

UV light (avoid excessive exposure to sunlight and sunlamps)

### INTERACTIONS

Interactions do not generally apply to tacrolimus used topically.

Concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists).

Risk of facial flushing and skin irritation with alcohol consumption (does not apply to tacrolimus taken systemically).

### SIDE-EFFECTS

- **Common or very common** Application-site infections • application-site reactions • herpes simplex infection • irritation (at application-site) • Kaposi’s varicelliform eruption • pain at application-site • rash
- **Uncommon** Acne
- **Frequency not known** Cutaneous lymphoma • malignancies • other types of lymphomas • rosacea • skin malignancy

### ALLERGY AND CROSS-SENSITIVITY

Contra-indicated if history of hypersensitivity to macrolides.

### PREGNANCY

Manufacturer advises avoid unless essential; toxicity in animal studies following systemic administration.

### BREAST FEEDING

Avoid—present in breast milk (following systemic administration).

### PATIENT AND CARER ADVICE

Avoid excessive exposure to UV light including sunlight.

### NATIONAL FUNDING/ACCESS DECISIONS

### NICE technology appraisals (TAs)

**Tacrolimus and pimecrolimus for atopic eczema (August 2004) NICE TA82**

Topical tacrolimus is an option for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy).

Topical tacrolimus is recommended for moderate to severe atopic eczema in adults and children over 2 years. Tacrolimus should be used within its licensed indications.

www.nice.org.uk/TA82

### Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (March 2010) that tacrolimus ointment (Protopic®) is accepted for restricted use within NHS Scotland for the prevention of flares in patients aged over 2 years with moderate to severe atopic eczema in accordance with the licensed indications; initiation of treatment is restricted to doctors (including general practitioners) with a specialist interest and experience in treating atopic eczema with immunomodulatory therapy.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

**CAUTIONARY AND ADVISORY LABELS** 4, 11, 28

**EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol

- **Elidel** (Meda Pharmaceuticals Ltd)
  - **Pimecrolimus 10 mg per 1 gram** Elidel 1% cream | 30 gram [Pom] £19.69 DT price = £19.69 | 60 gram [Pom] £37.41 DT price = £37.41 | 100 gram [Pom] £59.07 DT price = £59.07

### RETINOID AND RELATED DRUGS

**Acitretin**

**DRUG ACTION** Acitretin is a metabolite of etretinate.

- **INDICATIONS AND DOSE**

  **Severe extensive psoriasis resistant to other forms of therapy (under expert supervision)**

  - **Palmoplantar pustulosis psoriasis (under expert supervision)**

    - **Severe congenital ichthyosis (under expert supervision)**

    - **Severe Darier’s disease (keratosis follicularis) (under expert supervision)**

- **BY MOUTH**

  - Adult: Initially 25–30 mg daily for 2–4 weeks, then adjusted according to response to 25–50 mg daily, increased to up to 75 mg daily, dose only increased to 75 mg daily for short periods in psoriasis

### CONTRA-INDICATIONS

Hyperlipidaemia
CAUTIONS Avoid excessive exposure to sunlight and unsupervised use of sunlamps - diabetes (can alter glucose tolerance - initial frequent blood glucose checks) - do not donate blood during and for 2 years after stopping therapy (teratogenic risk) - investigate atypical musculoskeletal symptoms

INTERACTIONS → Appendix 1 (retinoids). Avoid concomitant use of keratolytics.

SIDE-EFFECTS
▶ Common or very common Abdominal pain - abnormal hair texture - alopecia (reversible on withdrawal) - arthralgia - brittle nails - dermatitis - diarrhoea - dryness and inflammation of mucous membranes - dryness of conjunctiva (causing conjunctivitis and decreased tolerance to contact lenses) - epidermal fragility - erythema - headache - myalgia - nausea - paronychia - peripheral oedema - pruritus - reversible increase in serum-cholesterol (with high doses) - reversible increase in serum-triglyceride concentrations (with high doses) - skin exfoliation - sticky skin - vomiting
▶ Uncommon Dizziness - hepatitis - photosensitivity - visual disturbances
▶ Rare Peripheral neuropathy
▶ Very rare Benign intracranial hypertension - bone pain - exostosis - nystagmus - ulcerative keratitis

FREQUENCY NOT KNOWN Drowsiness - dry skin - flushing - granulomatous lesions - impaired hearing - initial worsening of psoriasis - malaise - rectal haemorrhage - sweating - taste disturbance - tinnitus

CAUTIONARY AND ADVISORY LABELS

CONCEPTION AND CONTRACEPTION Effective contraception must be used. Pregnancy prevention In females of child-bearing potential (including those with a history of infertility), exclude pregnancy up to 3 days before treatment, every month during treatment, and every 1–3 months for 3 years after stopping treatment. Treatment should be started on day 2 or 3 of menstrual cycle. Females of child-bearing age must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 3 years after stopping treatment. Females should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone but can be used in conjunction with other contraceptive methods. Females should be advised to seek medical attention immediately if they become pregnant during treatment or within 3 years of stopping treatment. They should also be advised to avoid alcohol during treatment and for 2 months after stopping treatment.

PREGNANCY Avoid - teratogenic.

BREAST FEEDING Avoid.

HEPATIC IMPAIRMENT Avoid in severe impairment - risk of further impairment.

RENAL IMPAIRMENT Avoid in severe impairment; increased risk of toxicity.

MONITORING REQUIREMENTS
▶ Monitor serum-triglyceride and serum-cholesterol concentrations before treatment, 1 month after starting, then every 3 months.
▶ Check liver function at start, then every 2–4 weeks for first 2 months and then every 3 months.

PRESCRIBING AND DISPENSING INFORMATION
Prescribing for women of child-bearing potential Each prescription for acitretin should be limited to a supply of up to 30 days’ treatment and dispensed within 7 days of the date stated on the prescription.

PATIENT AND CARER ADVICE A patient information leaflet should be provided. Patient advice required around conception and contraception Females of child-bearing potential must be advised on pregnancy prevention.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Capsule

CAUTIONARY AND ADVISORY LABELS 10, 11, 21
▶ Acitretin (Non-proprietary)
Acitretin 10 mg Acitretin 10 mg capsules | 60 capsule £23.80 DT price = £23.80
Acitretin 25 mg Acitretin 25 mg capsules | 60 capsule £55.24 DT price = £55.24
▶ Neotigason (Teva UK Ltd)
Acitretin 10 mg Neotigason 10 mg capsules | 60 capsule £17.30 DT price = £23.80 (Hospital only)
Acitretin 25 mg Neotigason 25 mg capsules | 60 capsule £43.00 DT price = £55.24 (Hospital only)

ALITRETINOIN

INDICATIONS AND DOSE
Severe chronic hand eczema refractory to potent topical corticosteroids
▶ BY MOUTH
Adult (prescribed by or under supervision of a consultant dermatologist): 30 mg once daily; reduced if not tolerated to 10 mg once daily for 12–24 weeks total duration of treatment, discontinue if no response after 12 weeks, course may be repeated in those who relapse

Severe chronic hand eczema refractory to potent topical corticosteroids in patients with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease
▶ BY MOUTH
Adult (prescribed by or under supervision of a consultant dermatologist): Initially 10 mg once daily, increased if necessary up to 30 mg once daily for 12–24 weeks total duration of treatment, discontinue if no response after 12 weeks, course may be repeated in those who relapse

CONTRA-INDICATIONS Hypervitaminosis A - uncontrolled hyperlipidaemia - uncontrolled hypothyroidism

CAUTIONS Avoid blood donation during treatment and for at least 1 month after stopping treatment - dry eye syndrome - history of depression

INTERACTIONS → Appendix 1 (retinoids).

SIDE-EFFECTS
▶ Common or very common Alopecia - anaemia - arthralgia - changes in thyroid function tests - cheilitis - conjunctivitis - dry eyes - dryness of lips - dryness of skin - erythema - eye irritation - flushing - headache - myalgia - raised creatine kinase - raised serum concentration of triglycerides and of cholesterol (risk of pancreatitis if triglycerides above 9 mmol/litre)
▶ Uncommon Ankylosing spondylitis - osteoarthritic eczema - blurred vision - catarexis - epistaxis - hyperostosis - pruritus
▶ Rare Benign intracranial hypertension - vasculitis
▶ Frequency not known Decreased tolerance to contact lenses - depression - impaired night vision - keratitis - mood changes - suicidal ideation
alitretinoin for the treatment of severe chronic hand eczema

1114 inflammatory skin conditions

side-effects, further information

- dry eyes: dry eyes may respond to lubricating eye ointment or tear replacement therapy.
- benign intracranial hypertension: discontinue treatment if severe headache, nausea, vomiting, papilloedema, or visual disturbances occur.

conception and contraception: effective contraception must be used.

Pregnancy: In women of child-bearing potential, exclude pregnancy 1 month before treatment, up to 3 days before treatment, every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle.

Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone but can be used in conjunction with other contraceptive methods.

Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.

Pregnancy: Avoid—teratogenic.

breast feeding: Manufacturer advises avoid.

hepatic impairment: Manufacturer advises avoid—no information available.

renal impairment: Manufacturer advises avoid in severe impairment—no information available.

monitoring requirements: Monitor serum lipids (more frequently in those with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease)—discontinue if uncontrolled hyperlipidaemia.

prescribing and dispensing information: Prescribing for women of child-bearing potential. Each prescription for alitretinoin should be limited to a supply of up to 30 days’ treatment and dispensed within 7 days of the date stated on the prescription.

Alitretinoin is teratogenic and must not be given to women of child-bearing potential unless they practise effective contraception and then only after detailed assessment and explanation by the physician.

PATIENT AND CARER ADVICE: A patient information leaflet should be provided.

Patient advice required around conception and contraception.

Women of child-bearing potential must be counselled on pregnancy prevention.

National funding/access decisions

NICE technology appraisals (TAs)

- Alitretinoin for the treatment of severe chronic hand eczema in adults (August 2009) NICE TA177

Alitretinoin is recommended for the treatment of severe chronic hand eczema that has not responded to potent topical corticosteroids. Treatment should be stopped as soon as an adequate response has been achieved (hands clear or almost clear), or if the eczema remains severe after 12 weeks, or if an adequate response has not been achieved by 24 weeks.

www.nice.org.uk/TA177

medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS: 10, 11, 21

- Toc tin (Stiefel Laboratories (UK) Ltd)
  - Alitretinoin 10 mg: Toc tin 10mg capsules | 30 capsule £411.43
  - Alitretinoin 30 mg: Toc tin 30mg capsules | 30 capsule £411.43

Tazarotene

indications and dose

Mild to moderate plaque psoriasis affecting up to 10% of skin area

- TO THE SKIN
- Adult: Apply once daily usually for up to 12 weeks, apply in the evening

- CAUTIONS: Avoid contact with eczematous skin • avoid contact with eyes • avoid contact with face • avoid contact with hair-covered scalp • avoid contact with inflamed skin • avoid contact with intertriginous areas

- SIDE-EFFECTS

  - Rare: Dry or painful skin • stinging and inflammation
  - Frequency not known: Burning • contact dermatitis • desquamation • erythema • local irritation • non-specific rash • pruritus • worsening of psoriasis

- Local irritation: Local irritation is more common with higher concentration and may require discontinuation.

- CONCEPTION AND CONTRACEPTION: Effective contraception required (oral progestogen-only contraceptives not considered effective).

- PREGNANCY: Avoid.

- BREAST FEEDING: Manufacturer advises avoid—present in milk in animal studies.

- PATIENT AND CARER ADVICE: Avoid excessive exposure to UV light (including sunlight, solariums, PUVA or UVB treatment). Do not apply emollients or cosmetics within 1 hour of application. Wash hands immediately after use.

medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Gel

EXCIPIENTS: May contain Benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, disodium edetate, polyacrylates

- Zorac (Allergan Ltd)
  - Tazarotene 1 mg per 1 gram: Zorac 0.1% gel | 30 gram £14.80
  - Tazarotene 500 microgram per 1 gram: Zorac 0.05% gel | 30 gram £14.09

Salicylic acid and derivatives

Salicylic acid with zinc oxide

- INDICATIONS AND DOSE

Hyperkeratotic skin disorders

- TO THE SKIN
- Adult: Apply twice daily

- CAUTIONS: Avoid broken skin • avoid inflamed skin

- SIDE-EFFECTS: Excessive drying • irritation • sensitivity • systemic effects (after widespread use)
Calcipotriol
(1,25-Dihydroxycholecalciferol)

**INDICATIONS AND DOSE**
Mild to moderate plaque psoriasis

- **TO THE SKIN**
  - Adult: Apply twice daily, not more than 35% of body surface to be treated daily; maximum 30 g per day

**CONTRA-INDICATIONS**
Do not apply under occlusion - patients with calcium metabolism disorders

**CAUTIONS**
- Erythrodermic exfoliative psoriasis (enhanced risk of hypercalcaemia) - generalised pustular psoriasis (enhanced risk of hypercalcaemia)

**SIDE-EFFECTS**
- **Common or very common** Burning - dermatitis - erythema - itching - local skin reactions - paraesthesia
- **Rare** Facial dermatitis - perioral dermatitis
- **Frequency not known** Aggravation of psoriasis - dry skin - photosensitivity

**PREGNANCY**
Manufacturers advise avoid unless essential.

**BREAST FEEDING**
No information available.

**PATIENT AND CARER ADVICE**
Advice on application. Patient information leaflet for Dovonex ® ointment advises liberal application. However, patients should be advised of maximum recommended weekly dose.

Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas.

**MEDITICAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Ointment**
- **Siliks** (Gelderma (UK) Ltd)
  - Calcitriol 3 microgram per 1 gram Siliks ointment | 100 g | £18.06 DT price = £18.06

**Tacalcitol**

**INDICATIONS AND DOSE**
Plaque psoriasis

- **TO THE SKIN**
  - Adult: Apply once daily, preferably at bedtime, maximum 10 g in week

**CONTRA-INDICATIONS**
Calcium metabolism disorders

**CAUTIONS**
- Avoid eyes - erythrodermic exfoliative psoriasis (enhanced risk of hypercalcaemia) - generalised pustular psoriasis (enhanced risk of hypercalcaemia) - if used in conjunction with UV treatment

**SIDE-EFFECTS**
- **Common or very common** Burning - dermatitis - erythema - itching - local skin reactions - paraesthesia

**Calcipotriol 50 microgram per 1 gram**
- **Dovonex** (LEO Pharma)
  - Calcipotriol 50 microgram per 1 gram Dovonex 50 micrograms/g ointment | 30 gram (Pos) £5.78 DT price = £5.78 | 60 gram (Pos) £11.56

Combinations available: Calcipotriol with betamethasone, p. 1098
Skin

ANTIMUSCARINICS

Glycopyrronium bromide
(Glycopyrrolate)

- INDICATIONS AND DOSE
  - Iontophoretic treatment of hyperhidrosis
    - TO THE SKIN
      - Adult: Only 1 site to be treated at a time, maximum 2 sites treated in any 24 hours, treatment not to be repeated within 7 days (consult product literature)

- CONTRA-INDICATIONS
  - Infections affecting the treatment site

- CONTRA-INDICATIONS, FURTHER INFORMATION
  - Contra-indications applicable to systemic use should be considered; however, glycopyrronium is poorly absorbed and systemic effects unlikely with topical use.

- CAUTIONS
  - Cautions applicable to systemic use should be considered; however, glycopyrronium is poorly absorbed and systemic effects unlikely with topical use.

- SIDE-EFFECTS
  - Tingling at administration site

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  - Liquid
    - EXCipients: May contain Disodium edetate, propylene glycol
      - Curadeterm (Almirall Ltd)
        - Tacalcitol (as Tacalcitol monohydrate) 4 microgram per 1 gram Curadeterm 4micrograms/g lotion | 30 ml (PoM) £12.73
      - Curadeterm (Almirall Ltd)
        - Tacalcitol (as Tacalcitol monohydrate) 4 microgram per 1 gram Curadeterm 4micrograms/g ointment | 30 gram (PoM) £13.40 DT price = £13.40 | 60 gram (£p) £23.14 DT price = £23.14 | 100 gram (£p) £30.86 DT price = £30.86

- PRESCRIBING AND DISPENSING INFORMATION
  - Palliative care
    - For further information on the use of glycopyrronium bromide in palliative care, see www.palliativedrugs.com/formulary/en/glycopyrronium.html.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  - Powder for solution for iontophoresis
    - Glycopyrronium bromide (Non-proprietary)
      - Glycopyrronium bromide 1 mg per 1 mg glycopyrronium bromide powder for solution for iontophoresis | 3 gram (£p) £131.92

DERMATOLOGICAL DRUGS

Aluminium chloride hexahydrate

- INDICATIONS AND DOSE
  - Hyperhidrosis affecting axillae, hands or feet
    - TO THE SKIN
      - Adult: Apply once daily, apply liquid formulation at night to dry skin, wash off the following morning, reduce frequency as condition improves—do not bathe immediately before use
    - Hyperhidrosis | Bromidrosis | Intertrigo | Prevention of tinea pedis and related conditions
      - TO THE SKIN
      - Adult: Apply powder to dry skin

- CAUTIONS
  - Avoid contact with eyes • avoid contact with mucous membranes • avoid use on broken or irritated skin • do not shave axillae or use depilatories within 12 hours of application

- SIDE-EFFECTS
  - Skin irritation

- PATIENT AND CARER ADVICE
  - Avoid contact with clothing.

- EXCEPTIONS TO LEGAL CATEGORY
  - A 30 mL pack of aluminium chloride hexahydrate 20% is on sale to the public.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  - Liquid
    - CAUTIONARY AND ADVISORY LABELS
      - Aluminium chloride hexahydrate (Non-proprietary)
        - Aluminium chloride 200 mg per 1 ml Aluminium chloride 20% solution | 60 ml (£p) no price available DT price = £2.51
        - Anhydrol (Dermal Laboratories Ltd)
          - Aluminium chloride 200 mg per 1 ml Anhydrol Forte 20% solution | 60 ml (£) £2.51 DT price = £2.51
        - Driclor (GlaxoSmithKline Consumer Healthcare)
          - Aluminium chloride 200 mg per 1 ml Driclor 20% solution | 75 ml (£) £3.01 DT price = £3.01

4 Perspiration

Antiperspirants

Overview
Aluminium chloride hexahydrate below is a potent antiperspirant used in the treatment of hyperhidrosis. Aluminium salts are also incorporated in preparations used for minor fungal skin infections associated with hyperhidrosis.

In more severe cases specialists use glycopyrronium bromide below as a hyperhidrosis. A 0.05% solution in the iontophoretic treatment of hyperhidrosis of plantar and palmar areas. Botox® contains botulinum toxin type A complex p. 380 and is licensed for use intradermally for severe hyperhidrosis of the axillae unresponsive to topical antiperspirant or other antihidrotic treatment.

4.1 Hyperhidrosis

Other drugs used for Hyperhidrosis Botulinum toxin type A, p. 380

ANTIMUSCARINICS

Glycopyrronium bromide

17-Oct-2016
5 Pruritus

Topical local antipruritics

Overview
Pruritus may be caused by systemic disease (such as obstructive jaundice, endocrine disease, chronic renal disease, iron deficiency, and certain malignant diseases), skin disease (e.g. psoriasis, eczema, urticaria, and scabies), drug hypersensitivity, or as a side-effect of opioid analgesics. Where possible, the underlying causes should be treated. An emollient may be of value where the pruritus is associated with dry skin. Pruritus that occurs in otherwise healthy elderly people can also be treated with an emollient.

Preparations containing crotamiton below are sometimes used but are of uncertain value. Preparations containing calamine are often ineffective. A topical preparation containing doxepin 5% below is licensed for the relief of pruritus in eczema; it can cause drowsiness and there may be a risk of sensitisation. Pruritus is common in biliary obstruction, especially in primary biliary cirrhosis and drug-induced cholestasis. Oral administration of colestyramine p. 186 is the treatment of choice.

Topical antihistamines and local anaesthetics are only marginally effective and occasionally cause hypersensitivity. For insect stings and insect bites, a short course of a topical corticosteroid is appropriate. Short-term treatment with a sedating antihistamine may help in insect stings and in intractable pruritus where sedation is desirable. Calamine preparations are of little value for the treatment of insect stings or bites.

Topical local anaesthetics are indicated for the relief of local pain. Preparations may be absorbed, especially through mucosal surfaces, therefore excessive application should be avoided and they should preferably not be used for more than 3 days; not generally suitable for young children and are less suitable for prescribing.

Topical antihistamines should be avoided in eczema and are not recommended for longer than 3 days. They are less suitable for prescribing.

Other drugs used for Pruritus

ANTIPRURITICS

Calamine with zinc oxide

INDICATIONS AND DOSE
Pruritus
► TO THE SKIN
► Child: (consult product literature)
► Adult: (consult product literature)

CONTRA-INDICATIONS
Avoid application of preparations containing zinc oxide prior to x-ray (zinc oxide may affect outcome of x-ray)

IMPORANT SAFETY INFORMATION
MHRA/CHM UPDATE (APRIL 2016): FIRE RISK WITH PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING
See Emollient and barrier preparations p. 1075.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Liquid
► Calamine with zinc oxide (Non-proprietary)
Phenol liquefied 5 mg per 1 ml, Sodium citrate 5 mg per 1 ml, Bentonite 30 mg per 1 ml, Glycerol 50 mg per 1 ml, Zinc oxide 50 mg per 1 ml, Calamine 150 mg per 1 ml Calamine lotion 200 ml GSI £0.81–£0.96 DT price = £0.96
► Cala Soothe (Ennogen Healthcare Ltd)
Phenol liquefied 5 mg per 1 ml, Sodium citrate 5 mg per 1 ml, Bentonite 30 mg per 1 ml, Glycerol 50 mg per 1 ml, Zinc oxide 50 mg per 1 ml, Calamine 150 mg per 1 ml Cala Soothe lotion 200 ml £19.50 DT price = £0.96

Cream

OTHER DRUGS

Crotamiton

INDICATIONS AND DOSE
Pruritus (including pruritus after scabies)
► TO THE SKIN
► Child 1 month–2 years (on doctor's advice only): Apply once daily
► Child 3–17 years: Apply 2–3 times a day
► Adult: Apply 2–3 times a day

CONTRA-INDICATIONS
Acute exudative dermatoses

CAUTIONS
Avoid use in buccal mucosa - avoid use near eyes - avoid use on broken skin - avoid use on very inflamed skin - use on doctor's advice for children under 3 years

PREGNANCY
Manufacturer advises avoid, especially during the first trimester — no information available.

BREAST FEEDING
No information available; avoid application to nipple area.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Cream
EXCIPIENTS: May contain Beeswax, cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, hydroxybenzoates (parabens)
► Crotamiton (Non-proprietary)
Crotamiton 100 mg per 1 gram 30 gram GSI no price available DT price = £2.50
► Brains may include Eurax

Doxepin

INDICATIONS AND DOSE
Pruritus in eczema
► TO THE SKIN
► Child 12–17 years: Apply up to 3 g 3–4 times a day, apply thinly; coverage should be less than 10% of body surface area; maximum 12 g per day
► Adult: Apply up to 3 g 3–4 times a day, apply thinly; coverage should be less than 10% of body surface area; maximum 12 g per day

LESS SUITABLE FOR PRESCRIBING
Less suitable for prescribing.
MENTHOL AND DERIVATIVES

Levomenthol

- INDICATIONS AND DOSE
  - Pruritus
  - TO THE SKIN
  - Adult: Apply 1–2 times a day

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

Cream

- Aqua-cool (Pinewood Healthcare)
  - Menthol 5 mg per 1 gram Aqua-cool 0.5% cream | 500 gram £15.30 DT price = £16.07
  - Menthol 10 mg per 1 gram Aqua-cool 1% cream | 100 gram £3.25 DT price = £3.97 | 500 gram £15.30 DT price = £16.59
  - Menthol 20 mg per 1 gram Aqua-cool 2% cream | 500 gram £15.30 DT price = £16.97
- Arjun (Arjun Products Ltd)
  - Menthol 5 mg per 1 gram Arjun 0.5% cream | 500 gram £15.30 DT price = £16.07
  - Menthol 10 mg per 1 gram Arjun 1% cream | 100 gram £3.25 DT price = £3.97 | 500 gram £15.30 DT price = £16.59
  - Menthol 20 mg per 1 gram Arjun 2% cream | 500 gram £15.30 DT price = £16.97
- Dermacool (Pern Consumer Products Ltd)
  - Menthol 5 mg per 1 gram Dermacool 0.5% cream | 100 gram £3.85 | 500 gram £16.07 DT price = £16.07
  - Menthol 10 mg per 1 gram Dermacool 1% cream | 100 gram £3.97 DT price = £3.97 | 250 gram £8.99 | 500 gram £16.59 DT price = £16.59
  - Menthol 20 mg per 1 gram Dermacool 2% cream | 100 gram £4.07 | 500 gram £16.97 DT price = £16.97
  - Menthol 50 mg per 1 gram Dermacool 5% cream | 100 gram £4.69 | 500 gram £17.48

Menthol and derivatives

6 Rosacea and acne

Rosacea and Acne

Acne

Treatment of acne should be commenced early to prevent scarring. Patients should be counselled that an improvement may not be seen for at least a couple of months. The choice of treatment depends on whether the acne is predominantly inflammatory or comedonal and its severity.

*Mild to moderate acne* is generally treated with topical preparations. Systemic treatment with oral antibacterials is generally used for *moderate to severe acne* or where topical preparations are not tolerated or are ineffective or where application to the site is difficult. Another oral preparation used for acne is the hormone treatment co-cyprindol (cyproterone acetate with ethinylestradiol) p. 1119; it is for women only.

Severe acne, acne unresponsive to prolonged courses of oral antibacterials, scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist who may prescribe isotretinoin p. 1122 for administration by mouth.

Topical preparations for acne

In mild to moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide p. 1121 or to a topical retinoid. Alternatively, topical application of an antibacterial such as erythromycin or clindamycin p. 1120 may be effective for inflammatory acne. If topical preparations prove inadequate, oral preparations may be needed.

Benzoyl peroxide and azelaic acid

Benzoyl peroxide is effective in mild to moderate acne. Both comedones and inflamed lesions respond well to benzoyl peroxide. The lower concentrations seem to be as effective as higher concentrations in reducing inflammation. It is usual to start with a lower strength and to increase the concentration of benzoyl peroxide gradually. Adverse effects include local skin irritation, particularly when therapy is initiated, but the scaling and redness often subside with treatment continued at a reduced frequency of application. If the acne does not respond after 2 months then use of a topical antibacterial should be considered.

Azelaic acid p. 1121 has antimicrobial and comedomedonal properties. It may be an alternative to benzoyl peroxide or to a topical retinoid for treating mild to moderate comedonal acne, particularly of the face. Some patients prefer azelaic acid because it is less likely to cause local irritation than benzoyl peroxide.

Topical antibacterials for acne

For many patients with mild to moderate inflammatory acne, topical antibacterials may be no more effective than topical benzoyl peroxide or tretinoin. Topical antibacterials are probably best reserved for patients who wish to avoid oral antibacterials or who cannot tolerate them. Topical preparations of erythromycin and clindamycin are effective for inflammatory acne. Topical antibacterials can produce mild irritation of the skin, and on rare occasions cause sensitisation; gastro-intestinal disturbances have been reported with topical clindamycin.

Antibacterial resistance of *Propionibacterium acnes* is increasing; there is cross-resistance between erythromycin and clindamycin. To avoid development of resistance:

- when possible use non-antibiotic antimicrobials (such as benzoyl peroxide or azelaic acid);
- avoid concomitant treatment with different oral and topical antibacterials;
- if a particular antibacterial is effective, use it for repeat courses if needed (short intervening courses of benzoyl...
peroxide or azelaic acid may eliminate any resistant propionibacteria);  
- do not continue treatment for longer than necessary (however, treatment with a topical preparation should be continued for at least 6 months).

Some manufacturers of topical antibacterial preparations for acne advise that preparations containing alcohol are not suitable for use with benzoyl peroxide.

**Topical retinoids and related preparations for acne**

Topical tretinoin, its isomer isotretinoin, and adapalene p. 1122 (a retinoid-like drug), are useful for treating comedones and inflammatory lesions in mild to moderate acne. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. Isotretinoin is given by mouth in severe acne.

**Other topical preparations for acne**

Preparations containing aluminium oxide p. 1121 are not considered beneficial in acne.

A topical preparation of nicotinamide p. 1125 is available for inflammatory acne.

**Oral preparations for acne**

Systemic antibacterial treatment is useful for inflammatory acne if topical treatment is not adequately effective or if it is inappropriate. Anticomедonal treatment (e.g. with topical benzoyl peroxide) may also be required.

Either oxytetracycline p. 523 or tetracycline p. 523 is usually given for acne. If there is no improvement after the first 3 months another oral antibacterial should be used. Maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer.

Doxycline p. 521 and lymecycline p. 522 are alternatives to tetracycline.

Although minocycline p. 522 is as effective as other tetracyclines for acne, it is associated with a greater risk of lupus erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation; it is given in a once or twice daily dose.

Erythromycin in a twice daily dose is an alternative for the management of acne but *propionibacteria* strains resistant to erythromycin are becoming widespread and this may explain poor response.

Trimethoprim p. 529 may be used for acne resistant to other antibacterials [unlicensed indication]. Prolonged treatment with trimethoprim may depress haematopoiesis; it should generally be initiated by specialists.

Concomitant use of different topical and systemic antibacterials is undesirable owing to the increased likelihood of the development of bacterial resistance.

**Hormone treatment for acne**

Co-cyprindiol (cyproterone acetate and ethinylestadiol) contains an anti-androgen. It is licensed for use in women with moderate to severe acne that has not responded to topical therapy or oral antibacterials, and for moderately severe hirsutism. Although it is an effective hormonal contraceptive, it should not be used solely for contraception.

Improvement of acne with co-cyprindiol probably occurs because of decreased sebum secretion which is under androgen control. Some women with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent.

**Oral retinoid for acne**

The retinoid isotretinoin reduces sebum secretion. It is used for the systemic treatment of nodulo-cystic and conglobate acne, severe acne, scarring, acne which has not responded to an adequate course of a systemic antibacterial, or acne which is associated with psychological problems. It is also useful in women who develop acne in the third or fourth decades of life, since late onset acne is frequently unresponsive to antibacterials.

Isotretinoin is a toxic drug that should be prescribed only by, or under the supervision of, a consultant dermatologist. It is given for at least 16 weeks; repeat courses are not normally required.

Side-effects of isotretinoin include severe dryness of the skin and mucous membranes, nose bleeds, and joint pains. The drug is teratogenic and must not be given to women of child-bearing age unless they practise effective contraception (oral progesterone-only contraceptives not considered effective) and then only after detailed assessment and explanation by the physician. Women must also be registered with a pregnancy prevention programme.

Although a causal link between isotretinoin p. 1122 use and psychiatric changes (including suicidal ideation) has not been established, the possibility should be considered before initiating treatment; if psychiatric changes occur during treatment, isotretinoin should be stopped, the prescriber informed, and specialist psychiatric advice should be sought.

**Rosacea**

Rosacea is not comedonal (but may exist with acne which may be comedonal). Brimonidine tartrate p. 1125 is licensed for the treatment of facial erythema in rosacea. The pustules and papules of rosacea respond to topical azelaic acid p. 1121, topical ivermectin or to topical metronidazole p. 499. Alternatively oral administration of oxytetracycline p. 523 or tetracycline p. 523, or erythromycin p. 497, can be used; courses usually last 6–12 weeks and are repeated intermittently. Doxycycline p. 521 can be used [unlicensed indication] if oxytetracycline or tetracycline is inappropriate (e.g. in renal impairment). A modified-release preparation of doxycycline is licensed in low daily doses for the treatment of facial rosacea. Isotretinoin is occasionally given in refractory cases [unlicensed indication]. Camouflagers may be required for the redness.

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### 6.1 Acne

**ANTI-ANDROGENS**

#### Co-cyprindiol

- **INDICATIONS AND DOSE**
  - Moderate to severe acne in females of child-bearing age refractory to topical therapy or oral antibacterials | Moderately severe hirsutism
    - **BY MOUTH**
    - Females of childbearing potential: 1 tablet daily for 21 days, to be started on day 1 of menstrual cycle; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs), time to symptom remission, at least 3 months; review need for treatment regularly

- **CONTRA-INDICATIONS**
  - Acute porphyria • gallstones • heart disease associated with pulmonary hypertension or risk of embolus • history during pregnancy of cholestatic jaundice • history during pregnancy of chorea • history during pregnancy of pemphigoid gestationis • history during pregnancy of pruritus • history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable • history of haemolytic uraemic syndrome • migraine with aura • personal history of venous or arterial thrombosis • sclerosing treatment for varicose veins • severe or multiple risk factors for arterial disease or for venous thromboembolism • systemic lupus erythematosus with (or unknown) antiphospholipid antibodies • transient cerebral ischaemic attacks without headaches • undiagnosed vaginal bleeding
CAUTIONS  Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - arterial disease - gene mutations associated with breast cancer (e.g. BRCA 1).- history of severe depression especially if induced by hormonal contraceptive - hyperprolactinaemia—seek specialist advice - inflammatory bowel disease including Crohn’s disease - migraine - personal or family history of hereditary haemorrhagic telangiectasia (increased risk of pancreatitis) - risk factors for venous thromboembolism - sickle-cell disease - undiagnosed breast mass

CAUTIONS, FURTHER INFORMATION

Venous thromboembolism  There is an increased risk of venous thromboembolism in women taking co-cyprindiol, particularly during the first year of use. The incidence of venous thromboembolism is 1.5–2 times higher in women using co-cyprindiol than in women using combined oral contraceptives containing levonorgestrel, but the risk may be similar to that associated with use of combined oral contraceptives containing third-generation progestogens (desogestrel and gestodene) or drospirenone. Women requiring co-cyprindiol may have an inherently increased risk of cardiovascular disease.

INTERACTIONS  

Rarely gallstones - systemic lupus erythematosus

Very rare Photosensitivity

Frequency not known Abdominal cramps - absence of withdrawal bleeding - amenorrhoea after discontinuation - breast enlargement - breast secretion - breast tenderness - cervical erosion - changes in libido - changes in lipids - metabolism - changes in vaginal discharge - chloasma - contact lenses may irritate - depression - fluid retention - headache - hepatic tumours - hyperthermia - irritability - leg cramps - liver impairment - nausea - nervousness - reduced menstrual loss - skin reactions - thrombosis (more common when factor V Leiden present in blood groups A, B, and AB) - visual disturbances - vomiting. 'Spotting' in early cycles

PREGNANCY  Avoid — risk of feminisation of male fetus with cyproterone.

BREAST FEEDING  Manufacturer advises avoid; possibility of anti-androgen effects in neonate with cyproterone.

HEPATIC IMPAIRMENT  Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

PRESCRIBING AND DISPENSING INFORMATION  A mixture of cyproterone acetate and ethinylestradiol in the mass proportions 2000 parts to 35 parts, respectively.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet

Co-cyprindiol (Non-proprietary)
Cyproterone acetate 2 mg, Ethinylestradiol 35 microgram  Co-cyprindiol 2000microgram/35microgram tablets | 63 tablet (Pom) £5.70 DT price = £5.70

Clairette (Stragen UK Ltd) ▼
Cyproterone acetate 2 mg, Ethinylestradiol 35 microgram Clairette 2000/35 tablets | 63 tablet (Pom) £5.90 DT price = £5.70

Dianette (Bayer Plc) ▼
Cyproterone acetate 2 mg, Ethinylestradiol 35 microgram Dianette tablets | 63 tablet (Pom) £7.71 DT price = £5.70

Teragezza (Morningside Healthcare Ltd)
Cyproterone acetate 2 mg, Ethinylestradiol 35 microgram Teragezza 2000microgram/35microgram tablets | 63 tablet (Pom) £11.10 DT price = £5.70

ANTIBACTERIALS  LINCOSAMIDES

Clindamycin

INDICATIONS AND DOSE

DALACIN T® LOTION
Acne vulgaris

TO THE SKIN

Child: Apply twice daily, to be applied thinly

Adult: Apply twice daily, to be applied thinly

DALACIN T® SOLUTION
Acne vulgaris

TO THE SKIN

Child: Apply twice daily, to be applied thinly

Adult: Apply twice daily, to be applied thinly

ZINDACLIN® GEL
Acne vulgaris

TO THE SKIN

Child 12–17 years: Apply once daily, to be applied thinly

Adult: Apply once daily, to be applied thinly

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Liquid

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), propylene glycol

Dalacin T® (Pfizer Ltd)
Clindamycin (as Clindamycin phosphate) 10 mg per 1 ml Dalacin T® 1% topical lotion | 30 ml (Pom) £5.08 DT price = £5.08 | 60 ml (Pom) £10.16
Dalacin T® 1% topical solution | 30 ml (Pom) £4.34 DT price = £4.34 | 50 ml (Pom) £7.23

Gel

EXCIPIENTS: May contain Propylene glycol

Zindacin (Crawford Healthcare Ltd)
Clindamycin (as Clindamycin phosphate) 10 mg per 1 gram Zindacin 1% gel | 30 gram (Pom) £6.66 DT price = £6.66

Combinations available: Benzoyl peroxide with clindamycin, p. 1121 - Tretinoin with clindamycin, p. 1124

ANTIBACTERIALS  MACROLIDES

Erythromycin with zinc acetate

INDICATIONS AND DOSE

Acne vulgaris

TO THE SKIN

Child: Apply twice daily

Adult: Apply twice daily

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Liquid

Zinryten (LEO Pharma)
Zinc acetate 12 mg per 1 ml, Erythromycin 40 mg per 1 ml Zinryten lotion | 30 ml (Pom) £7.71 DT price = £7.71 | 90 ml (Pom) £16.68 DT price = £16.68

Some manufacturers advise preparations containing alcohol are not suitable for use with benzoyl peroxide.
ANTISEPTICS AND DISINFECTANTS > PEROXIDES

Benzoyl peroxide

INDICATIONS AND DOSE

Acne vulgaris

➤ TO THE SKIN
➤ Child 12-17 years: Apply 1–2 times a day, preferably apply after washing with soap and water, start treatment with lower-strength preparations
➤ Adult: Apply 1–2 times a day, preferably apply after washing with soap and water, start treatment with lower-strength preparations

CAUTIONS
Avoid contact with broken skin - avoid contact with eyes - avoid contact with mouth - avoid contact with mucous membranes - avoid excessive exposure to sunlight

SIDE-EFFECTS
Skin irritation

SIDE-EFFECTS, FURTHER INFORMATION
Skin irritation Reduce frequency or suspend use until irritation subsides and re-introduce at reduced frequency.

PATIENT AND CARER ADVICE
May bleach fabrics and hair.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream
EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, isopropyl palmitate, propylene glycol
➤ Brevoxyl® (GlaxoSmithKline Consumer Healthcare)
Benzoyl peroxide 40 mg per 1 gram Brevoxyl 4% cream | 50 gram | £4.13 DT price = £4.13

Gel
EXCIPIENTS: May contain Fragrances, propylene glycol
➤ Acnecide® (Salderna UK Ltd)
Benzoyl peroxide 50 mg per 1 gram Acnecide 5% gel | 30 gram | £5.44 DT price = £5.44 | 60 gram | £10.68 DT price = £10.68
Acnecide Wash 5% gel | 50 gram | £5.44 DT price = £5.44
➤ Panoxyl Aquegel® (GlaxoSmithKline Consumer Healthcare)
Benzoyl peroxide 100 mg per 1 gram Panoxyl 10 Aquegel | 40 gram | £2.13 DT price = £2.13
Panoxyl Acnegel® (GlaxoSmithKline Consumer Healthcare)
Benzoyl peroxide 100 mg per 1 gram Panoxyl 10 Acnegel | 40 gram | £1.99 DT price = £1.99
Combinations available: Adapalene with benzoyl peroxide, p. 1122

Benzoyl peroxide with clindamycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, benzoyl peroxide above, clindamycin p. 1120.

INDICATIONS AND DOSE

Acne vulgaris

➤ TO THE SKIN
➤ Child 12-17 years: Apply once daily, dose to be applied in the evening
➤ Adult: Apply once daily, dose to be applied in the evening

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gel
EXCIPIENTS: May contain Disodium edetate
➤ Duac® (Stiefel Laboratories (UK) Ltd)
Clindamycin (as Clindamycin phosphate) 10 mg per 1 gram, Benzoyl peroxide 75 mg per 1 gram Duac Once Daily gel (5% and 1%) | 30 gram | £6.60 DT price = £6.60 | 60 gram | £13.14 DT price = £13.14
➤ Brevoxyl® (GlaxoSmithKline Consumer Healthcare)
Clindamycin (as Clindamycin phosphate) 50 mg per 1 gram, Benzoyl peroxide 50 mg per 1 gram Duac Once Daily gel (5% and 1%) | 30 gram | £13.14 DT price = £13.14 | 60 gram | £26.28 DT price = £26.28

DERMATOLOGICAL DRUGS > ABRASIVE AGENTS

Aluminium oxide

INDICATIONS AND DOSE

Acne vulgaris

➤ TO THE SKIN
➤ Adult: Apply 1–3 times a day, to be used instead of soap

CONTRA-INDICATIONS
Superficial venules - telangiectasia

CAUTIONS
Avoid contact with eyes

SIDE-EFFECTS
Skin irritation (discontinue use temporarily)

PATIENT AND CARER ADVICE
Patients should discontinue use temporarily if skin becomes irritated.

LESS SUITABLE FOR PRESCRIBING
Less suitable for prescribing (not considered beneficial).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Paste
EXCIPIENTS: May contain Fragrances, n-(3-chlorallyl)hexaminium chloride (quaternium 15)
➤ Brasivol® (GlaxoSmithKline Consumer Healthcare)
Aluminium oxide 380 mg per 1 gram Brasivol Fine No.1 38% paste | 75 gram | £2.76

DERMATOLOGICAL DRUGS > ANTIMICROBIALS

Azelaic acid

INDICATIONS AND DOSE

FINacea®

Facial acne vulgaris

➤ TO THE SKIN
➤ Child 12-17 years: Apply twice daily, discontinue if no improvement after 1 month
➤ Adult: Apply twice daily, discontinue if no improvement after 1 month

Papulopustular rosacea

➤ TO THE SKIN
➤ Adult: Apply twice daily, discontinue if no improvement after 2 months

SKINoren®

Acne vulgaris

➤ TO THE SKIN
➤ Child 12-17 years: Apply twice daily
➤ Adult: Apply twice daily

Acne vulgaris in patients with sensitive skin

➤ TO THE SKIN
➤ Child 12-17 years: Apply once daily for 7 days, then apply twice daily
➤ Adult: Apply once daily for 1 week, then apply twice daily

CAUTIONS
Avoid contact with eyes - avoid contact with mouth - avoid contact with mucous membranes

SIDE-EFFECTS
➤ Common or very common Local irritation (reduce frequency or discontinue temporarily)
➤ Uncommon Skin discoloration
➤ Frequency not known Worsening of asthma
**Adapalene with benzoyl peroxide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, adapalene, above, benzoyl peroxide p. 1121.

- **INDICATIONS AND DOSE**
  - **Acne vulgaris**
    - TO THE SKIN
    - Child 9–17 years: Apply once daily, to be applied thinly in the evening
    - Adult: Apply once daily, to be applied thinly in the evening

- **CONCEPTION AND CONTRACEPTION** Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

- **PATIENT AND CARER ADVICE** Gel may bleach clothing and hair.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions**
    - The **Scottish Medicines Consortium** has advised (March 2014) that **Epiduo®** should be restricted for use in mild to moderate facial acne when monotherapy with benzoyl peroxide or adapalene is inappropriate.

**Isotretinoin**

- **INDICATIONS AND DOSE**
  - **Topical treatment of mild to moderate acne**
    - TO THE SKIN
    - Adult: Apply 1–2 times a day, to be applied thinly
  - **Severe acne (under expert supervision) | Acne which is associated with psychological problems (under expert supervision) | Acne which has not responded to an adequate course of a systemic antibacterial (under expert supervision) | Systemic treatment of nodulo-cystic and conglobate acne (under expert supervision)**
    - BY MOUTH
    - Adult: Initially 500 micrograms/kg daily in 1–2 divided doses, increased if necessary to 1 mg/kg daily for 16–24 weeks, repeat treatment course after a period of at least 8 weeks if relapse after first course; maximum 150 mg/kg per course

- **CONTRA-INDICATIONS**
  - With oral use Hyperlipidaemia · Hypervitaminosis A
  - With topical use Perioral dermatitis · Rosacea

- **CAUTIONS**
  - With oral use Avoid blood donation during treatment and for at least 1 month after treatment · diabetes · dry eye syndrome (associated with risk of keratitis) · history of depression · monitor for depression
CONCEPTION AND CONTRACEPTION

Pregnancy prevention

With oral use Effective contraception must be used. In women of child-bearing potential, exclude pregnancy up to 3 days before treatment (start treatment on day 2 or 3 of menstrual cycle), every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle. Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogens—only contraceptives are not considered effective. Barrier methods should not be used alone, but can be used in conjunction with other contraceptive methods. Each prescription for isotretinoin should be limited to a supply of up to 30 days’ treatment and dispensed within 7 days of the date stated on the prescription; repeat prescriptions or faxed prescriptions are not acceptable. Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.

With topical use Females of child-bearing age must use effective contraception (oral progestogen—only contraceptives not considered effective).

PREGNANCY Contra-indicated in pregnancy (teratogenic).

BREAST FEEDING Avoid.

HEPATIC IMPAIRMENT

With oral use Avoid—further impairment may occur.

RENAL IMPAIRMENT

With oral use In severe impairment, reduce initial dose (e.g. 10 mg daily) and increase gradually up to 1 mg/kg daily as tolerated.

MONITORING REQUIREMENTS

With oral use Measure hepatic function and serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase or serum lipids persistently raised).

PREScribing AND DISPensing INFORMATION Isotretinoin is an isomer of tretinoin.

PATIENT AND CARER ADVICE

With oral use Warn patient to avoid wax epilation (risk of epidermal stripping), dermabrasion, and laser skin treatments (risk of scarring) during treatment and for at least 6 months after stopping; patient should avoid exposure to UV light (including sunlight) and use sunscreen and emollient (including lip balm) preparations from the start of treatment.

Patients and carers should be told how to recognise signs and symptoms of psychiatric disorders such as depression, anxiety, and rarely suicidal thoughts.

With topical use Patients should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. If sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used.
**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10, 11, 21</th>
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<tbody>
<tr>
<td>Isotretinoin (Non-proprietary)</td>
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<tr>
<td>Isotretinoin 5 mg</td>
<td>Isotretinoin 5mg capsules</td>
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<td>£10.15</td>
<td>£5 capsule POM</td>
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<tr>
<td>Isotretinoin 10 mg</td>
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<td>£38.98 DT price</td>
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<tr>
<td>Roaccutane (Roche Products Ltd)</td>
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<td>£14.54 DT price</td>
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<td>Roaccutane 20mg capsules</td>
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<td>£20.02 DT price</td>
<td>£16.43</td>
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**Gel**

<table>
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<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tbody>
<tr>
<td>EXCIPIENTS: May contain Butylated hydroxytoluene</td>
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</tr>
<tr>
<td>Isotrex (Stiefel Laboratories (UK) Ltd)</td>
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</tr>
<tr>
<td>Isotretinoin 500 microgram per 1 gram</td>
<td>Isotrex 0.05% gel</td>
</tr>
<tr>
<td>£5.94 DT price</td>
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</table>

**Isotretinoin with erythromycin**
The properties listed below are those particular to the combination only. For the properties of the components please consider, isotretinoin p. 1122.

**INDICATIONS AND DOSE**

**TO THE SKIN**

- Adult: (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Gel**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>11</th>
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<tbody>
<tr>
<td>EXCIPIENTS: May contain Butylated hydroxytoluene</td>
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</tr>
<tr>
<td>Erythromycin (as Erythromycin phosphate) 20 mg per 1 gram, Tretinoin 250 microgram per 1 gram</td>
<td>Tretin 1%/0.025% gel</td>
</tr>
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<td>£11.94</td>
<td></td>
</tr>
</tbody>
</table>

**Tretinoin with clindamycin**
The properties listed below are those particular to the combination only. For the properties of the components please consider, clindamycin p. 1120.

**INDICATIONS AND DOSE**

**TO THE SKIN**

- Child: 1–2 times a day, apply thinly
- Adult: 1–2 times a day, apply thinly

**CONTRA-INDICATIONS** Perioral dermatitis - personal or familial history of non-melanoma skin cancer - rosacea

**CAUTIONS** Allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid - alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application) - avoid accumulation in angles of the nose - avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin - avoid exposure to UV light (including sunlight, solariums) - avoid in severe acne involving large areas - avoid use of topical retinoids with abrasive cleaners, comedogenic or astringent cosmetics - caution in sensitive areas such as the neck

**SIDE-EFFECTS** Blistering of skin - burning - crusting of skin - dry or peeling skin (discontinue if severe) - erythema - eye irritation - increased sensitivity to UVB light or sunlight - oedema - pruritus - stinging - temporary changes of skin pigmentation

**CONCEPTION AND CONTRACEPTION** Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).
Rosacea

6.2 Rosacea

Other drugs used for Rosacea Azelaic acid, p. 1121

VITAMINS AND TRACE ELEMENTS  VITAMIN B GROUP

Nicotinamide

- **INDICATIONS AND DOSE**
  
  **Inflammatory acne vulgaris**
  
  ▶ **TO THE SKIN**
  
  Adult: Apply twice daily, reduced to once daily or on alternate days, dose reduced if irritation occurs

- **CAUTIONS** Avoid contact with eyes - avoid contact with mucous membranes (including nose and mouth) - reduce frequency of application if excessive dryness, irritation or peeling

- **SIDE-EFFECTS** Burning - dry skin - erythema - irritation - peeling

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Gel**
  
  Freederm (Dendron Ltd)
  
  Nicotinamide 40 mg per 1 gram Freederm 4% gel | 25 gram P £5.56
  
  Nicam (Dermal Laboratories Ltd)
  
  Nicotinamide 40 mg per 1 gram Nicam 4% gel | 60 gram P £7.10

SYMPATHOMIMETICS  ALPHA_2-ADRENOCEPTOR AGONISTS

Brimonidine tartrate

- **DRUG ACTION**
  
  Brimonidine, an alpha_2-adrenoceptor agonist, is used to reduce erythema in rosacea by cutaneous vasoconstriction.

- **INDICATIONS AND DOSE**
  
  Facial erythema in rosacea
  
  ▶ **TO THE SKIN**
  
  Adult: Apply once daily until erythema subsides, apply thinly, divide dose over forehead, chin, nose, and cheeks; maximum 5 mg per day

- **CAUTIONS**
  
  Cerebral insufficiency · coronary insufficiency · depression · postural hypotension · Raynaud’s syndrome · severe cardiovascular disease · thromboangiitis obliterans

- **INTERACTIONS**
  
  → Appendix 1 (brimonidine).

- **SIDE-EFFECTS**
  
  ▶ Common or very common  Burning sensation at application site · stinging at application site
  
  ▶ Uncommon  Dry mouth · dry skin · headache · paraesthesia · skin irritation

- **PREGNANCY**
  
  Limited information available; manufacturer advises avoid.

- **BREAST FEEDING**
  
  Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  
  Manufacturer advises use with caution.

- **RENAL IMPAIRMENT**
  
  Manufacturer advises use with caution.

- **DIRECTIONS FOR ADMINISTRATION**
  
  Avoid contact with eyes, mouth, and mucous membranes; avoid use on irritated skin or open wounds; apply other topical preparations (including cosmetics) only after brimonidine gel has dried on skin.

- **PATIENT AND CARER ADVICE**
  
  Patients should be advised on administration of gel.

  Driving and skilled tasks
  
  Drowsiness may affect performance of skilled tasks (e.g. driving).

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (December 2014) that brimonidine (Mirvaso®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of moderate to severe persistent facial erythema associated with rosacea in adult patients.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Gel**
  
  CAUTIONARY AND ADVISORY LABELS 28
  
  EXCIPIENTS: May contain Hydroxybenzoates (parabens), propylene glycol
  
  Mirvaso (Galderma (UK) Ltd)
  
  Brimonidine (as Brimonidine tartrate) 3 mg per 1 gram Mirvaso 3mg/g gel | 30 gram PoM £33.69

Other drugs used for Rosacea Azelaic acid, p. 1121
7 Scalp and hair conditions

Scalp and hair conditions

Overview
Dandruff is considered to be a mild form of seborrhoeic dermatitis. Shampoos containing antimicrobial agents such as pyrithione zinc (which are widely available) and selenium below may have beneficial effects. Shampoos containing tar extracts may be useful and they are also used in psoriasis. Ketoconazole shampoo p. 1087 should be considered for more persistent or severe dandruff or for seborrhoeic dermatitis of the scalp.

Corticosteroid gels and lotions can also be used. Shampoos containing coal tar with salicylic acid p. 1110 may also be useful. A cream or an ointment containing coal tar with salicylic acid is very helpful in seborrhoeic dermatitis of the scalp. Cradle cap in infants may be treated with coconut oil or olive oil applications followed by shampooing.

Hirsutism
Hirsutism may result from hormonal disorders or as a side-effect of drugs such as minoxidil p. 1127, corticosteroids, anabolic steroids, androgens, danazol p. 678, and progesterones. Weight loss can reduce hirsutism in obese women. Women should be advised about local methods of hair removal, and in the mildest cases this may be all that is required.

Efollithine p. 1127 an antiprotozoal drug, inhibits the enzyme ornithine decarboxylase in hair follicles. Topical efollithine can be used as an adjunct to laser therapy for facial hirsutism in women. Co-cyprindiol p. 1119 may be effective for moderately severe hirsutism. Metformin hydrochloride p. 631 is an alternative in women with polycystic ovary syndrome [unlicensed indication]. Systemic treatment is required for 6–12 months before benefit is seen.

Androgenetic alopecia
Finasteride p. 720 is licensed for the treatment of androgenetic alopecia in men. Continuous use for 3–6 months is required before benefit is seen, and effects are reversed 6–12 months after treatment is discontinued. Topical application of minoxidil may stimulate limited hair growth in a small proportion of adults but only for as long as it is used.

Other drugs used for Scalp and hair conditions
Coal tar, p. 1109 - Coal tar with lecithin, p. 1110 - Coal tar with salicylic acid and precipitated sulfur, p. 1111.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Shampoo
- Ceanel (Alliance Pharmaceuticals Ltd)
  Undecenoic acid 10 mg per 1 ml, Phenylethyl alcohol 75 mg per 1 ml, Cetrimide 100 mg per 1 ml
  Ceanel Concentrate shampoo | 150 ml | £3.40 | 500 ml | £9.80

Antiseptics and disinfectants

Benzalkonium chloride

Indications and dose
Seborrhoeic scalp conditions associated with dandruff and scaling
- To the skin
  - Child: Apply as required
  - Adult: Apply as required

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Shampoo
- Dermax (Dermal Laboratories Ltd)
  Benzalkonium chloride 5 mg per 1 ml
  Dermax Therapeutic 0.5% shampoo | 250 ml | £5.69

Vitamins and trace elements

Selenium

Indications and dose
Seborrhoeic dermatitis | Dandruff
- To the skin using shampoo
  - Child 5–17 years: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required
  - Adult: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required

Pityriasis versicolor
- To the skin using shampoo
  - Adult: Apply once daily for 7 days, apply to the affected area and leave on for 10 minutes before rinsing off. The course may be repeated if necessary. Diluting with a small amount of water prior to application can reduce irritation

Unlicensed use
The use of selenium sulfide shampoo as a lotion for the treatment of pityriasis (tinea) versicolor is an unlicensed indication.

Patient and carer advice
Avoid using 48 hours before or after applying hair colouring, straightening or waving preparations.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Shampoo
Excipients: May contain Fragrances
- Selsun (Chattem (U.K.) Ltd)
  Selenium sulfide 25 mg per 1 ml
  Selsun 2.5% shampoo | 50 ml | £1.61 DT price = £1.61 | 100 ml | £2.15 DT price = £2.15 | 150 ml | £3.06 DT price = £3.06

Antiseptics and disinfectants

Cetrimide with undecenoic acid

Indications and dose
Scalp psoriasis | Seborrhoeic dermatitis | Dandruff
- To the skin
  - Child: Apply 3 times a week for 1 week, then apply twice weekly
  - Adult: Apply 3 times a week for 1 week, then apply twice weekly
7.1 Alopecia

Other drugs used for Alopecia

REGAINE® FOR MEN EXTRA STRENGTH FOAM

Androgenetic alopecia

TO THE SKIN

Adult: Apply 0.5 capful twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 16 weeks

REGAINE® FOR MEN EXTRA STRENGTH SOLUTION

Androgenetic alopecia

TO THE SKIN

Adult: Apply 1 mL twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 1 year

REGAINE® FOR WOMEN REGULAR STRENGTH

Androgenetic alopecia

TO THE SKIN

Adult: Apply 1 mL twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 1 year

CONTRA-INDICATIONS Phaeochromocytoma

CAUTIONS Avoid contact with broken, infected, shaved, or inflamed skin • avoid contact with eyes • avoid contact with mouth • avoid contact with mucous membranes • avoid inhalation of spray mist • avoid occlusive dressings

CAUTIONS, FURTHER INFORMATION

When used topically systemic effects unlikely; only about 1–2% absorbed (greater absorption may occur with use on inflamed skin).

INTERACTIONS Caution—avoid topical drugs which enhance absorption.

SIDE-EFFECTS

Common or very common Headache • local irritation

Uncommon Changes in hair colour or texture (discontinue if increased hair loss persists for more than 2 weeks) • hypotension

SIDE-EFFECTS, FURTHER INFORMATION

When used topically systemic effects unlikely; only about 1–2% absorbed (greater absorption may occur with use on inflamed skin).

PREGNANCY Avoid—possible toxicity including reduced placental perfusion. Neonatal hirsutism reported.

BREAST FEEDING Present in milk but not known to be harmful.

PATIENT AND CARER ADVICE Ensure hair and scalp dry before application. Patients and their carers should be advised to wash hands after application of liquid or foam.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Foam

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Propylene glycol

REGAINE (McNeil Products Ltd)

Minoxidil 20 mg per 1 mL Regaine for Women Regular Strength 2% solution | 60 mL | £14.16

Minoxidil 50 mg per 1 mL Regaine for Men Extra Strength 5% solution | 180 mL | £39.71

7.2 Hirsutism

Other drugs used for Hirsutism

CO-CYPRINDIOL, p. 1119

ANTIPROTOZOAIS

Efornithine

Drug Action

An antiprotozoal drug that inhibits the enzyme ornithine decarboxylase in hair follicles.

INDICATIONS AND DOSE

Adjunct to laser therapy for facial hirsutism in women

TO THE SKIN

Adult: Apply twice daily, to be applied thinly, discontinue if no improvement after 4 months of treatment

SIDE-EFFECTS

Common or very common Acne • burning at application site • rash • stinging at application site

Uncommon Abnormal hair growth • abnormal hair texture

PREGNANCY Toxicity in animal studies—manufacturer advises avoid.

BREAST FEEDING Manufacturer advises avoid—no information available.

PATIENT AND CARER ADVICE

Medicines must be rubbed in thoroughly. Cosmetics may be applied over treated area 5 minutes after efornithine, do not wash treated area for 4 hours after application.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (September 2005) that efornithine for facial hirsutism be restricted for use in women in whom alternative drug treatment cannot be used.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens)

VANIQA (Almirall Ltd)

Efornithine (as Efornithine monohydrate chloride) 115 mg per 1 gram Vaniqa 11.5% cream | 60 gram | £56.87

8 Skin cleansers, antiseptics and desloughing agents

Skin cleansers, antiseptics and desloughing agents

Skin cleansers and antiseptics

Soap or detergent is used with water to cleanse intact skin; emollient preparations such as aqueous cream or...
emulsifying ointment can be used in place of soap or detergent for cleansing dry skin.

An antiseptic is used for skin that is infected or that is susceptible to recurrent infection. Detergent preparations containing chlorhexidine p. 1129 or povidone-iodine below, which should be thoroughly rinsed off, are used. Emollients may also contain antiseptics.

Antiseptics such as chlorhexidine or povidone-iodine are used on intact skin before surgical procedures; their antiseptic effect is enhanced by an alcoholic solvent. Antiseptic solutions containing cetrimide can be used if a detergent effect is also required.

Hydrogen peroxide p. 1130, an oxidising agent, can be used in solutions of up to 6% for skin disinfection, such as cleansing and deodorising wounds and ulcers. Hydrogen peroxide is also available as a cream for superficial bacterial skin infections.

For irrigating ulcers or wounds, lukewarm sterile sodium chloride 0.9% solution is used, but tap water is often appropriate.

Potassium permanganate solution 1 in 10000 below, a mild antiseptic with astringent properties, can be used for exudative eczematous areas; treatment should be stopped when the skin becomes dry.

Desloughing agents

Alginate, hydrogel and hydrocolloid dressings are effective at wound debridement. Sterile larvae (maggots) (available from BioMonde) are also used for managing sloughing at wound debridement. Sterile larvae (maggots) (available from BioMonde) are also used for managing sloughing.

For desloughing wounds or ulcers, lukewarm sterile sodium chloride 0.9% solution is used, but tap water is often appropriate.

Potassium permanganate solution 1 in 10 000 below, a mild antiseptic with astringent properties, can be used for exudative eczematous areas; treatment should be stopped when the skin becomes dry.

Desloughing agents

Alginate, hydrogel and hydrocolloid dressings are effective at wound debridement. Sterile larvae (maggots) (available from BioMonde) are also used for managing sloughing wounds and are prescribable on the NHS.

Desloughing solutions and creams are of little clinical value. Substances applied to an open area are easily absorbed and perilesional skin is easily sensitised. Gravitational dermatitis may be complicated by absorption and perilesional skin is easily sensitised.

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Desloughing agents

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**VIDENE® SURGICAL SCRUB®**

**Skin disinfection**
- TO THE SKIN
- Child: Use as a pre-operative scrub for hand and skin disinfection
- Adult: Use as a pre-operative scrub for hand and skin disinfection

**VIDENE® TINCTURE**

**Skin disinfection**
- TO THE SKIN
- Adult: Apply undiluted in pre-operative skin disinfection

**CONTRA-INDICATIONS** Avoid regular use in patients with thyroid disorders (in adults) - concomitant use of lithium - corrected gestational age under 32 weeks - infants body weight under 1.5 kg - regular use in neonates

**CAUTIONS** Broken skin - large open wounds

**SIDE-EFFECTS** Rare Sensitivity

**PREGNANCY** Sufficient iodine may be absorbed to affect the fetal thyroid in the second and third trimester.

**BREAST FEEDING** Avoid regular or excessive use.

**RENAL IMPAIRMENT** Avoid regular application to inflamed or broken skin or mucosa.

**EFFECT ON LABORATORY TESTS** May interfere with thyroid function tests.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

- **Liquid**
  - CAUTIONARY AND ADVISORY LABELS 15 (Only for use with alcoholic solutions)
  - **Videne** (Ecolab Healthcare Division)
    - Povidone-Iodine 75 mg per 1 ml Videne 7.5% surgical scrub solution | 500 ml | £7.30
    - Povidone-Iodine 100 mg per 1 ml Videne 10% antiseptic solution | 500 ml | £7.30
  - **Spray**
    - Betadine (Aspire Pharma Ltd)
      - Povidone-Iodine 25 mg per 1 gram Betadine 2.5% dry powder spray | 100 ml | £9.95 DT price = £9.95

**ANTISEPTICS AND DESLoughING AGENTS > OTHER**

**Chlorhexidine**

- **INDICATIONS AND DOSE**
  - **CX ANTISEPTIC DUSTING POWDER**
    - For skin disinfection
      - TO THE SKIN
      - Adult: (consult product literature)
  - **CEPTON® LOTION**
    - For skin disinfection in acne
      - TO THE SKIN
      - Child: (consult product literature)
      - Adult: (consult product literature)

**CEPTON® SKIN WASH**

For use as skin wash in acne
- TO THE SKIN
- Child: (consult product literature)
- Adult: (consult product literature)

**HIBITANE PLUS 5% CONCENTRATE SOLUTION**

General and pre-operative skin disinfection
- TO THE SKIN
- Child: (consult product literature)

**HIBISCRUB®**

Pre-operative hand and skin disinfection | General hand and skin disinfection
- TO THE SKIN
- Child: Use as alternative to soap (consult product literature)
- Adult: Use as alternative to soap (consult product literature)

**HIBITANE OBSTETRIC®**

For use in obstetrics and gynaecology as an antiseptic and lubricant
- TO THE SKIN
- Adult: To be applied to skin around vulva and perineum and to hands of midwife or doctor

**HIBI® LIQUID HAND RUB+**

Hand and skin disinfection
- TO THE SKIN
- Child: To be used undiluted (consult product literature)
- Adult: To be used undiluted (consult product literature)

**HYDREX® SOLUTION**

For pre-operative skin disinfection
- TO THE SKIN
- Child: (consult product literature)
- Adult: (consult product literature)

**HYDREX® SURGICAL SCRUB**

For pre-operative hand and skin disinfection | General hand disinfection
- TO THE SKIN
- Child: (consult product literature)
- Adult: (consult product literature)

**UNISEPT®**

For cleansing and disinfecting wounds and burns and swabbing in obstetrics
- TO THE SKIN
- Child: (consult product literature)
- Adult: (consult product literature)

**CONTRA-INDICATIONS** Alcoholic solutions not suitable before diathermy - not for use in body cavities

**CAUTIONS** Avoid contact with brain - avoid contact with eyes - avoid contact with meninges - avoid contact with middle ear

**SIDE-EFFECTS** Sensitivity

**DIRECTIONS FOR ADMINISTRATION**

**HIBITANE PLUS 5% CONCENTRATE SOLUTION** For pre-operative skin preparation, dilute 1 in 10 (0.5%) with alcohol 70%. For general skin disinfection, dilute 1 in 100 (0.05%) with water. Alcoholic solutions not suitable for use before diathermy or on neonatal skin.
Chlorhexidine with cetrimide

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1129.

### Indications and dose

**Skin disinfection such as wound cleansing and obstetrics**

- **To the skin**
- **Child:** To be used undiluted
- **Adult:** To be used undiluted

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

- Savlon disinfectant (Novartis Consumer Health UK Ltd)
  - Chlorhexidine gluconate 3 mg per 1 ml, Cetrime 30 mg per 1 ml
  - Savlon disinfectant liquid | 500 ml £1.32
- Sterets Tisept (Molnlycke Health Care Ltd)
  - Cetrime 1.5 mg per 1 ml, Chlorhexidine gluconate 150 microgram per 1 ml
  - Sterets Tisept solution 25ml sachets | 25 sachet £0.53
  - Sterets Tisept solution 100ml sachets | 10 sachet £6.85

**Cream**

- Chlorhexidine with cetrimide (Non-proprietary)
  - Chlorhexidine gluconate 1 mg per 1 gram, Cetrime 5 mg per 1 gram
  - Savlon antiseptic cream | 15 gram £0.91 | 60 gram £1.19 | 100 gram £2.78

**Irrigation solution**

- Chlorhexidine with cetrimide (Non-proprietary)
  - Cetrime 1.5 mg per 1 ml, Chlorhexidine acetate 150 microgram per 1 ml
  - Chlorhexidine acetate 0.015% / Cetrime 0.15% irrigation solution 1 litre bottles | 1 bottle no price available

Diethyl phthalate with methyl salicylate

### Indications and dose

**Skin preparation before injection**

- **To the skin**
- **Child:** Apply to the area to be disinfected

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

- **Diethyl phthalate with methyl salicylate (Non-proprietary)**
  - Methyl salicylate 5 ml per 1 litre, Diethyl phthalate 20 ml per 1 litre
  - Castor oil 25 ml per 1 litre, Industrial methylated spirit 950 ml per 1 litre
  - Surgical spirit | 200 ml G55 £0.63 | 500 ml G55 £1.95 | 1000 ml G55 £3.35

Hydrogen peroxide

### Drug action

Hydrogen peroxide is an oxidising agent.

### Indications and dose

**For skin disinfection, particularly cleansing and deodorising wounds and ulcers**

- **To the skin**
- **Adult:** Use 3% and 6% solutions (consult product literature)

**Cryosadie®**

**Superficial bacterial skin infection**

- **To the skin**
- **Child:** Apply 2–3 times a day for up to 3 weeks
- **Adult:** Apply 2–3 times a day for up to 3 weeks
Sodium chloride 0.9% irrigation solution 20ml Clinipod unit dose
- Mayors Healthcare Ltd

Sodium chloride 0.9% irrigation solution 20ml ISO-POD unit dose
- St Georges Medical Ltd

Sodium chloride 0.9% irrigation solution 20ml Irripod unit dose
- C D Medical Ltd

Sodium chloride 0.9% irrigation solution 20ml Sal-e Pods unit dose
- Ennogen Healthcare Ltd

Sodium chloride 0.9% irrigation solution 20ml Salipod unit dose
- Ennogen Healthcare Ltd

Sodium chloride 0.9% irrigation solution 20ml Steriplast Healthcare Ltd

Sodium chloride 0.9% irrigation solution 20ml Steripod unit dose
- Steroplast Healthcare Ltd

Sodium chloride 0.9% irrigation solution 20ml Sterowash unit dose
- Steroplast Healthcare Ltd

Sodium chloride 0.9% irrigation solution 20ml unit dose
- Alissa Healthcare Research Ltd

Sodium chloride 0.9% irrigation solution 20ml unit dose
- Crest Medical Ltd

Sodium chloride 0.9% irrigation solution 20ml unit dose
- Mylan Ltd

Sodium chloride 0.9% irrigation solution 20ml unit dose
- C D Medical Ltd

Stericrilens sodium chloride 0.9% irrigation solution aerosol spray
- C D Medical Ltd

8.1 Minor cuts and abrasions

Minor cuts and abrasions

Management

Many preparations traditionally used to manage minor burns, and abrasions have fallen out of favour. Preparations containing camphor and sulfonamides should be avoided. Preparations such as magnesium sulfate paste are now rarely used to treat carbuncles and boils as these are best treated with antibiotics.

Cetrimide is used to treat minor cuts and abrasions and proflavin above may be used to treat infected wounds or burns, but its use has now been largely superseded by other antiseptics or suitable antibacterials. The effervescent effect of hydrogen peroxide p. 1130 is used to clean minor cuts and abrasions.

Flexible colloid (see castor oil with collodion and colophony p. 1132) may be used to seal minor cuts and wounds that have partially healed; skin tissue adhesives are used similarly, and also for additional suture support.
9 Skin disfigurement

Camouflages

Overview
Disfigurement of the skin can be very distressing to patients and may have a marked psychological effect. In skilled hands, or with experience, camouflage cosmetics can be very effective in concealing scars and birthmarks. The depigmented patches in vitiligo are also very disfiguring and camouflage creams are of great cosmetic value.

Opaque cover foundation or cream is used to mask skin pigment abnormalities; careful application using a combination of dark- and light-coloured cover creams set with powder helps to minimise the appearance of skin deformities.

Borderline substances
The preparations marked 'ACBS' can be prescribed on the NHS for postoperative scars and other deformities and as adjunctive therapy in the relief of emotional disturbances due to disfiguring skin disease, such as vitiligo.

Camouflages

- **Camouflages**

  **Covermark classic foundation** (Derma UK Ltd)
  15 ml (ACBS) - NHS indicative price = £11.86

  **Covermark finishing powder** (Derma UK Ltd)
  25 gram (ACBS) - NHS indicative price = £11.86

  **Covermark removing cream** (Derma UK Ltd)
  200 ml - No NHS indicative price available

  **Dermablend Dermasmooth Corrective Foundation** (Vichy)
  30 ml - No NHS indicative price available

  **Dermacolor Creme Effectiv** (Charles H Fox Ltd)
  50 ml - NHS indicative price = £5.48

  **Dermacolor body cover** (Charles H Fox Ltd)
  75 ml - No NHS indicative price available

  **Dermacolor camouflage creme** (Charles H Fox Ltd)
  25 ml (ACBS) - NHS indicative price = £10.52

  **Dermacolor cleansing cream** (Charles H Fox Ltd)
  75 gram - No NHS indicative price available

  **Dermacolor fixing powder** (Charles H Fox Ltd)
  50 gram (ACBS) - NHS indicative price = £9.05

  **Keromask finishing powder** (Bellava Ltd)
  20 gram (ACBS) - NHS indicative price = £5.80

  **Veil cleansing cream** (Thomas Blake Cosmetic Creams Ltd)
  50 gram - NHS indicative price = £2.45100 gram - NHS indicative price = £4.00

  **Veil cover cream** (Thomas Blake Cosmetic Creams Ltd)
  13 gram (ACBS) - NHS indicative price = £22.4244 gram (ACBS) - NHS indicative price = £33.3570 gram (ACBS) - NHS indicative price = £42.10

  **Veil finishing powder** (Thomas Blake Cosmetic Creams Ltd)
  35 gram (ACBS) - NHS indicative price = £24.58

10 Sun protection and photodamage

Photodamage

Patients should be advised to use a high-SPF sunscreen and to minimise exposure of the skin to direct sunlight or sun lamps.

Topical treatments can be used for actinic keratosis. An emollient may be sufficient for mild lesions. Diclofenac sodium gel p. 1133 is suitable for the treatment of superficial
lesions in mild disease. Fluorouracil cream below is effective against most types of non-hypertrophic actinic keratosis; a solution containing fluorouracil with salicylic acid below is available for the treatment of low or moderately thick hyperkeratotic actinic keratosis. Imiquimod p. 1136 is used for lesions on the face and scalp when cryotherapy or other topical treatments cannot be used. Fluorouracil and imiquimod produce a more marked inflammatory reaction than diclofenac sodium but lesions resolve faster. A short course of ingenol mebutate p. 1134 is licensed for the treatment of non-hypertrophic actinic keratosis; response to treatment can usually be assessed 8 weeks after the course. Photodynamic therapy in combination with methyl-5-aminolevulinate cream (Metvix®, available from Galderma) or 5-aminolaevulinic acid gel (Ameluz®, available from Spirit Healthcare) is used in specialist centres for treating superficial and confluent, non-hypertrophic actinic keratosis when other treatments are inadequate or unsuitable; it is particularly suitable for multiple lesions, for periorbital lesions, or for lesions located at sites of poor healing. Imiquimod or topical fluorouracil is used for treating superficial basal cell carcinomas. Photodynamic therapy in combination with methyl-5-aminolevulinic acid cream is used in specialist centres for treating superficial, nodular basal cell carcinomas when other treatments are unsuitable.

**ANTINEOPLASTIC DRUGS**

**Fluorouracil**

**INDICATIONS AND DOSE**

**Superficial malignant and pre-malignant skin lesions**
- TO THE SKIN USING CREAM
  - Adult: Apply once daily for up to 3 weeks, reduced to 1–2 times a day for 3–4 weeks (usual duration of initial therapy), apply thinly to the affected area, maximum area of skin 500 cm² (e.g. 23 cm x 23 cm) treated at one time, alternative regimens may be used in some settings

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

| Excipients: May contain Benzyl alcohol, fragrances, propylene glycol
| Solaraze (Almirall Ltd) | Diclofenac sodium 30 mg per 1 gram | Solaraze 3% gel | 50 gram | £38.30 DT price = £38.30 | 100 gram | £76.60 |

**Fluorouracil with salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluorouracil above, salicylic acid p. 1137.

**INDICATIONS AND DOSE**

**Low or moderately thick hyperkeratotic actinic keratosis**
- TO THE SKIN
  - Adult: Apply once daily for up to 12 weeks, reduced to 3 times a week if severe side effects occur and until side-effects improve, to be applied to the affected area, if treating area with thin epidermis, reduce frequency of application and monitor response more often; maximum area of skin treated at one time, 25 cm² (e.g. 5 cm x 5 cm)


**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cutaneous solution**
CAUTIONARY AND ADVISORY LABELS 15

- Actikerall (Almirall Ltd)
- Fluorouracil 5 mg/g. Salicylic acid 100 mg/g. Actikerall 5mg/g / 100mg/g cutaneous solution | 25 ml | £38.30

**PROTEIN KINASE C ACTIVATORS**

- **INDICATIONS AND DOSE**
  - **Actinic keratosis on face and scalp**
    - TO THE SKIN
    - Adult: Apply once daily for 3 days, use the 150 microgram/g gel
  - **Actinic keratosis on trunk and extremities**
    - TO THE SKIN
    - Adult: Apply once daily for 2 days, use the 500 microgram/g gel

- **CAUTIONS**
  - Avoid contact with broken skin · avoid contact with eyes · avoid contact with inside of ears · avoid contact with inside of nostrils · avoid contact with lips · avoid occlusive dressings on treated area

- **SIDE-EFFECTS**
  - Common or very common Blistering · crusting · erosion · erythema · exfoliation · headache · infection · local reactions · oedema · pain · pruritus
  - Uncommon Local ulceration · paraesthesia

- **PREGNANCY**
  - Not absorbed from skin, but manufacturer advises avoid.

- **BREAST FEEDING**
  - Not absorbed from skin; ensure infant does not come in contact with treated area for 6 hours after application.

- **DIRECTIONS FOR ADMINISTRATION**
  - One tube covers skin area of 25 cm². Allow gel to dry on treatment area for 15 minutes. Avoid washing or touching the treated area for 6 hours after application; after this time, area may be washed with mild soap and water. Avoid use immediately after shower or less than 2 hours before bedtime.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Gel**
    - CAUTIONARY AND ADVISORY LABELS 15
    - EXCIPIENTS: May contain Benzyl alcohol
    - Picato (LEO Pharma) ▼
      - Ingelen mebutate 150 microgram per 1 gram Picato 150micrograms/g gel | 1.41 gram | £65.00
      - Ingelen mebutate 500 microgram per 1 gram Picato 500micrograms/g gel | .94 gram | £65.00

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**HEPARINOIDs**

- **Heparinoid**
  - **INDICATIONS AND DOSE**
    - **Superficial thrombophlebitis | Bruising | Haematoma**
      - TO THE SKIN
      - Adult: Apply up to 4 times a day
  - **CONTRA-INDICATIONS**
    - Should not be used on large areas of skin, broken or sensitive skin, or mucous membranes
  - **LESS SUITABLE FOR PRESCRIBING**
    - Hirudoid is less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzates (parabens)
    - Hirudoid (Genus Pharmaceuticals Ltd)
      - Heparinoid 3 mg per 1 gram Hirudoid 0.3% cream | 50 gram | £3.99 DT price = £3.99
  - **Gel**
    - EXCIPIENTS: May contain Fragrances, propylene glycol
    - Hirudoid (Genus Pharmaceuticals Ltd)
      - Heparinoid 3 mg per 1 gram Hirudoid 0.3% gel | 50 gram | £3.99 DT price = £3.99

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**12 Warts and calluses**

**Warts and calluses**

**Overview**
Warts (verrucae) are caused by a human papillomavirus, which most frequently affects the hands, feet (plantar warts), and the anogenital region; treatment usually relies on local tissue destruction. Warts may regress on their own and treatment is required only if the warts are painful, unsightly, persistent, or cause distress.

Preparations of salicylic acid. Podophyllotoxin, p. 1135, glutaraldehyde p. 1135, formaldehyde p. 1135, imiquimod p. 1136 are available for purchase by the public; they are suitable for the removal of warts on hands and feet. Salicylic acid is a useful keratolytic which may be considered first-line; it is also suitable for the removal of corns and callouses. Preparations of salicylic acid in a collodion basis are available but some patients may develop an allergy to colophony in the formulation; collodion should be avoided in children allergic to elastic adhesive plaster. Cryotherapy causes pain, swelling, and blistering, and may be no more effective than topical salicylic acid in the treatment of warts.

**Anogenital warts**
The treatment of anogenital warts (condylomata acuminata) should be accompanied by screening for other sexually transmitted infections. Podophyllotoxin, p. 1135, (the major active ingredient of podophyllum) may be used for soft, non-keratinised external anogenital warts. Patients with a limited number of external warts or keratinised lesions may be better treated with cryotherapy or other forms of physical ablation.

Imiquimod p. 1136 cream is licensed for the treatment of external anogenital warts; it may be used for both keratinised and non-keratinised lesions. It is also licensed for the treatment of superficial basal cell carcinoma and actinic keratosis.

Inosine pranobex p. 585 is licensed for adjunctive treatment of genital warts but it has been superseded by more effective drugs.
ANTINEOPLASTIC DRUGS > PLANT ALKALOIDS

Podophyllotoxin

- **INDICATIONS AND DOSE**
  **CONDYLINE®**
  Condylomata acuminata affecting the penis or the female external genitalia
  - TO THE LESION
  - Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of 5 3-day treatment courses, direct medical supervision for lesions in the female and for lesions greater than 4 cm² in the male, maximum 50 single applications (‘loops’) per session (consult product literature)

  **WARTICON® CREAM**
  Condylomata acuminata affecting the penis or the female external genitalia
  - TO THE LESION
  - Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses, direct medical supervision for lesions greater than 4 cm², maximum 50 single applications (‘loops’) per session (consult product literature)

- **CAUTIONS** Avoid normal skin • avoid open wounds • keep away from face • very irritant to eyes
- **SIDE-EFFECTS** Local irritation
- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Liquid**
  - **Condyline** (Takeda UK Ltd)
    - Podophyllotoxin 5 mg per 1 ml Condyline 0.5% solution | 3.5 ml £14.49
    - **Warticon** (Stiefel Laboratories (UK) Ltd)
      - Podophyllotoxin 5 mg per 1 ml Warticon 0.9% solution | 3 ml £14.86
  **Cream**
  EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), sorbic acid
  - **Warticon** (Stiefel Laboratories (UK) Ltd)
    - Podophyllotoxin 1.5 mg per 1 gram Warticon 0.15% cream | 5 gram £17.83 DT price = £17.83

ANTISEPTICS AND DISINFECTANTS > ALDEHYDES AND DERIVATIVES

Formaldehyde

- **INDICATIONS AND DOSE**
  Warts, particularly plantar warts
  - TO THE LESION
  - Child: Apply twice daily
  - Adult: Apply twice daily

- **UNLICENSED USE** Licensed for use in children (age range not specified by manufacturer).
- **CAUTIONS** Impaired peripheral circulation • not suitable for application to anogenital region • not suitable for application to face • not suitable for application to large areas • patients with diabetes at risk of neuropathic ulcers • protect surrounding skin and avoid broken skin • significant peripheral neuropathy
- **SIDE-EFFECTS** Skin irritation • skin ulceration (with high concentrations)

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid
  **Liquid**
  - **Formaldehyde (Non-proprietary)**
    - Formaldehyde 40 mg per 1 ml Formaldehyde (Buffered) 4% solution | 1000 ml £3.90
  **Gel**
  - **Veracur** (Typharm Ltd)
    - Formaldehyde 7.5 mg per 1 gram Veracur 0.75% gel | 15 gram £2.41
  **Liquid**
  - **Formaldehyde (Non-proprietary)**
    - Formaldehyde 350 mg per 1 gram Formaldehyde solution | 500 ml £5.84 DT price = £5.84 | 2000 ml £16.67

Glutaraldehyde

- **INDICATIONS AND DOSE**
  Warts, particularly plantar warts
  - TO THE LESION
  - Child: Apply twice daily
  - Adult: Apply twice daily

- **UNLICENSED USE** Licensed for use in children (age range not specified by manufacturer).
- **CAUTIONS** Not for application to anogenital areas • not for application to face • not for application to mucosa • protect surrounding skin
- **SIDE-EFFECTS** Rashes • skin irritation (discontinue if severe) • stains skin brown

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Paint**
  - **Glutarol** (Dermal Laboratories Ltd)
    - Glutaraldehyde 100 mg per 1 ml Glutarol 10% cutaneous solution | 10 ml £2.07 DT price = £2.07
**Silver nitrate**

### Indications and Dose

**Common warts**
- **Child:** Apply every 24 hours for up to 3 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application.
- **Adult:** Apply every 24 hours for up to 3 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application.

** verrucas**
- **Child:** Apply every 24 hours for up to 6 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application.
- **Adult:** Apply every 24 hours for up to 6 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application.

**Umbilical granulomas**
- **Child:** Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes, protect surrounding skin with soft paraffin.
- **Adult:** Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes, protect surrounding skin with soft paraffin.

### Unlicensed Use

No age range specified by manufacturer.

### Cautions

- Avoid broken skin · not suitable for application to ano-genital region · not suitable for application to face · not suitable for application to large areas · protect surrounding skin.

### Side-effects

Chemical burns on surrounding skin · stains skin.

### Patient and Carer Advice

Patients should be advised that silver nitrate may stain fabric.

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

**Silver nitrate (Non-proprietary)**
- Silver nitrate 400 mg per 1 gram: Silver nitrate 40% caustic pencils | 1 applicator (P) no price available.
- Avoca 40% silver nitrate pencils | 1 applicator (P) £1.03.
- Silver nitrate 750 mg per 1 gram: Avoca 75% silver nitrate applicators | 100 applicator (P) £44.48.
- Avoca 75% silver nitrate applicators with thick handles | 50 applicator (P) £43.41.
- Silver nitrate 950 mg per 1 gram: Avoca 95% silver nitrate applicators | 100 applicator (P) £44.52.
- Avoca 95% silver nitrate pencils | 1 applicator (P) £1.99 DT price = £2.44.

## Imiquimod

### Indications and Dose

**Aldara®**

**Warts (external genital and perianal)**
- **Common or very common:** Burning sensation · erosion · erythema · excoriations · headache · influenza-like symptoms · itching · local reactions · myalgia · oedema · scabbing.
- **Rare:** Cutaneous lupus erythematosus-like effect · Stevens-Johnson syndrome.
- **Very rare** Dysturia.

**Actinic keratoses**
- **Common or very common** Burning sensation · eritema · excoriations · headache · influenza-like symptoms · itching · local reactions · myalgia · oedema · scabbing.
- **Rare:** Cutaneous lupus erythematosus-like effect · Stevens-Johnson syndrome.
- **Very rare** Dysturia.

**Frequency not known** Permanent hyperpigmentation · permanent hypopigmentation.

**Conception and Contraception** May damage latex condoms and diaphragms.

**Pregnancy** No evidence of teratogenicity or toxicity in animal studies; manufacturer advises caution.

**Breastfeeding** No information available.

**Directions for Administration**

**Aldara®**

**Important** Should be rubbed in and allowed to stay on the treated area for 8 hours, then washed off with mild soap and water.

**Zyclara®**

**Important** Should be rubbed in and allowed to stay on the treated area for 6–10 hours for warts or for 8 hours for basal cell carcinoma and actinic keratosis, then washed off with mild soap and water (uncircumcised males treating warts under foreskin should wash the area daily). The cream should be washed off before sexual contact.

**Patient and Carer Advice** A patient information leaflet should be provided.
Salicylic acid with lactic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, salicylic acid, above.

- **INDICATIONS AND DOSE**

  **CUPLEX®**

  Plantar and mosaic warts | Corns | Calluses

  ➤ TO THE LESION
  ➤ Adult: Apply daily, treatment may need to be continued for up to 3 months

  **DUOFILM®**

  Plantar and mosaic warts

  ➤ TO THE LESION
  ➤ Adult: Apply daily, treatment may need to be continued for up to 3 months

- **PREScribing AND Dispensing INFORMATION**

  Preparations of salicylic acid in a collodion basis (Cuplex® and Salactol®) are available but some patients may develop an allergy to colophony in the formulation.

- **MEdICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Gel**

  CAUTIONARY AND ADVISORY LABELS 15

  - Cuplex (Crawford Healthcare Ltd)
    Salicylic acid 40 mg per 1 gram, salicylic acid 110 mg per 1gram
    Cuplex Verruca gel | 1 gram £2.88 DT price = £2.88
  - Salatac (Dermal Laboratories Ltd)
    Salicylic acid 40 mg per 1 gram, salicylic acid 120 mg per 1 gram
    Salatac gel | 8 gram | £2.98 DT price = £2.98

  **Paint**

  CAUTIONARY AND ADVISORY LABELS 15

  - Duofilm (GlaxoSmithKline UK Ltd)
    Lactic acid 150 mg per 1 gram, Salicylic acid 167 mg per 1 gram
    Duofilm paint | 15 ml | £2.25
  - Salactol (Dermal Laboratories Ltd)
    Lactic acid 167 mg per 1 gram, Salicylic acid 167 mg per 1 gram
    Salactol paint | 10 ml | £1.71 DT price = £1.71

- **SALICYLIC ACID AND DERIVATIVES**

  **Salicylic acid**

  - **INDICATIONS AND DOSE**

    **OCCLUSAL®**

    Common and plantar warts

    ➤ TO THE LESION
    ➤ Child: Apply daily, treatment may need to be continued for up to 3 months
    ➤ Adult: Apply daily, treatment may need to be continued for up to 3 months

    **VERRUGON®**

    For plantar warts

    ➤ TO THE LESION
    ➤ Child: Apply daily, treatment may need to be continued for up to 3 months
    ➤ Adult: Apply daily, treatment may need to be continued for up to 3 months

  - **UNLICENSED USE** Not licensed for use in children under 2 years.

  - **CAUTIONS** Avoid broken skin - impaired peripheral circulation - not suitable for application to anogenital region - not suitable for application to face - not suitable for application to large areas - patients with diabetes at risk of neuropathic ulcers - significant peripheral neuropathy

  - **SIDE-EFFECTS** Skin irritation - skin ulceration (with high concentrations)

  - **PATIENT AND CARER ADVICE** Advise patient to apply carefully to wart and to protect surrounding skin (e.g. with soft paraffin or specially designed plaster); rub wart surface gently with file or pumice stone once weekly.

  - **MEdICINAL FORMS**

    There can be variation in the licensing of different medicines containing the same drug.

    **Liquid**

    CAUTIONARY AND ADVISORY LABELS 15

    - Occlusal (Alliance Pharmaceuticals Ltd)
      Salicylic acid 260 mg per 1 ml Occlusal 26% solution | 10 ml £3.56 DT price = £3.56

    **Ointment**

    - Verrugon (Optima Consumer Health Ltd)
      Salicylic acid 500 mg per 1 gram Verrugon complete 50% ointment | 6 gram £3.61 DT price = £3.61
Chapter 14
Vaccines

I 1 Immunoglobulin therapy

IMMUNE SERA AND IMMUNOGLOBULINS > IMMUNOGLOBULINS

Immunoglobulins

Passive immunity

Immunity with immediate protection against certain infective organisms can be obtained by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. The duration of this passive immunity varies according to the dose and the type of immunoglobulin. Passive immunity may last only a few weeks; when necessary, passive immunisation can be repeated. Antibodies of human origin are usually termed immunoglobulins. The term antiserum is applied to material prepared in animals. Because of serum sickness and other allergic-type reactions that may follow injections of antiserum, this therapy has been replaced wherever possible by the use of immunoglobulins. Reactions are theoretically possible after injection of human immunoglobulins but reports of such reactions are very rare.

Two types of human immunoglobulin preparation are available, normal immunoglobulin p. 1141 and disease-specific immunoglobulins.

Human immunoglobulin is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma or serum obtained from outside the UK, tested and found non-reactive for hepatitis B surface antigen and for antibodies against hepatitis C virus and human immunodeficiency virus (types 1 and 2). A global shortage of human immunoglobulin and the rapidly increasing range of clinical indications for treatment with immunoglobulins has resulted in the need for a Demand Management programme in the UK, for further information consult www.ivig.nhs.uk and Clinical Guidelines for Immunoglobulin Use, www.gov.uk/dh.

Further information on the use of immunoglobulins is included in Public Health England’s Immunoglobulin Handbook www.gov.uk/phe, and in the Department of Health’s publication, Immunisation against Infectious Disease, www.gov.uk/dh.

Availability

Normal immunoglobulin for intramuscular administration is available from some regional Public Health laboratories for protection of contacts and the control of outbreaks of hepatitis A, measles, and rubella only. For other indications, subcutaneous or intravenous normal immunoglobulin should be purchased from the manufacturer.

Disease-specific immunoglobulins are available from some regional Public Health laboratories, with the exception of tetanus immunoglobulin p. 1143 which is available from BPL, hospital pharmacies, or blood transfusion departments. Rabies immunoglobulin p. 1143 is available from the Specialist and Reference Microbiology Division, Public Health England, Colindale. Hepatitis B immunoglobulin p. 1141 required by transplant centres should be obtained commercially.

In Scotland all immunoglobulins are available from the Scottish National Blood Transfusion Service (SNBTS).

In Wales all immunoglobulins are available from the Welsh Blood Service (WBS).

In Northern Ireland all immunoglobulins are available from the Northern Ireland Blood Transfusion Service (NIBTS).

Normal immunoglobulin

Human normal immunoglobulin (‘HNIG’) is prepared from pools of at least 1000 donations of human plasma; it contains immunoglobulin G (IgG) and antibodies to hepatitis A, measles, mumps, rubella, varicella, and other viruses that are currently prevalent in the general population.

Uses

Normal immunoglobulin (containing 10%–18% protein) is administered by intramuscular injection for the protection of susceptible contacts against hepatitis A, measles, mumps, rubella, varicella, and, to a lesser extent, rubella. Injection of immunoglobulin produces immediate protection lasting several weeks.

Normal immunoglobulin (containing 3%–12% protein) for intravenous administration is used as replacement therapy for patients with congenital agammaglobulinaemia and hypogammaglobulinaemia, and for the short-term treatment of idiopathic thrombocytopenic purpura and Kawasaki disease; it is also used for the prophylaxis of infection following bone-marrow transplantation and in children with symptomatic HIV infection who have recurrent bacterial infections. Normal immunoglobulin for replacement therapy may also be given intramuscularly or subcutaneously, but intravenous formulations are normally preferred.

Intravenous immunoglobulin is also used in the treatment of Guillain–Barré syndrome as an alternative to plasma exchange.

For guidance on the use of intravenous normal immunoglobulin and alternative therapies for certain conditions, consult Clinical Guidelines for Immunoglobulin Use (www.gov.uk/dh).

Hepatitis A

Hepatitis A vaccine p. 1164 is preferred for individuals at risk of infection including those visiting areas where the disease is highly endemic (all countries excluding Northern and Western Europe, North America, Japan, Australia, and New Zealand). In unimmunised individuals, transmission of hepatitis A is reduced by good hygiene. Intramuscular normal immunoglobulin is no longer recommended for routine prophylaxis in travellers, but it may be indicated for immunocompromised patients if their antibody response to the vaccine is unlikely to be adequate.
Intramuscular normal immunoglobulin is recommended for prevention of infection in close contacts (of confirmed cases of hepatitis A) who have chronic liver disease or HIV infection, or who are immunosuppressed or over 50 years of age; normal immunoglobulin should be given as soon as possible, preferably within 14 days of exposure to the primary case. However, normal immunoglobulin can still be given to contacts at risk of severe disease up to 28 days after exposure to the primary case. Hepatitis A vaccine can be given at the same time, but it should be given at a separate injection site.

**Measles**

Intravenous or subcutaneous normal immunoglobulin may be given to prevent or attenuate an attack of measles in individuals who do not have adequate immunity. Patients with compromised immunity who have come into contact with measles should receive intravenous or subcutaneous normal immunoglobulin as soon as possible after exposure. It is most effective if given within 72 hours but can be effective if given within 6 days.

Subcutaneous or intramuscular normal immunoglobulin should also be considered for the following individuals if they have been in contact with a confirmed case of measles or with a person associated with a local outbreak:

- non-immune pregnant women
- infants under 9 months

Further advice should be sought from the Centre for Infections, Public Health England (tel. (020) 8200 6868).

Individuals with normal immunity who are not in the above categories and who have not been fully immunised against measles, can be given measles, mumps and rubella vaccine, live p. 1169 for prophylaxis following exposure to measles.

**Rubella**

Intramuscular immunoglobulin after exposure to rubella does not prevent infection in non-immune contacts and is not recommended for protection of pregnant women exposed to rubella. It may, however, reduce the likelihood of a clinical attack which may possibly reduce the risk to the fetus. Risk of intra-uterine transmission is greatest in the first 11 weeks of pregnancy, between 16 and 20 weeks there is minimal risk of deafness only, after 20 weeks there is no increased risk. Intramuscular normal immunoglobulin should be used only if termination of pregnancy would be unacceptable to the pregnant woman—it should be given as soon as possible after exposure. Serological follow-up of recipients is essential to determine if the woman has become infected despite receiving immunoglobulin.

For routine prophylaxis against Rubella, see measles, mumps and rubella vaccine, live p. 1169.

**Disease-specific immunoglobulins**

Specific immunoglobulins are prepared by pooling the plasma of selected human donors with high levels of the specific antibody required. For further information, see Immunoglobulin Handbook (www.gov.uk/phe).

There are no specific immunoglobulins for hepatitis A, measles, or rubella—normal immunoglobulin p. 1141 is used in certain circumstances. There is no specific immunoglobulin for mumps; neither normal immunoglobulin nor measles, mumps and rubella vaccine, live is effective as post-exposure prophylaxis.

**Hepatitis B immunoglobulin**

Disease-specific hepatitis B immunoglobulin p. 1141 (‘HBIG’) is available for use in association with hepatitis B vaccine p. 1165 for the prevention of infection in laboratory and other personnel who have been accidentally inoculated with hepatitis B virus, and in infants born to mothers who have become infected with this virus in pregnancy or who are high-risk carriers. Hepatitis B immunoglobulin will not inhibit the antibody response when given at the same time as hepatitis B vaccine but should be given at different sites.

An intravenous and subcutaneous preparation of hepatitis B immunoglobulin is licensed for the prevention of hepatitis B recurrence in HBV-DNA negative patients who have undergone liver transplantation for liver failure caused by the virus.

**Rabies immunoglobulin**

Following exposure of an unimmunised individual to an animal in or from a country where the risk of rabies is high the site of the bite should be washed with soapy water and specific rabies immunoglobulin p. 1143 of human origin administered. All of the dose should be injected around the site of the wound; if this is difficult or the wound has completely healed it can be given in the anterolateral thigh (remote from the site used for vaccination).

Rabies vaccine p. 1170 should also be given intramuscularly at a different site (for details see rabies vaccine). If there is delay in giving the rabies immunoglobulin, it should be given within 7 days of starting the course of rabies vaccine.

**Tetanus immunoglobulin**

For the management of tetanus-prone wounds, tetanus immunoglobulin p. 1143 should be used in addition to wound cleansing and, where appropriate, antibacterial prophylaxis and a tetanus-containing vaccine. Tetanus immunoglobulin, together with metronidazole p. 499 and wound cleansing, should also be used for the treatment of established cases of tetanus.

**Varicella-zoster immunoglobulin**

Varicella-zoster immunoglobulin p. 1144 (VZIG) is recommended for individuals who are at increased risk of severe varicella and who have no antibodies to varicella–zoster virus and who have significant exposure to chickenpox or herpes zoster. Those at increased risk include:

- neonates whose mothers develop chickenpox in the period 7 days before to 7 days after delivery;
- susceptible neonates exposed in the first 7 days of life;
- susceptible neonates or infants exposed whilst requiring intensive or prolonged special care nursing;
- susceptible women exposed at any stage of pregnancy (but when supplies of VZIG are short, may only be issued to those exposed in the first 20 weeks’ gestation or to those near term) providing VZIG is given within 10 days of contact;
- immunocompromised individuals including those who have received corticosteroids in the previous 3 months at the following dose equivalents of prednisolone: children 2 mg/kg daily for at least 1 week or 1 mg/kg daily for 1 month; adults about 40 mg daily for more than 1 week.

**Important:** for full details consult Immunisation against Infectious Disease. Varicella–zoster vaccine p. 1171 is available.

**Anti-D (Rh(D)) immunoglobulin**

Anti-D (Rh(D)) immunoglobulin p. 1140 is prepared from plasma taken from rhesus-negative donors who have been immunised against the anti-D-antigen. Anti-D (Rh(D)) immunoglobulin is used to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells which may pass into the maternal circulation. The objective is to protect any subsequent child from the hazard of haemolytic disease of the newborn.

Anti-D (Rh(D)) immunoglobulin should be administered to the mother following any sensitising episode (e.g. abortion, miscarriage and birth); it should be injected within 72 hours of the episode but even if a longer period has elapsed it may still give protection and should be administered. Anti-D (Rh(D)) immunoglobulin is also given when significant fetomaternal haemorrhage occurs in rhesus-negative women during delivery. The dose of anti-D (Rh(D)) immunoglobulin is
determined according to the level of exposure to rhesus-positive blood.

Use of routine antenatal anti-D prophylaxis should be given irrespective of previous anti-D prophylaxis for a sensitising event early in the same pregnancy. Similarly, postpartum anti-D prophylaxis should be given irrespective of previous routine antenatal anti-D prophylaxis or antenatal anti-D prophylaxis for a sensitising event in the same pregnancy.

Anti-D (Rh₀) immunoglobulin is also given to women of child-bearing potential after the inadvertent transfusion of rhesus-incompatible blood components and is used for the treatment of idiopathic thrombocytopenia purpura.

MMR vaccine

Measles, mumps and rubella vaccine, live may be given in the postpartum period with anti-D (Rh₀) immunoglobulin injection provided that separate syringes are used and the products are administered into different limbs. If blood is transfused, the antibody response to the vaccine may be inhibited—measure rubella antibodies after 6–8 weeks and revaccinate if necessary.

Anti-D (Rh₀) immunoglobulin

**INDICATIONS AND DOSE**

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following birth of rhesus-positive infant

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 500 units, dose to be administered immediately or within 72 hours; for transplacental bleed of over 4 mL fetal red cells, extra 100–125 units per mL fetal red cells, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following any potentially sensitising episode (e.g. stillbirth, abortion, amniocentesis) up to 20 weeks’ gestation

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 250 units per episode, dose to be administered immediately or within 72 hours, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following any potentially sensitising episode (e.g. stillbirth, abortion, amniocentesis) after 20 weeks’ gestation

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 500 units per episode, dose to be administered immediately or within 72 hours, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, antenatal prophylaxis

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 500 units, dose to be given at weeks 28 and 34 of pregnancy, if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, antenatal prophylaxis (alternative NICE recommendation)

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 1000–1650 units, dose to be given at weeks 28 and 34 of pregnancy, alternatively 1500 units for 1 dose, dose to be given between 28 and 30 weeks gestation

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following Rh₀(D) incompatibility blood transfusion

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 100–125 units per mL of transfused rhesus-positive red cells, subcutaneous route used for patients with bleeding disorders

RHOPHYLAC®

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following birth of rhesus-positive infant

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
  - Females of childbearing potential: 1000–1500 units, dose to administered immediately or within 72 hours; for large transplacental bleed, extra 100 units per mL fetal red cells (preferably by intravenous injection), intravenous route recommended for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following any potentially sensitising episode (e.g. abortion, amniocentesis, chorionic villous sampling) up to 12 weeks' gestation

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
  - Females of childbearing potential: 1500 units, dose to be given between weeks 28–30 of pregnancy; if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery, intravenous route recommended for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh₀(D) sensitisation, following Rh₀(D) incompatibility blood transfusion

- **BY INTRAVENOUS INJECTION**
  - Females of childbearing potential: 50 units per mL of transfused rhesus-positive blood, alternatively 100 units per mL of erythrocyte concentrate, intravenous route recommended for patients with bleeding disorders

**CONTRA-INDICATIONS** Treatment of idiopathic thrombocytopenia purpura in rhesus negative patients • treatment of idiopathic thrombocytopenia purpura in splenectomised patients

**CAUTIONS** Immunoglobulin A deficiency • possible interference with live virus vaccines

**CAUTIONS, FURTHER INFORMATION**

MMR vaccine MMR vaccine may be given in the postpartum period with anti-D (Rh₀) immunoglobulin injection provided that separate syringes are used and the products are administered into different limbs. If blood is transfused, the antibody response to the vaccine may be inhibited—measure rubella antibodies after 6–8 weeks and revaccinate if necessary.

**INTERACTIONS** Appendix 1 (immunoglobulins).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Rare Anaphylaxis • dyspnoea • hypotension • tachycardia • urticaria

- Frequency not known Abdominal pain • arthralgia • asthenia • back pain • diarrhoea • dizziness • drowsiness • fever
headache • hypertension • hypotension • injection site pain • malaise • myalgia • nausea • pruritus • rash • sweating • vomiting

**SPECIFIC SIDE-EFFECTS**
- With intravenous use: Abdominal distension • blood pressure fluctuations • deep vein thrombosis • haemolytic anaemia • injection site reactions • myocardial infarction • pulmonary embolism • stroke • thromboembolic events

**HANDLING AND STORAGE** Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. **Refrigerated storage** is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**
- Routine antenatal anti-D prophylaxis for rhesus-negative women (August 2008) NICE TA156
  - Routine antenatal anti-D prophylaxis should be offered to all non-sensitised pregnant women who are rhesus negative.
  - www.nice.org.uk/TA156

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **D-Gam (Bio Products Laboratory Ltd)**
  - Anti-D (RH0) immunoglobulin 250 unit | 1 vial £23.75
  - Anti-D (RH0) immunoglobulin 500 unit | 1 vial £33.75
  - Anti-D (RH0) immunoglobulin 1,500 unit | 1 vial £58.00
- **Rhophylac (CSL Behring UK Ltd)**
  - Anti-D (RH0) immunoglobulin 750 unit per 1 ml Rhophylac 1,500 units/2ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £39.52

**Hepatitis B immunoglobulin**

**INDICATIONS AND DOSE**
- **Prophylaxis against hepatitis B infection**
  - **By intramuscular injection**
    - Adult: 500 units, dose to be administered as soon as possible after exposure; ideally within 12–48 hours, but no later than 7 days after exposure
- **Prophylaxis against hepatitis B infection, after exposure to hepatitis B virus-contaminated material**
  - **By intravenous infusion**
    - Adult: Dose to be administered as soon as possible after exposure, but no later than 72 hours (consult product literature)
- **Prevention of hepatitis B in haemodialysed patients**
  - **By intravenous infusion**
    - Adult: (consult product literature)
- **Prophylaxis against re-infection of transplanted liver**
  - **By intravenous infusion**
    - Adult: (consult product literature)
- **Prevention of hepatitis B re-infection more than 6 months after liver transplantation in stable HBV-DNA negative patients**
  - **By subcutaneous injection**
    - Adult (body-weight up to 75 kg): 500 units once weekly, increased if necessary up to 1000 units once weekly

**dose to be started 2–3 weeks after last dose of intravenous hepatitis B immunoglobulin**
- Adult (body-weight 75 kg and above): 1000 units once weekly, dose to be started 2–3 weeks after last dose of intravenous hepatitis B immunoglobulin

**CAUTIONS**
- IgA deficiency • interference with live virus vaccines

**SIDE-EFFECTS**
**GENERAL SIDE-EFFECTS**
- **Common or very common** Injection site reactions
- **Uncommon** Abdominal pain • anaphylaxis • arthralgia • buccal ulceration • chest pain • dizziness • dyspnoea • glossitis • headache • tremor

**SPECIFIC SIDE-EFFECTS**
- With intravenous use: Abdominal distension • blood pressure fluctuations • deep vein thrombosis • haemolytic anaemia • injection site reactions • myocardial infarction • pulmonary embolism • stroke • thromboembolic events

**PRESCRIBING AND DISPENSING INFORMATION**
Vials containing 200 units or 500 units (for intramuscular injection), available from selected Public Health England and NHS laboratories (except for Transplant Centres), also available from BPL.

**HANDLING AND STORAGE**
Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. **Refrigerated storage** is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Hepatitis B immunoglobulin (Non-proprietary)**
  - Hepatitis B immunoglobulin human 200 unit | 1 vial £122.44
  - Hepatitis B immunoglobulin human 500 unit | 1 vial £266.33
- **Zutectra (Biotest (UK) Ltd)**
  - Zutectra 500 units/1ml solution for injection pre-filled syringes | 5 syringe £1,275.00

**Solution for infusion**
- **Hepactep (Biotest (UK) Ltd)**
  - Hepactep CP human 50 unit per 1 ml | 1 vial £93.35
  - Hepactep CP 200 units/40ml solution for infusion vials | 1 vial £237.50
  - Omri-Hep-B (Imported (Israel))
  - Hepatitis B immunoglobulin human 50 unit per 1 ml | 1 vial £1,150.00

**Normal immunoglobulin**

**INDICATIONS AND DOSE**
- **To control outbreaks of hepatitis A**
  - **By deep intramuscular injection**
    - Adult: 500 mg
- **Rubella in pregnancy, prevention of clinical attack**
  - **By deep intramuscular injection**
    - Females of childbearing potential: 750 mg continued →
Antibody deficiency syndromes

- **BY SUBCUTANEOUS INFUSION**
- **Adult:** (consult product literature)

**SUBGAM**

**Hepatitis A prophylaxis in outbreaks**

- **BY INTRAMUSCULAR INJECTION**
- **Adult:** 750 mg

**UNLICENSED USE**

SUBGAM is not licensed for prophylactic use, but due to difficulty in obtaining suitable immunoglobulin products, Public Health England recommends intramuscular use for prophylaxis against Hepatitis A or rubella.

**CONTRA-INDICATIONS**

Patients with selective IgA deficiency who have known antibody against IgA PRIVIGEN Hyperprolinaemia (contains -proline)

GAMMAPLEX Hereditary fructose intolerance (contains sorbitol)

HIZENTRA Hyperprolinaemia (contains -proline)

FLEBOGAMMA® DIF Hereditary fructose intolerance (contains sorbitol)

**CAUTIONS**

Agammaglobulinaemia with or without IgA deficiency - hypogammaglobulinaemia with or without IgA deficiency - interference with live virus vaccines

**CAUTIONS, FURTHER INFORMATION**

Interference with live virus vaccines. Normal immunoglobulin may interfere with the immune response to live virus vaccines which should therefore only be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).

OCTAGAM False elevated results with blood glucose testing systems (contains maltose)

**INTERACTIONS** → Appendix 1 (immunoglobulins).

**SIDE-EFFECTS**

- **Rare** Acute renal failure - anaphylaxis - aseptic meningitis - cutaneous skin reactions - hypotension
- **Frequency not known** Arthralgia - chills - diarrhoea - dizziness - fever - headache - low back pain - muscle spasms - myalgia - nausea

**SIDE-EFFECTS, FURTHER INFORMATION**

Adverse reactions are more likely to occur in patients receiving normal immunoglobulin for the first time, or following a prolonged period between treatments, or when a different brand of normal immunoglobulin is administered.

**MONITORING REQUIREMENTS**

Monitor for acute renal failure; consider discontinuation if renal function deteriorates. Intravenous preparations with added sucrose have been associated with cases of renal dysfunction and acute renal failure.

**DIRECTIONS FOR ADMINISTRATION**

Preparations for subcutaneous use may be administered by intramuscular injection if subcutaneous route not possible; intramuscular route not for patients with thrombocytopenia or other bleeding disorders.

GAMUNEK® KIOVIG® Use Glucose 5% intravenous infusion if dilution prior to infusion is required.

**PRESCRIBING AND DISPENSING INFORMATION**

Antibody titres can vary widely between normal immunoglobulin preparations from different manufacturers — formulations are not interchangeable; patients should be maintained on the same formulation throughout long-term treatment to avoid adverse effects.

- With intramuscular use Available from the Centre for Infections and other regional Public Health England offices (for contacts and control of outbreaks only).

**HANDLING AND STORAGE**

Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**ELECTROLYTES:** May contain Sodium

- Gammanorm (Octapharma Ltd)
  - Normal immunoglobulin human 165 mg per 1 ml Gammanorm 8g/48ml solution for injection vials | 1 vial [Pom] £469.20
  - Gammanorm 2g/12ml solution for injection vials | 1 vial [Pom] £117.30
  - Gammanorm 4g/24ml solution for injection vials | 1 vial [Pom] £234.60
  - Gammanorm 1.65g/10ml solution for injection vials | 1 vial [Pom] £96.77 | 10 vial [Pom] no price available (Hospital only)
  - Gammanorm 3.3g/20ml solution for injection vials | 1 vial [Pom] £193.55 | 10 vial [Pom] no price available (Hospital only)
  - Gammanorm 1g/6ml solution for injection vials | 1 vial [Pom] £58.65

- Subcutiva (Baxalta UK Ltd)
  - Normal immunoglobulin human 160 mg per 1 ml Subcutiva 800mg/5ml solution for injection vials | 1 vial [Pom] no price available
  - Subcutiva 1.6g/10ml solution for injection vials | 1 vial [Pom] no price available

- Subgam (Bio Products Laboratory Ltd)
  - Normal immunoglobulin human 150 mg per 1 ml Subgam 750mg/5ml solution for injection vials | 1 vial [Pom] £34.20
  - Subgam 1.5g/10ml solution for injection vials | 1 vial [Pom] £68.40

**Powder and solvent for solution for injection**

- Gammagard S/D (Baxalta UK Ltd)
  - Normal immunoglobulin human 500 mg Gammagard S/D 500mg powder and solvent for solution for injection bottles | 1 bottle [Pom] no price available
  - Normal immunoglobulin human 2.5 gram Gammagard S/D 2.5g powder and solvent for solution for injection bottles | 1 bottle [Pom] no price available
  - Normal immunoglobulin human 5 gram Gammagard S/D 5g powder and solvent for solution for injection bottles | 1 bottle [Pom] no price available
  - Normal immunoglobulin human 10 gram Gammagard S/D 10g powder and solvent for solution for injection bottles | 1 bottle [Pom] no price available

**Solution for infusion**

**EXCIPIENTS:** May contain Glucose, maltose, sorbitol, sucrose

- Normal immunoglobulin human 100 mg per 1 ml Normal immunoglobulin human 5g/50ml solution for infusion vials | 1 vial [Pom] no price available
  - Normal immunoglobulin human 2.5g/25ml solution for infusion vials | 1 vial [Pom] no price available
  - Normal immunoglobulin human 20g/200ml solution for infusion vials | 1 vial [Pom] no price available
  - Normal immunoglobulin human 10g/100ml solution for infusion vials | 1 vial [Pom] no price available
  - Normal immunoglobulin human 30g/300ml solution for infusion vials | 1 vial [Pom] no price available

- Aragam (Oxbridge Pharma Ltd)
  - Normal immunoglobulin human 50 mg per 1 ml Aragam 5g/100ml solution for infusion vials | 1 vial [Pom] no price available
  - Aragam 2.5g/50ml solution for infusion vials | 1 vial [Pom] no price available

- FlebogammaDif (Grifols UK Ltd)
  - Normal immunoglobulin human 50 mg per 1 ml Flebogamma Dif 10g/200ml solution for infusion vials | 1 vial [Pom] £10.00
  - Flebogamma Dif 2.5g/50ml solution for infusion vials | 1 vial [Pom] £127.50
Immunoglobulin therapy

Rabies immunoglobulin

- **INDICATIONS AND DOSE**
  - **Post-exposure prophylaxis against rabies infection**
    - **By local infiltration, or by intramuscular injection**
    - **Child:** 20 units/kg, dose administered by infiltration in and around the cleansed wound; if the wound not visible or healed or if infiltration of whole volume not possible, give remainder by intramuscular injection into anterolateral thigh (remote from vaccination site).
    - **Adult:** 20 units/kg, dose administered by infiltration in and around the cleansed wound; if the wound not visible or healed or if infiltration of whole volume not possible, give remainder by intramuscular injection into anterolateral thigh (remote from vaccination site).

- **CAUTIONS**
  - IgA deficiency - interference with live virus vaccines.
  - **SIDE-EFFECTS**
    - Rare: Anaphylaxis, arthralgia, buccal ulceration, chest tightness, dizziness, dyspnoea, glossitis, tremor.
    - Frequency not known: Facial oedema, injection site pain, injection site swelling.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The potency of individual batches of rabies immunoglobulin from the manufacturer may vary; potency may also be described differently by different manufacturers. It is therefore critical to know the potency of the batch to be used and the weight of the patient in order to calculate the specific volume required to provide the necessary dose.
  - Available from Specialist and Reference Microbiology Division, Public Health England (also from BPL).

- **HANDLING AND STORAGE**
  - Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. **Refrigerated storage** is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - **Rabies immunoglobulin (Non-proprietary)**
    - **Rabies immunoglobulin human 500 unit**
      - Rabies immunoglobulin human 500 unit solution for injection vials | 1 vial (Pom) £412.13

Tetanus immunoglobulin

- **INDICATIONS AND DOSE**
  - **Post-exposure prophylaxis**
    - **By intramuscular injection**
    - **Child:** Initially 250 units, then increased to 500 units, dose is only increased if more than 24 hours have elapsed or there is risk of heavy contamination or following burns.
    - **Adult:** Initially 250 units, then increased to 500 units, dose is only increased if more than 24 hours have elapsed or there is risk of heavy contamination or following burns.
Treatment of tetanus infection

- **BY INTRAMUSCULAR INJECTION**
  - Child: 150 units/kg, dose may be given over multiple sites
  - Adult: 150 units/kg, dose may be given over multiple sites

- **CAUTIONS** IgA deficiency - interference with live virus vaccines
- **SIDE-EFFECTS**
  - Rare Anaphylaxis, arthralgia (in children) - buccal ulceration (in children) - chest tightness (in children) - dizziness (in children) - dyspnoea (in children) - glossitis (in children) - tremor (in children)
  - Frequency not known Facial oedema (in children) - injection site swelling - pain at injection site
- **HANDLING AND STORAGE** Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **Varicella-Zoster** (Bio Products Laboratory Ltd)
      - Varicella-Zoster immunoglobulin human 250 mg
      - Varicella-Zoster immunoglobulin human 250 mg solution for injection vials | 1 vial

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<thead>
<tr>
<th>2 Post-exposure prophylaxis</th>
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<tr>
<td>IMMUNE SERA AND IMMUNOGLOBULINS</td>
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<td>ANTITOXINS</td>
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**Botulism antitoxin**

- **DRUG ACTION** A preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by types A, B, and E of *Clostridium botulinum*.

- **INDICATIONS AND DOSE**
  - **Post-exposure prophylaxis of botulism**
    - **BY INTRAMUSCULAR INJECTION**
    - **Adult:** (consult product literature)

- **SIDE-EFFECTS**
  - Hypersensitivity reactions

- **FURTHER INFORMATION**
  - Hypersensitivity reactions It is essential to read the contra-indications, warnings, and details of sensitivity tests on the package insert. Prior to treatment checks should be made regarding previous administration of any antitoxin and history of any allergic condition, e.g. asthma, hay fever, etc.

- **PRE-TREATMENT SCREENING**
  - All patients should be tested for sensitivity (diluting the antitoxin if history of allergy).

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Available from local designated centres, for details see TOXBASE (requires registration) www.toxbase.org. For supplies outside working hours apply to other designated centres or to the Public Health England Colindale duty doctor (Tel (020) 8200 6868). For major incidents, obtain supplies from the local blood bank.

  - The BP title Botulinum Antitoxin is not used because the preparation currently in use may have a different specification.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for infusion**
    - **Botulism-antitoxin** (Novartis Vaccines and Diagnostics Ltd)
      - Botulinum antitoxin type E 50 unit per 1 ml
      - Botulinum antitoxin type B 500 unit per 1 ml
      - Botulinum antitoxin type A 750 unit per 1 ml

  - **Botulinum-Antitoxin Behring** 25g/250ml solution for infusion bottles | 1 bottle

**Varicella-zoster immunoglobulin**

*(Antivaricella-zoster Immunoglobulin)*

- **INDICATIONS AND DOSE**
  - **Prophylaxis against varicella infection**
    - **BY DEEP INTRAMUSCULAR INJECTION**
    - **Adult:** 1 g, to be administered as soon as possible—not later than 10 days after exposure, second dose to be given if further exposure occurs more than 3 weeks after first dose, no evidence that effective in severe disease

- **CAUTIONS** IgA deficiency - interference with live virus vaccines
- **SIDE-EFFECTS**
  - Rare Anaphylaxis
  - Frequency not known Injection site pain - injection site swelling
- **DIRECTIONS FOR ADMINISTRATION** Normal immunoglobulin for intravenous use may be used in those unable to receive intramuscular injections.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Available from selected Public Health England and NHS laboratories (also from BPL).

- **HANDLING AND STORAGE** Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **Varicella-Zoster** (Bio Products Laboratory Ltd)
      - Varicella-Zoster immunoglobulin human 250 mg

<table>
<thead>
<tr>
<th>Diphtheria antitoxin</th>
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<td><em>(Dip/Ser)</em></td>
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| **INDICATIONS AND DOSE**
  - Passive immunisation in suspected cases of diphtheria
    - **BY INTRAVENOUS INFUSION**
    - **Adult:** Dose should be given without waiting for bacteriological confirmation (consult product literature)
## Vaccination

### Tuberculosis diagnostic test

#### DIAGNOSTIC AGENTS

**Tuberculin purified protein derivative** (Tuberculin PPD)

- **INDICATIONS AND DOSE**
  - **Mantoux test**
    - **BY INTRADERMAL INJECTION**
      - Child: 2 units for one dose
      - Adult: 2 units for one dose
  - **Mantoux test (if first test is negative and a further test is considered appropriate)**
    - **BY INTRADERMAL INJECTION**
      - Child: 10 units for 1 dose
      - Adult: 10 units for 1 dose

- **DOSE EQUIVALENCE AND CONVERSION**
  - 2 units is equivalent to 0.1 mL of 20 units/mL strength.
  - 10 units is equivalent to 0.1 mL of 100 units/mL strength.

- **CAUTIONS**
  - Mantoux test: Response to tuberculin may be suppressed by viral infection, sarcoidosis, corticosteroid therapy, or immunosuppression due to disease or treatment and the MMR vaccine. If a tuberculin skin test has already been initiated, then the MMR should be delayed until the skin test has been read unless protection against measles is required urgently. If a child has had a recent MMR, and requires a tuberculin test, then a 4 week interval should be observed. Apart from tuberculin and MMR, all other live vaccines can be administered at any time before or after tuberculin.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Available from ImmForm (SSI brand).
    - The strength of tuberculin PPD in currently available products may be different to the strengths of products used previously for the Mantoux test; care is required to select the correct strength.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

- **Solution for injection**
  - **Tuberculin purified protein derivative (Non-proprietary)**
    - tuberculin purified protein derivative 10 tuberculin unit per 1 ml
    - tuberculin purified protein derivative 20 tuberculin unit per 1 ml
  - **Tuberculin purified protein derivative 100 tuberculin unit per 1 ml**

### 4 Vaccination

#### Vaccines

**Active immunity**

Active immunity can be acquired by natural disease or by vaccination. Vaccines stimulate production of antibodies and other components of the immune mechanism; they consist of either:

- **a live attenuated form of a virus** (e.g. measles, mumps and rubella vaccine) or bacteria (e.g. BCG vaccine), or
- **inactivated preparations of the virus** (e.g. influenza vaccine) or bacteria, or
- **detoxified exotoxins produced by a micro-organism** (e.g. tetanus vaccine), or
- **extracts of a micro-organism**, which may be derived from the organism (e.g. pneumococcal vaccine) or produced by recombinant DNA technology (e.g. hepatitis B vaccine).

**Live attenuated vaccines** usually produce a durable immunity, but not always as long-lasting as that resulting from natural infection.

**Inactivated vaccines** may require a primary series of injections of vaccine to produce an adequate antibody response, and in most cases booster (reinforcing) injections are required; the duration of immunity varies from months to many years. Some inactivated vaccines are adsorbed onto an adjuvant (such as aluminium hydroxide) to enhance the antibody response.

Advice reflects that in the handbook *Immunisation against Infectious Disease* (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI).


The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates.

#### Immunisation schedule

Vaccines for the childhood immunisation schedule should be obtained from local health organisations or from ImmForm ([www.immform.dh.gov.uk](http://www.immform.dh.gov.uk) — not to be prescribed on FP10 (HS21 in Northern Ireland; GP10 in Scotland; WP10 in Wales).

For the most up to date immunisation schedule consult ‘The complete routine immunisation schedule’, available at [www.gov.uk](http://www.gov.uk).

**Preterm birth**

Babies born preterm should receive all routine immunisations based on their actual date of birth. The risk of apnoea following vaccination is increased in preterm babies, particularly in those born at or before 28 weeks gestational age. If babies at risk of apnoea are in hospital at the time of their first immunisation, they should be monitored for 48–72 hours after immunisation. If a baby develops apnoea, bradycardia, or desaturation after the first immunisation, the
# Routine immunisation schedule

<table>
<thead>
<tr>
<th>When to immunise</th>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
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| **Neonates at risk only (see BCG vaccine and Hepatitis B vaccine, below)** | ▶ Bacillus Calmette-Guérin vaccine p. 1159  
▶ Hepatitis B vaccine p. 1165 |
| **2 months** | ▶ Diphtheria with hemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus p. 1158 First dose  
▶ Meningococcal group B vaccine (rDNA, component, adsorbed) p. 1161 First dose  
▶ Pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1162 First dose  
▶ Rotavirus vaccine p. 1170 First dose |
| **3 months** | ▶ Diphtheria with hemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus p. 1158 Second dose  
▶ Rotavirus vaccine p. 1170 Second dose |
| **4 months** | ▶ Diphtheria with hemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus p. 1158 Third dose  
▶ Meningococcal group B vaccine (rDNA, component, adsorbed) p. 1161 Second dose  
▶ Pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1162 Second dose |
| **12-13 months** | ▶ Measles, mumps and rubella vaccine, live p. 1169 First dose  
▶ Meningococcal group B vaccine (rDNA, component, adsorbed) p. 1161 Single booster dose  
▶ Pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1162 Single booster dose  
▶ Haemophilus influenzae type B with meningococcal group C vaccine p. 1160 Single booster dose |
| **2-7 years (including children in school years 1, 2 and 3)** | ▶ Influenza vaccine p. 1167 Each year from September. *Note:* Flu nasal spray is recommended (*Fluenz Tetra*®). If contra-indicated and child is in clinical risk group, use inactivated flu vaccine |
| **Between 3 years and 4 months, and 5 years** | ▶ Diphtheria with pertussis, poliomyelitis vaccine and tetanus p. 1158 Single booster dose. *Note:* Preferably allow interval of at least 3 years after completing primary course  
▶ Measles, mumps and rubella vaccine, live p. 1169 Second dose |
| **11-14 years (females only). First dose of HPV vaccine will be offered to females aged 12-13 years of age in England, Wales, and Northern Ireland, and 11-13 years of age in Scotland.** | ▶ Human papillomavirus vaccines p. 1167 2 doses; second dose 6-24 months after first dose. If a 3-dose course of HPV vaccine has been started under the 2013/2014 programme, where possible, the course should be completed (2 doses less than 6 months apart does not provide long-term protection). The two human papillomavirus vaccines are not interchangeable and, ideally, one vaccine product should be used for the entire course. However, since 2012, only Gardasil® is offered as part of the national immunisation programme; for those females who started the schedule with Cervarix® under the national immunisation programme, but did not complete the vaccination course, the course can be completed with Gardasil®. |
| **13-15 years** | ▶ Meningococcal groups A with C and W135 and Y vaccine p. 1161 Single booster dose |
| **13-18 years** | ▶ Diphtheria with poliomyelitis and tetanus vaccine p. 1158 Single booster dose. *Note:* Can be given at the same time as the dose of meningococcal group A with C and W135 and Y vaccine at 13-15 years of age. |
| **During adult life, women of child-bearing age susceptible to rubella** | ▶ Measles, mumps and rubella vaccine, live p. 1169 Women of child-bearing age who have not received 2 doses of a rubella-containing vaccine or who do not have a positive antibody test for rubella should be offered rubella immunisation (using the MMR vaccine)—exclude pregnancy before immunisation. |
| **Pregnant women** | ▶ Acellular pertussis-containing vaccine administered as diphtheria with pertussis, poliomyelitis vaccine and tetanus p. 1158 (*Boostrix-IPV*®) 1 dose from the 16th week of pregnancy, preferably after the foetal anomaly scan (weeks 18-20)  
▶ Influenza vaccine p. 1167 (inactivated), Single dose administered from September, regardless of the stage of pregnancy |
| **Under 25 years, those entering university who are at risk of meningococcal disease** | ▶ Meningococcal groups A with C and W135 and Y vaccine p. 1161 Single dose. *Note:* Should be offered to those aged under 25 years entering university who have not received the meningococcal groups A with C and W135 and Y vaccine p. 1161 over the age of 10 years |
| **During adult life, if not previously immunised** | ▶ Diphtheria with poliomyelitis and tetanus vaccine p. 1158 |
| **65 years** | ▶ Pneumococcal polysaccharide vaccine p. 1162 |
| **From 65 years** | ▶ Influenza vaccine p. 1167 Each year from September |
| **70 years** | ▶ Varicella-zoster vaccine p. 1171 Single dose |

Second immunisation should also be given in hospital with similar monitoring. Seroconversion may be unreliable in babies born earlier than 28 weeks’ gestation or in babies treated with corticosteroids for chronic lung disease; consideration should be given to testing for antibodies against *Haemophilus influenzae* type b, meningococcal C, and hepatitis B after primary immunisation.

## Vaccines and HIV infection

HIV-positive individuals with or without symptoms can receive the following live vaccines:

- MMR (but avoid if immunity significantly impaired; use of normal immunoglobulin should be considered after exposure to measles), varicella-zoster vaccine against chickenpox (but avoid if immunity significantly impaired—consult product literature; varicella-zoster
immunoglobulin should be considered after exposure to chickenpox or herpes zoster), rotavirus; and the following inactivated vaccines:

- anthrax, cholera (oral), diphtheria, haemophilus influenzae type b, hepatitis A, hepatitis B, human papillomavirus, influenza (injection), meningococcal, pertussis, pneumococcal, poliomyelitis, rabies, tetanus, tick-borne encephalitis, typhoid (injection).

HIV-positive individuals should not receive:
- BCG, influenza nasal spray (unless stable HIV infection and receiving antiretroviral therapy), typhoid (oral), yellow fever (if yellow fever risk is unavoidable, specialist advice should be sought)

The above advice differs from that for other immunocompromised patients; Immunisation Guidelines for HIV-infected Adults issued by British HIV Association (BHIVA) are available at www.bhiva.org and, immunisation of HIV-infected Children issued by Children’s HIV Association (CHIVA) are available at www.chiva.org.uk

Vaccines and asplenia
The following vaccines are recommended for asplenic patients, those with splenic dysfunction or complement disorders, depending on the age at which their condition is diagnosed:

- Haemophilus influenzae type B with meningococcal group C vaccine p. 1160;
- Influenza vaccine p. 1167;
- Meningococcal groups A with C and W135 and Y vaccine p. 1161 and meningococcal group B vaccine (rDNA, component, adsorbed) p. 1161;
- pneumococcal polysaccharide vaccine.

Children first diagnosed under 1 year of age should be vaccinated according to the Immunisation Schedule. Additionally, one dose of meningococcal groups A with C and W135 and Y vaccine should be given during infancy followed by a second dose at least one month apart. Two months following the routine 12 month booster vaccines, give a dose of meningococcal groups A with C and W135 and Y vaccine and an additional dose of 13-valent pneumococcal polysaccharide vaccine. An additional dose of haemophilus influenzae type B with meningococcal group C vaccine and 23-valent pneumococcal polysaccharide vaccine should be given after the second birthday. The influenza vaccine should be administered annually in children aged 6 months or older.

Children first diagnosed between 1 and 2 years of age should be vaccinated according to the Immunisation Schedule, including the 12 month boosters. Two months after the routine 12 month booster vaccines, give a dose of meningococcal groups A with C and W135 and Y vaccine and an additional dose of 13-valent pneumococcal polysaccharide vaccine. An additional dose of haemophilus influenzae type B with meningococcal group C vaccine and 23-valent pneumococcal polysaccharide vaccine should be given after the second birthday. The influenza vaccine should be administered annually.

Children first diagnosed over 2 years of age should be vaccinated according to the Immunisation schedule, including the 12 month boosters. The child should receive one additional booster dose of haemophilus influenzae type B with meningococcal group C vaccine along with the 23-valent pneumococcal polysaccharide vaccine, followed by one dose of meningococcal groups A with C and W135 and Y vaccine after 2 months. The influenza vaccine should be administered annually.

Vaccines and antisera availability
Anthrax vaccine p. 1159 and yellow fever vaccine, live p. 1172, botulism antitoxin p. 1144, diphtheria antitoxin p. 1144, and snake and spider venom antitoxins are available from local designated holding centres.

For antivenom, see Emergency treatment of poisoning p. 1204.

Enquiries for vaccines not available commercially can also be made to:

- Vaccines and Countermeasures Response Department
  Public Health England
  Wellington House
  133–155 Waterloo Road
  London
  SE1 8UG
  vaccinesupply@phe.gov.uk

In Scotland information about availability of vaccines can be obtained from a Specialist in Pharmaceutical Public Health.

In Wales enquiries for vaccines not available commercially should be directed to:
- Welsh Medicines Information Centre
  University Hospital of Wales
  Cardiff
  CF14 4XW
  (029) 2074 2979

In Northern Ireland:
- Pharmacy and Medicines Management Centre
  Northern Health and Social Care Trust
  Beech House
  Antrim Hospital Site
  Bush Road
  Antrim
  BT41 2RL
  rphs.admin@northerntrust.hscni.net

For further details of availability, see under individual vaccines.

Anthrax vaccine
Anthrax vaccine is made from antigens from B. anthracis. Anthrax immunisation is indicated for individuals who handle infected animals, for those exposed to imported infected animal products, and for laboratory staff who work with B. anthracis. A 4-dose regimen is used for primary immunisation; booster doses should be given annually to workers at continued risk of exposure to anthrax.

In the event of possible contact with B. anthracis, post-exposure immunisation may be indicated, in addition to antimicrobial prophylaxis. Advice on the use of anthrax vaccine for post-exposure prophylaxis must be obtained from Public Health England Colindale (tel. 020 8200 4400).

BCG vaccine
Bacillus Calmette-Guérin vaccine p. 1159 should be given intradermally by operators skilled in the technique.

The expected reaction to successful Bacillus Calmette-Guérin vaccine is induration at the site of injection followed by a local lesion which starts as a papule 2 or more weeks after vaccination; the lesion may ulcerate then subside over several weeks or months, leaving a small, flat scar. A dry dressing may be used if the ulcer discharges, but air should not be excluded.

BCG is recommended for the following groups if BCG immunisation has not previously been carried out and they are negative for tuberculosis protein hypersensitivity:

- neonates with a family history of tuberculosis in the last 5 years;
- all neonates and infants (0–12 months) born in areas where the incidence of tuberculosis is greater than 40 per 100 000;
- neonates, infants, and children under 16 years with a parent or grandparent born in a country with an incidence of tuberculosis greater than 40 per 100 000;

newly immigrants aged under 16 years who were born in, or lived for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000;
• new immigrants aged 16–35 years from Sub-Saharan Africa or a country with an incidence of tuberculosis greater than 500 per 100,000;
• contacts aged under 36 years of those with active respiratory tuberculosis (for healthcare or laboratory workers who have had contact with clinical materials or patients with tuberculosis, age limit does not apply);
• healthcare workers and laboratory staff (irrespective of age) who are likely to have contact with patients’ clinical materials, or derived isolates; other individuals under 35 years (there is inadequate evidence of protection by BCG vaccine in adults aged over 35 years; however, vaccination is recommended for healthcare workers irrespective of age because of the increased risk to them or their patients) at occupational risk including veterinary and other staff who handle animal species susceptible to tuberculosis, and staff working directly with prisoners, in care homes for the elderly, or in hostels or facilities for the homeless or refugees;
• individuals under 16 years intending to live with local people for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100,000.

List of countries or primary care trusts where the incidence of tuberculosis is greater than 40 cases per 100,000 is available at www.gov.uk/phe.

Bladder instillations of BCG are licensed for the management of bladder carcinoma.

See also Tuberculosis p. 533 for advice on chemoprophylaxis; for the treatment of infection following vaccination, seek expert advice.

Tuberculosis Diagnostic Agents

The Mantoux test is recommended for tuberculin skin testing, but no licensed preparation is currently available. Guidance for healthcare professionals is available at www.gov.uk/phe.

In the Mantoux test, the diagnostic dose is administered by intradermal injection of tuberculin purified protein derivative (PPD) p. 1145.

The Heaf test (involving the use of multiple puncture apparatus) is no longer available.

Two interferon gamma release assay (IGRA) tests are also available as an aid in the diagnosis of tuberculosis infection: QuantiFERON® TB Gold and T-SPOT. TB. Both tests measure T-cell mediates immune response to synthetic antigens. For further information on the use of interferon gamma release assay tests for tuberculosis, see www.gov.uk/phe.

Botulism antitoxin

A polyvalent botulism antitoxin p. 1144 is available for the post-exposure prophylaxis of botulism and for the treatment of persons thought to be suffering from botulism. It specifically neutralises the toxins produced by Clostridium botulinum types A, B, and E. It is not effective against infantile botulism as the toxin (type A) is seldom, if ever, found in the blood in this type of infection.

Cholera vaccine

Cholera vaccine p. 1160 (oral) contains inactivated Inaba (including El–Tor biotype) and Ogawa strains of Vibrio cholerae, serotype O1 together with recombinant B-subunit of the cholera toxin produced in Inaba strains of V. cholerae, serotype O1.

Oral cholera vaccine is licensed for travellers to endemic or epidemic areas on the basis of current recommendations. Immunisation should be completed at least 1 week before potential exposure. However, there is no requirement for cholera vaccination for international travel.

Injectable cholera vaccine provides unreliable protection and is no longer available in the UK.

Diphtheria vaccine

Diphtheria–containing vaccines are prepared from the toxin of Corynebacterium diphtheriae and adsorption on aluminium hydroxide or aluminium phosphate improves antigenicity. The vaccine stimulates the production of the protective antibody. The quantity of diphtheria toxoid in a preparation determines whether the vaccine is defined as ‘high dose’ or ‘low dose’. Vaccines containing the higher dose of diphtheria toxoid are used for primary immunisation of children under 10 years of age. Vaccines containing the lower dose of diphtheria toxoid are used for primary immunisation in adults and children over 10 years. Single-antigen diphtheria vaccine is not available and adsorbed diphtheria vaccine is given as a combination product containing other vaccines.

For primary immunisation of children aged between 2 months and 10 years vaccination is recommended usually in the form of 3 doses (separated by 1-month intervals) of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (see Immunisation schedule). In unimmunised individuals aged over 10 years the primary course comprises of 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine.

A booster dose should be given 3 years after the primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed). Children under 10 years should receive either adsorbed diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine or adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine. Individuals aged over 10 years should receive adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine. A second booster dose, of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, should be given 10 years after the previous booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed).

Diphtheria-containing vaccines for children over 10 years and adults

A low dose of diphtheria toxoid is sufficient to recall immunity in individuals previously immunised against diphtheria but whose immunity may have diminished with time; it is insufficient to cause serious reactions in an individual who is already immune. Preparations containing low dose diphtheria should be used for adults and children over 10 years, for both primary immunisation and booster doses.

Travel

Those intending to travel to areas with a risk of diphtheria infection should be fully immunised according to the UK schedule. If more than 10 years have lapsed since completion of the UK schedule, a dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine should be administered.

Contacts

Staff in contact with diphtheria patients or with potentially pathogenic clinical specimens or working directly with C. diphtheriae or C. ulcerans should receive a booster dose if fully immunised (with 5 doses of diphtheria-containing vaccine given at appropriate intervals); further doses should be given at 10-year intervals if risk persists. Individuals at risk who are not fully immunised should complete the primary course; a booster dose should be given after 5 years and then at 10-year intervals. Adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine is used for this purpose; immunity should be checked by antibody testing at least 3 months after completion of immunisation.
Advice on the management of cases, carriers, contacts and outbreaks must be sought from health protection units. The immunisation history of infected individuals and their contacts should be determined; those who have been incompletely immunised should complete their immunisation and fully immunised individuals should receive a reinforcing dose. See advice on antibacterial treatment to prevent a secondary case of diphtheria in a non-immune individual.

**Haemophilus influenzae type B conjugate vaccine**

**Haemophilus influenzae type b (Hib) vaccine** is made from capsular polysaccharide; it is conjugated with a protein such as tetanus toxoid to increase immunogenicity, especially in young children. Haemophilus influenzae type b vaccine immunisation is given in combination with diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated vaccine), as a component of the primary course of childhood immunisation (see Immunisation schedule). For infants under 1 year, the course consists of 3 doses of a vaccine containing *Haemophilus influenzae* type b component with an interval of 1 month between doses. A booster dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) should be given at 12–13 months of age.

Children 1–10 years who have not been immunised against *Haemophilus influenzae* type b need to receive only 1 dose of Haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine). However, if a primary course of immunisation has not been completed, these children should be given 3 doses of diphtheria with haemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus p. 1158. The risk of infection falls sharply in older children and the vaccine is not normally required for children over 10 years.

Haemophilus influenzae type b vaccine may be given to those over 10 years who are considered to be at increased risk of invasive *H. influenzae* type b disease (such as those with sickle-cell disease or complement deficiency, or those receiving treatment for malignancy).

**Invasive Haemophilus influenzae type b disease**

After recovery from infection, unimmunised and partially immunised index cases under 10 years of age should complete their age-specific course of immunisation. Previously vaccinated cases under 10 years of age should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if Hib antibody concentrations are low or if it is not possible to measure antibody concentrations. Index cases of any age with asplenia or splenic dysfunction should complete their immunisation according to the recommendations below; fully vaccinated cases with asplenia or splenic dysfunction should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if they received their previous dose over 1 year ago.

See also use of rifampicin p. 535 in the prevention of secondary cases of *Haemophilus influenzae* type b disease.

**Hepatitis A vaccine**

Hepatitis A vaccine p. 1164 is prepared from formaldehyde-inactivated hepatitis A virus grown in human diploid cells. Immunisation is recommended for:

- laboratory staff who work directly with the virus;
- staff and residents of homes for those with severe learning difficulties;
- workers at risk of exposure to untreated sewage;
- individuals who work with primates;
- patients with haemophilia or other conditions treated with plasma-derived clotting factors;
- patients with severe liver disease;
- travellers to high-risk areas;
- individuals who are at risk due to their sexual behaviour;
- parenteral drug abusers.

Immunisation should be considered for:

- patients with chronic liver disease including chronic hepatitis B or chronic hepatitis C;
- prevention of secondary cases in close contacts of confirmed cases of hepatitis A, within 14 days of exposure to the primary case (within 8 weeks of exposure to the primary case where there is more than 1 contact in the household).

A booster dose is usually given 6–12 months after the initial dose. A second booster dose can be given 20 years after the previous booster dose to those who continue to be at risk. Specialist advice should be sought on re-immunisation of immunocompromised individuals.

For rapid protection against hepatitis A after exposure or during an outbreak, in adults a single dose of a monovalent vaccine is recommended; for children under 16 years, a single dose of the combined vaccine Ambirix® can also be used.

Intramuscular normal immunoglobulin p. 1141 is recommended for use in addition to hepatitis A vaccine for close contacts (of confirmed cases of hepatitis A) who have chronic liver disease or HIV infection, or who are immunosuppressed or over 50 years of age.

Post-exposure prophylaxis is not required for healthy children under 1 year of age, so long as all those involved in nappy changing are vaccinated against hepatitis A. However, children 2–12 months of age can be given a dose of hepatitis A vaccine if it is not possible to vaccinate their carers, or if the child becomes a source of infection to others [unlicensed use]; in these cases, if the child goes on to require long-term protection against hepatitis A after the first birthday, the full course of 2 doses should be given.

**Hepatitis B vaccine**

Hepatitis B vaccine p. 1165 contains inactivated hepatitis B virus surface antigen (HBsAg) adsorbed onto aluminium hydroxide adjuvant. It is made biosynthetically using recombinant DNA technology. The vaccine is used in individuals at high risk of contracting hepatitis B. In the UK, groups at high-risk of hepatitis B include:

- parenteral drug misusers, their sexual partners, and household contacts; other drug misusers who are likely to ‘progress’ to injecting;
- individuals who change sexual partners frequently;
- close family contacts of a case or individual with chronic hepatitis B infection;
- babies whose mothers have had acute hepatitis B during pregnancy or are positive for hepatitis B surface antigen (regardless of e-antigen markers); hepatitis B vaccination is started immediately on delivery and hepatitis B immunoglobulin given at the same time (but preferably at a different site). Babies whose mothers are positive for hepatitis B surface antigen and for e-antigen antibody should receive the vaccine only (but babies weighing 1.5 kg or less should also receive the immunoglobulin regardless of the mother’s e-antigen antibody status);
- individuals with haemophilia, those receiving regular blood transfusions or blood products, and carers responsible for the administration of such products;
- patients with chronic renal failure including those on haemodialysis. Haemodialysis patients should be monitored for antibodies annually and re-immunised if necessary. Home carers (of dialysis patients) should be vaccinated;
- individuals with chronic liver disease;
- healthcare personnel (including trainees) who have direct contact with blood or blood-stained body fluids or with patients’ tissues;
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- laboratory staff who handle material that may contain the virus;
- other occupational risk groups such as morticians and embalmers;
- staff and patients of day-care or residential accommodation for those with severe learning difficulties;
- staff and inmates of custodial institutions;
- those travelling to areas of high or intermediate prevalence who are at increased risk or who plan to remain there for lengthy periods;
- families adopting children from countries with a high or intermediate prevalence of hepatitis B;
- foster carers and their families.

Different immunisation schedules for hepatitis B vaccine are recommended for specific circumstances. Generally, three or four doses are required for primary immunisation; an ‘accelerated schedule’ is recommended for pre-exposure prophylaxis in high-risk groups where rapid protection is required, and for post-exposure prophylaxis.

Immunisation may take up to 6 months to confer adequate protection; the duration of immunity is not known precisely, but a single booster 5 years after the primary course may be sufficient to maintain immunity for those who continue to be at risk.

Immunisation does not eliminate the need for commonsense precautions for avoiding the risk of infection from known carriers by the routes of infection which have been clearly established, consult Guidance for Clinical Health Care Workers: Protection against Infection with Blood-borne Viruses (available at www.dh.gov.uk). Accidental inoculation of hepatitis B virus-infected blood into a wound, incision, needle-prick, or abrasion may lead to infection, whereas it is unlikely that indirect exposure to a carrier will do so.

Following significant exposure to hepatitis B, an accelerated schedule, with the second dose given 1 month, and the third dose 2 months after the first dose, is recommended. For those at continued risk, a fourth dose should be given 12 months after the first dose. More detailed guidance is given in the handbook Immunisation against Infectious Disease. Specific hepatitis B immunoglobulin p. 1141 (‘HBIG’) is available for use with the vaccine in those accidentally inoculated and in neonates at special risk of infection.

A combined hepatitis A and B vaccine p. 1163 is also available.

Human papillomavirus vaccine

Human papillomavirus vaccine is available as a bivalent vaccine (Cervarix®) or a quadrivalent vaccine (Gardasil®). Since 2012, only Gardasil® is offered as part of the national immunisation programme. Cervarix® is licensed for use in females for the prevention of cervical cancer and other pre-cancerous lesions caused by human papillomavirus types 16 and 18. Gardasil® is licensed for use in females for the prevention of cervical and anal cancers, genital warts and pre-cancerous genital (cervical, vulvar, and vaginal) and anal lesions caused by human papillomavirus types 6, 11, 16, and 18. The vaccines may also provide limited protection against disease caused by other types of human papillomavirus. The two vaccines are not interchangeable and one vaccine product should be used for an entire course.

Human papillomavirus vaccine will be most effective if given before sexual activity starts. From September 2014, a 2-dose schedule is recommended, as long as the first dose is received before the age of 15 years. The first dose is given to females aged 11 to 14 years, and the second dose is given 6–24 months after the first dose (for the purposes of planning the national immunisation programme, it is appropriate to give the second dose 12 months after the first—see Immunisation schedule). If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose or if the girl is then aged 15 years or more.

Females receiving their first dose aged 15 years or older require a 3-dose schedule (see Cervarix® and Gardasil®), with the second and third doses given 1 and 4–6 months after the first dose; all 3 doses should be given within a 12-month period. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

If a 3-dose course of vaccination had been started before September 2014 in a female aged under 15 years, then where possible this should be completed; the interrupted course should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

Under the national programme in England, females remain eligible to receive the human papillomavirus vaccine up to the age of 18 years if they did not receive the vaccine when scheduled. Where appropriate, immunisation with human papillomavirus vaccine should be offered to females coming into the UK as they may not have been offered protection in their country of origin. The duration of protection has not been established, but current studies suggest that protection is maintained for at least 6 years after completion of the primary course.

As the vaccines do not protect against all strains of human papillomavirus, routine cervical screening should continue.

Influenza vaccine

While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly altering their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that influenza vaccine p. 1167 in use contain the H and N components of the prevalent strain or strains as recommended each year by the World Health Organization.

Immunisation is recommended for persons at high risk, and to reduce transmission of infection. Annual immunisation is strongly recommended for individuals aged over 6 months with the following conditions:

- chronic respiratory disease (includes asthma treated with continuous or repeated use of inhaled or systemic corticosteroids or asthma with previous exacerbations requiring hospital admission);
- chronic heart disease;
- chronic liver disease;
- chronic renal disease at stage 3, 4 or 5;
- chronic neurological disease;
- complement disorders;
- diabetes mellitus;
- immunosuppression because of disease (including asplenia or splenic dysfunction) or treatment (including prolonged systemic corticosteroid treatment [for over 1 month at dose equivalents of prednisolone: adult and child over 20 kg, 20 mg or more daily; child under 20 kg, 1 mg/kg or more daily] and chemotherapy);
- HIV infection (regardless of immune status).

Seasonal influenza vaccine (inactivated) is also recommended for all pregnant women, for all persons aged over 65 years, for residents of nursing or residential homes for the elderly and other long-stay facilities, and for carers of persons whose welfare may be at risk if the carer falls ill. Influenza immunisation should also be considered for household contacts of immunocompromised individuals. The Joint Committee on Vaccination and Immunisation (JCVI) has also advised that morbidity obese people (defined as BMI greater than 40 kg/m²) could also benefit from influenza vaccination.

As part of winter planning, NHS employers should offer vaccination to healthcare workers who are directly involved
in patient care. Employers of social care workers should consider similar action.

Unless contra-indicated, the live influenza vaccine, Fluenz Tetra™, is preferred in children aged 2–17 years because it provides a higher level of protection than inactivated influenza vaccine. In the 2016/2017 national influenza immunisation programme, seasonal influenza vaccine will also be offered to all children aged 2–7 years (including those in school years 1, 2 and 3).

Information on pandemic influenza, avian influenza and swine influenza may be found at www.gov.uk/guidance/pandemic-flu and at www.gov.uk/phe.

Japanese encephalitis vaccine
Japanese encephalitis vaccine p. 1168 is indicated for travellers to areas in Asia and the Far East where infection is endemic and for laboratory staff at risk of exposure to the virus. The primary immunisation course of 2 doses should be completed at least one week before potential exposure to Japanese encephalitis virus.

Up-to-date information on the risk of Japanese encephalitis in specific countries can be obtained from the National Travel Health Network and Centre (www.nathc.net).

Measles, Mumps and Rubella vaccine
Measles vaccine has been replaced by a combined live measles, mumps and rubella vaccine, live p. 1169 (MMR vaccine).

Measles, mumps and rubella vaccine, live aims to eliminate measles, mumps, and rubella (German measles) and congenital rubella syndrome. Each child should receive two doses of measles, mumps and rubella vaccine, live by entry to primary school, unless there is a valid contra-indication. Measles, mumps and rubella vaccine, live should be given irrespective of previous measles, mumps, or rubella infection or vaccination.

The first dose of measles, mumps and rubella vaccine, live is given to children aged 12–13 months. A second dose is given before starting school at 3 years and 4 months–5 years of age (see Immunisation Schedule).

Children presenting for pre-school booster who have not received the first dose of measles, mumps and rubella vaccine, live should be given a dose of measles, mumps and rubella vaccine, live followed 3 months later by a second dose.

At school-leaving age or at entry into further education, measles, mumps and rubella vaccine, live immunisation should be offered to individuals of both sexes who have not received 2 doses during childhood. In those who have received only a single dose of measles, mumps and rubella vaccine, live in childhood, a second dose is recommended to achieve full protection. If 2 doses of measles, mumps and rubella vaccine, live are required, the second dose should be given one month after the initial dose. The decision on whether to vaccinate adults should take into consideration their vaccination history, the likelihood of the individual remaining susceptible, and the future risk of exposure and disease.

Measles, mumps and rubella vaccine, live p. 1169 should be used to protect against rubella in seronegative women of child-bearing age (see Immunisation Schedule); unimmunised healthcare workers who might put pregnant women and other vulnerable groups at risk of rubella or measles should be vaccinated. Measles, mumps and rubella vaccine, live may also be offered to previously unimmunised and seronegative post-partum women (see measles, mumps and rubella vaccine, live)—vaccination a few days after delivery is important because about 60% of congenital abnormalities from rubella infection occur in babies of women who have borne more than one child. Immigrants arriving after the age of school immunisation are particularly likely to require immunisation.

Contacts
Measles, mumps and rubella vaccine, live may also be used in the control of outbreaks of measles and should be offered to susceptible children aged over 6 months who are contacts of a case, within 3 days of exposure to infection. Children immunised before 12 months of age should still receive two doses of measles, mumps and rubella vaccine, live at the recommended ages. If one dose of measles, mumps and rubella vaccine, live has already been given to a child, then the second dose may be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months–5 years should still be given. Children aged under 9 months for whom avoidance of measles infection is particularly important (such as those with history of recent severe illness) can be given normal immunoglobulin after exposure to measles; routine measles, mumps and rubella vaccine, live immunisation should then be given after at least 3 months at the appropriate age.

Measles, mumps and rubella vaccine, live is not suitable for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

Children and adults with impaired immune response should not receive live vaccines (see advice on HIV). If they have been exposed to measles infection they should be given normal immunoglobulin.

Travel
Unimmunised travellers, including children over 6 months, to areas where measles is endemic or epidemic should receive measles, mumps and rubella vaccine, live. Children immunised before 12 months of age should still receive two doses of measles, mumps and rubella vaccine, live at the recommended ages. If one dose of measles, mumps and rubella vaccine, live has already been given to a child, then the second dose should be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months–5 years should still be given.

Meningococcal vaccines
Almost all childhood meningococcal disease in the UK is caused by Neisseria meningitidis serogroups B and C. Meningococcal group C conjugate vaccine protects only against infection by serogroup C and Meningococcal group B vaccine protects only against infection by serogroup B. The risk of meningococcal disease declines with age—immunisation is not generally recommended after the age of 25 years.

Tetravalent meningococcal vaccines that cover serogroups A, C, W135, and Y are available. Although the duration of protection has not been established, the meningococcal groups A, C, W135, and Y conjugate vaccine is likely to provide longer–lasting protection than the unconjugated meningococcal polysaccharide vaccine. The antibody response to serogroup C in unconjugated meningococcal polysaccharide vaccines in young children may be suboptimal [not currently available in the UK].

A meningococcal group B vaccine, Bexsero®, is licensed in the UK against infection caused by Neisseria meningitidis serogroup B and is recommended in the Immunisation Schedule. Bexsero® contains 3 recombinant Neisseria meningitidis serogroup B proteins and the outer membrane vesicles from the NZ.98/254 strain, in order to achieve broad protection against Neisseria meningitidis serogroup B; the proteins are adsorbed onto an aluminium compound to stimulate an enhanced immune response.
Childhood immunisation

Meningococcal group C conjugate vaccine provides long-term protection against infection by serogroup C of *Neisseria meningitidis*. Immunisation consists of 1 dose given at 12 months of age (as the haemophilus influenzae type B with meningococcal group C vaccine p. 1160) and a second dose given at 13–15 years of age (as the meningococcal groups A with C and W135 and Y vaccine p. 1161) (see Immunisation Schedule).

Meningococcal group B vaccine provides protection against infection by serogroup B of *Neisseria meningitidis*. Immunisation consists of 1 dose given at 2 months of age, a second dose at 4 months of age, and a booster dose at 12 months of age (see Immunisation Schedule above).

Unimmunised children aged under 12 months should be given 1 dose of meningococcal group B vaccine (rDNA, component, adsorbed) p. 1161 followed by a second dose of meningococcal group B vaccine (rDNA, component, adsorbed) two months later. They should then be vaccinated according to the Immunisation Schedule (ensuring at least a two month interval between doses of meningococcal group B vaccines). Unimmunised children aged 12–23 months should be given 2 doses meningococcal group B vaccine (rDNA, component, adsorbed) separated by an interval of two months if they have received less than 2 doses in the first year of life. Unimmunised children aged 2–9 years should be given a single dose of meningococcal group C vaccine (as the haemophilus influenzae type B with meningococcal group C vaccine) followed by a booster dose of meningococcal groups A with C and W135 and Y vaccine at 13–15 years of age.

From 2015, unimmunised individuals aged 10–25 years, including those aged under 25 years who are attending university for the first time, should be given a single dose of meningococcal groups A with C and W135 and Y vaccine; a booster dose is not required.

Patients under 25 years of age with confirmed serogroup C disease, who have previously been immunised with meningococcal group C vaccine, should be offered meningococcal group C conjugate vaccine before discharge from hospital.

Travel

Individuals travelling to countries of risk should be immunised with meningococcal groups A, C, W135, and Y conjugate vaccine, even if they have previously received meningococcal group C conjugate vaccine. If an individual has recently received meningococcal group C conjugate vaccine, an interval of at least 4 weeks should be allowed before administration of the tetravalent (meningococcal groups A, C, W135, and Y) vaccine.

Vaccination is particularly important for those living or working with local people or visiting an area of risk during outbreaks.

Immunisation recommendations and requirements for visa entry for individual countries should be checked before travelling, particularly to countries in Sub-Saharan Africa, Asia, and the Indian sub-continent where epidemics of meningococcal outbreaks and infection are reported. Country-by-country information is available from the National Travel Health Network and Centre (www.nathnac.net).

Proof of vaccination with the tetravalent meningococcal groups A with C and W135 and Y vaccine is required for those travelling to Saudi Arabia during the Hajj and Umrah pilgrimages (where outbreaks of the W135 strain have occurred).

Contacts

For advice on the immunisation of laboratory workers and close contacts of cases of meningococcal disease in the UK and on the role of the vaccine in the control of local outbreaks, consult Guidance for Public Health Management of Meningococcal Disease in the UK at www.gov.uk/phe. Also see for antibacterial prophylaxis for prevention of secondary cases of meningococcal meningitis.

The need for immunisation of laboratory staff who work directly with *Neisseria meningitidis* should be considered.

**Pertussis vaccine**

**Pertussis vaccine** is given as a combination preparation containing other vaccines. Acellular vaccines are derived from highly purified components of *Bordetella pertussis*. Primary immunisation against pertussis (whooping cough) requires 3 doses of an acellular pertussis-containing vaccine (see Immunisation Schedule), given at intervals of 1 month from the age of 2 months.

All children up to the age of 10 years should receive primary immunisation with diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed).

A booster dose of an acellular pertussis-containing vaccine should ideally be given 3 years after the primary course, although, the interval can be reduced to 1 year if the primary course was delayed. Children aged 1–10 years who have not received a pertussis-containing vaccine as part of their primary immunisation should be offered 1 dose of a suitable pertussis-containing vaccine; after an interval of at least 1 year, a booster dose of a suitable pertussis-containing vaccine should be given. Immunisation against pertussis is not routinely recommended in individuals over 10 years of age.

**Vaccination of pregnant women against pertussis**

In response to the pertussis outbreak, the UK health departments introduced a temporary programme (October 2012) to vaccinate pregnant women against pertussis, and this programme will continue until further notice. The aim of the programme is to boost the levels of pertussis–specific antibodies that are transferred through the placenta, from the mother to the fetus, so that the newborn is protected before routine immunisation begins at 2 months of age.

Pregnant women should be offered a single dose of acellular pertussis-containing vaccine (as adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine; *Boostrix-IPV®*) between 16 and 32 weeks of pregnancy.

Public Health England has advised (2016) that the vaccine is probably best offered after the foetal anomaly scan at around 18–20 weeks. Pregnant women should be offered a single dose of acellular pertussis-containing vaccine up to the onset of labour if they missed the opportunity for vaccination at 16–32 weeks of pregnancy. A single dose of acellular pertussis-containing vaccine may also be offered to new mothers, who have never previously been vaccinated against pertussis, until the child receives the first vaccination.

While this programme is in place, women who become pregnant again should be offered vaccination during each pregnancy to maximise transplacental transfer of antibody.

**Contacts**

Vaccination against pertussis should be considered for close contacts of cases with pertussis who have been offered antibacterial prophylaxis. Unimmunised or partially immunised contacts under 10 years of age should complete their vaccination against pertussis. A booster dose of an acellular pertussis-containing vaccine is recommended for contacts aged over 10 years who have not received a pertussis-containing vaccine in the last 5 years and who have not received adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine in the last month.

**Side-effects**

Local reactions do not contra–indicate further doses.

The vaccine should not be withheld from children with a history to a preceding dose of:

- fever, irrespective of severity;
• persistent crying or screaming for more than 3 hours;
• severe local reaction, irrespective of extent.

**Pneumococcal vaccine**

Pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1162 protects against infection with *Streptococcus pneumoniae* (pneumococcus); the vaccines contain polysaccharide from capsular pneumococci. **Pneumococcal polysaccharide vaccine** contains purified polysaccharide from 23 capsular types of pneumococci, whereas **pneumococcal polysaccharide conjugate vaccine (adsorbed)** contains polysaccharide from either 10 capsular types (*Synflorix®*) or 13 capsular types (*Prevenar 13®*) and the polysaccharide is conjugated to protein.

The 13-valent conjugate vaccine (*Prevenar 13®*) is used in the childhood immunisation schedule. The recommended schedule consists of 3 doses, the first at 2 months of age, the second at 4 months, and the third at 12–13 months (see Immunisation Schedule).

Pneumococcal polysaccharide conjugate vaccine (adsorbed) is recommended for individuals at increased risk of pneumococcal infection as follows:

• age over 65 years;
• asplenia or splenic dysfunction (including homozygous sickle cell disease and coeliac disease which could lead to splenic dysfunction);
• chronic respiratory disease (includes asthma treated with continuous or frequent use of a systemic corticosteroid);
• chronic heart disease;
• chronic renal disease;
• chronic liver disease;
• chronic neurological conditions;
• complement disorders;
• diabetes mellitus requiring insulin or oral hypoglycaemic drugs;
• immune deficiency because of disease (e.g. HIV infection) or treatment (including prolonged systemic corticosteroid treatment for over 1 month at dose equivalents of prednisolone: adult and child over 20 kg, 20 mg or more daily; child under 20 kg, 1 mg/kg or more daily);
• presence of cochlear implant;
• conditions where leakage of cerebrospinal fluid may occur;
• child under 5 years with a history of invasive pneumococcal disease;
• at risk of occupational exposure to metal fume (e.g. welders).

Where possible, the vaccine should be given at least 2 weeks before splenectomy, cochlear implant surgery, chemotherapy, or radiotherapy; patients should be given advice about increased risk of pneumococcal infection. If it is not practical to vaccinate at least 2 weeks before splenectomy, chemotherapy, or radiotherapy, the vaccine should be given at least 2 weeks after the splenectomy or, where possible, at least 3 months after completion of chemotherapy or radiotherapy. Propylactic antibacterial therapy against pneumococcal infection should not be stopped after immunisation. A patient card and information leaflet for patients with asplenia are available from the Department of Health or in Scotland from the Scottish Government, Health Protection Division (Tel (0131) 244 2879).

**Choice of vaccine**

Children under 2 years at increased risk of pneumococcal infection (see list) should receive the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) at the recommended ages, followed by a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday. Children at increased risk of pneumococcal infection presenting late for vaccination should receive 2 doses (separated by at least 1 month) of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) before the age of 12 months, and a third dose at 12–13 months. Children over 12 months and under 5 years (who have not been vaccinated or not completed the primary course) should receive a single dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) (2 doses separated by an interval of 2 months in the immunocompromised or those with asplenia or splenic dysfunction). All children under 5 years at increased risk of pneumococcal infection should receive a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday and at least 2 months after the final dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed).

Children over 5 years and adults who are at increased risk of pneumococcal disease should receive a single dose of the 23-valent unconjugated pneumococcal polysaccharide vaccine.

**Revaccination**

In individuals with higher concentrations of antibodies to pneumococcal polysaccharides, revaccination with the 23-valent pneumococcal polysaccharide vaccine more commonly produces adverse reactions. Revaccination is therefore not recommended, except every 5 years in individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia, splenic dysfunction and nephrotic syndrome). If there is doubt, the need for revaccination should be discussed with a haematologist, immunologist, or microbiologist.

**Poliomyelitis vaccine**

Two types of poliomyelitis vaccines (containing strains of poliovirus types 1, 2, and 3) are available, inactivated poliomyelitis vaccine (for injection) and live (oral) poliomyelitis vaccine. **Inactivated** poliomyelitis vaccines, only available in combined preparation, is recommended for routine immunisation.

A course of primary immunisation consists of 3 doses of a combined preparation containing inactivated poliomyelitis vaccines, starting at 2 months of age with intervals of 1 month between doses (see Immunisation schedule). A course of 3 doses should also be given to all unimmunised adults; no adult should remain unimmunised against poliomyelitis.

Two booster doses of a preparation containing inactivated poliomyelitis vaccines are recommended, the first before school entry and the second before leaving school (see Immunisation schedule). Further booster doses are only necessary for adults at special risk, such as travellers to endemic areas, or laboratory staff likely to be exposed to the viruses, or healthcare workers in possible contact with cases; booster doses should be given to such individuals every 10 years.

**Live (oral) poliomyelitis vaccine** is no longer available for routine use; its use may be considered during large outbreaks, but advice should be sought from Public Health England. The live (oral) vaccine poses a very rare risk of vaccine-associated paralytic polio because the attenuated strain of the virus can revert to a virulent form. For this reason the live (oral) vaccine must not be used for immunosuppressed individuals or their household contacts. The use of inactivated poliomyelitis vaccines removes the risk of vaccine-associated paralytic polio altogether.

**Travel**

Unimmunised travellers to areas with a high incidence of poliomyelitis should receive a full 3-dose course of a preparation containing inactivated poliomyelitis vaccines. Those who have not been vaccinated in the last 10 years should receive a booster dose of **adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine**. Information about countries with a high incidence of poliomyelitis can be obtained from [www.travax.nhs.uk](http://www.travax.nhs.uk) or from the National Travel Health Network and Centre ([www.nathic.net](http://www.nathic.net)).
Rabies vaccine
Rabies vaccine p. 1170 contains inactivated rabies virus cultivated in either human diploid cells or purified chick embryo cells; vaccines are used for pre- and post-exposure prophylaxis.

Pre-exposure prophylaxis
Immunisation should be offered to those at high risk of exposure to rabies—laboratory staff who handle the rabies virus, those working in quarantine stations, animal handlers, veterinary surgeons and field workers who are likely to be bitten by infected wild animals, certain port officials, and bat handlers. Transmission of rabies by humans has not been recorded but it is advised that those caring for patients with the disease should be vaccinated.

Immunisation against rabies is also recommended where there is limited access to prompt medical care for those living in areas where rabies is enzootic, for those travelling to such areas for longer than 1 month, and for those on shorter visits who may be exposed to unusual risk.

Immunisation against rabies is indicated during pregnancy if there is substantial risk of exposure to rabies and rapid access to post-exposure prophylaxis is likely to be limited.

Up-to-date country-by-country information on the incidence of rabies can be obtained from the National Travel Health Network and Centre (www.nathnac.net) and, in Scotland, from Health Protection Scotland (www.hps.scot.nhs.uk).

Immunisation against rabies requires 3 doses of rabies vaccine, with further booster doses for those who remain at frequent risk. To ensure continued protection in persons at high risk (e.g. laboratory workers), the concentration of antirabies antibodies in plasma is used to determine the intervals between doses.

Post-exposure management
Following potential exposure to rabies, the wound or site of exposure (e.g. mucous membrane) should be cleansed under running water and washed for several minutes with soapy water as soon as possible after exposure. Disinfectant and a simple dressing can be applied, but suturing should be delayed because it may increase the risk of introducing rabies virus into the nerves.

Post-exposure prophylaxis against rabies depends on the level of risk in the country, the nature of exposure, and the individual’s immunity. In each case, expert risk assessment and advice on appropriate management should be obtained from the local Public Health England Centre or Public Health England’s Virus Reference Department, Colindale (tel. (020) 8200 4400) or the PHE Colindale Duty Doctor (tel. (020) 8200 6868), in Wales from the Public Health Wales local Health Protection Team or Public Health Wales Virus Reference Laboratory (tel. (029) 2074 7747), in Scotland from the local on-call infectious diseases consultant, and in Northern Ireland from the Public Health Agency Duty Room (tel (028) 9055 3997/(028) 9063 2662) or the Regional Virology Service (tel. (028) 9024 0503).

There are no specific contra-indications to the use of rabies vaccine for post-exposure prophylaxis and its use should be considered whenever a patient has been attacked by an animal in a country where rabies is enzootic, even if there is no direct evidence of rabies in the attacking animal. Because of the potential consequences of untreated rabies exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis.

For post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine), 2 doses of cell-derived vaccine are likely to be sufficient; the first dose is given on day 0 and the second dose is given between day 3–7. Rabies immunoglobulin p. 1143 is not necessary in such cases.

Post-exposure treatment for unimmunised individuals (or those whose prophylaxis is possibly incomplete) comprises 5 doses of rabies vaccine given over 1 month (on days 0, 3, 7, 14, and the fifth dose is given between day 28–30); also, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin p. 1143 is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine p. 1170. The immunisation course can be discontinued if it is proved that the individual was not at risk.

Rabies immunoglobulin
Rabies immunoglobulin p. 1145 contains human antirabies serum and is produced by the fractionation of human plasma. It is used to prevent rabies in persons who are at risk of exposure to rabies but who have neither been vaccinated against rabies nor received post-exposure prophylaxis.

Vaccination should be performed as soon as possible after exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis.

For post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine), 2 doses of cell-derived vaccine are likely to be sufficient; the first dose is given on day 0 and the second dose is given between day 3–7. Rabies immunoglobulin p. 1143 is not necessary in such cases.

Post-exposure treatment for unimmunised individuals (or those whose prophylaxis is possibly incomplete) comprises 5 doses of rabies vaccine given over 1 month (on days 0, 3, 7, 14, and the fifth dose is given between day 28–30); also, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin p. 1143 is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine p. 1170. The immunisation course can be discontinued if it is proved that the individual was not at risk.

Rotavirus vaccine
Rotavirus vaccine p. 1170 is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection. The recommended schedule consists of 2 doses, the first at 2 months of age, and the second at 3 months of age (see Immunisation schedule). The first dose of rotavirus vaccine must be given between 6–15 weeks of age and the second dose should be given after an interval of at least 4 weeks; the vaccine should not be started in children 15 weeks of age or older. Ideally, the full course should be completed before 16 weeks of age to provide protection before the main burden of disease, and to avoid a temporal association between vaccination and intussusception; the course must be completed before 24 weeks of age.

The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; however, vaccination of those with immunosuppressed close contacts may protect the contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus. Carers of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby’s nappies.

Smallpox vaccine
Limited supplies of smallpox vaccine are held at the Specialist and Reference Microbiology Division, Public Health England Colindale (Tel. (020) 8200 4400) for the exclusive use of workers in laboratories where pox viruses (such as vaccinia) are handled.

If a wider use of the vaccine is being considered, Guidelines for smallpox response and management in the post-eradication era should be consulted at www.gov.uk/phe.

Tetanus vaccine
Primary immunisation for children under 10 years consists of 3 doses of a combined preparation containing adsorbed tetanus vaccine, with an interval of 1 month between doses. Following routine childhood vaccination, 2 booster doses of a preparation containing adsorbed tetanus vaccine are recommended, the first before school entry and the second before leaving school (see Immunisation schedule).

The recommended schedule of tetanus vaccination not only provides protection against tetanus in childhood but also gives the basic immunity for subsequent booster doses. In most circumstances, a total of 5 doses of tetanus vaccine is considered sufficient for long term protection.

For primary immunisation of adults and children over 10 years previously unimmunised against tetanus, 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine are given with an interval of 1 month between doses (see Diphtheria-containing Vaccines).

When an individual presents for a booster dose but has not been vaccinated following a tetanus-prone wound, the vaccine preparation administered at the time of injury should be determined. If this is not possible, the booster
For Typhoid vaccine most prevalent, are at greatest risk of tick-borne Japan, particularly from April to November when ticks are warm forested areas of Central and Eastern Europe, in chick embryo cells. It is recommended for immunisation Tick-borne encephalitis vaccine, inactivated p.

\[\text{capsular polysaccharide}\] typhoid vaccine is usually given by intramuscular injection. Children under 2 years may respond suboptimally to the vaccine, but children aged between 1–2 years should be immunised if the risk of typhoid fever is considered high (immunisation is not recommended for infants under 12 months). Revaccination is needed every 3 years on continued exposure.

**Oral** typhoid vaccine p. 1163 is a live attenuated vaccine contained in an enteric-coated capsule. One capsule taken on alternate days for a total of 3 doses, provides protection 7–10 days after the last dose. Protection may persist for up to 3 years in those constantly (or repeatedly) exposed to Salmonella typhi, but those who only occasionally travel to endemic areas require further courses at intervals of 1 year.

**Varicella-zoster vaccine**

The live varicella–zoster vaccine p. 1171, Varilrix® and Varivax®, are licensed for immunisation against varicella (chickenpox) in seronegative individuals. They are not recommended for routine use in children, but can be given to seronegative healthy children over 1 year who come into close contact with individuals at high risk of severe varicella infection. The Department of Health recommends these vaccines for seronegative healthcare workers who come into direct contact with patients. Those with a history of chickenpox or shingles can be considered immune, but healthcare workers with a negative or uncertain history should be tested.

Rarely, the varicella–zoster vaccine virus has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:

- varicella-susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy;
- Healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with patients until the lesions have crusted. Those who develop a localised rash after vaccination should cover the lesions and be allowed to continue working unless in contact with patients at high risk of severe varicella.

**National shingles immunisation programme**

The aim of the national shingles immunisation programme is to lower the incidence and severity of shingles in older people using the high potency, live varicella–zoster vaccine, Zostavax®. It is recommended that vaccination is routinely offered to people aged 70 years. A catch-up programme has also been rolled out (since 2013) in those aged 70–79 years, as this age group is likely to have the greatest benefit from vaccination.

In the 2016–2017 immunisation programme, varicella–zoster vaccine is recommended in adults who were 70 or 78 years of age on 1st September 2016. Patients who were eligible for vaccination in the first 3 years of the programme but have not been vaccinated against herpes zoster remain eligible until their 80th birthday; this includes patients who were aged 71–73 or 79 on 1st September 2016. Patients who have reached 80 years are no longer eligible for vaccination. A single dose of Zostavax® is likely to give protection for at least 7 years, but the need for, or timing of, a booster dose has not been established. Although Zostavax® is not recommended for the treatment of shingles or post-herpetic neuralgia, it can be given to those with a previous history of shingles; ideally the vaccine should be delayed until systemic antiviral therapy has been completed.

Varicella–zoster immunoglobulin p. 1144 is used to protect susceptible individuals at increased risk of varicella infection.
Yellow fever vaccine

Yellow fever vaccine, live p. 1172 is indicated for those travelling or living in areas where infection is endemic and for laboratory staff who handle the virus or who handle clinical material from suspected cases. Infants under 6 months of age should not be vaccinated because there is a small risk of encephalitis; infants aged 6–9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (seek expert advice). The immunity which probably lasts for life is officially accepted for 10 years starting from 10 days after primary immunisation and for a further 10 years immediately after revaccination.

Vaccines for travel

Immunisation

See advice on Malaria, treatment p. 566.

No special immunisation is required for travellers to the United States, Europe, Australia, or New Zealand, although all travellers should have immunity to tetanus and poliomyelitis (and childhood immunisations should be up to date); Tick-borne encephalitis vaccine is recommended for immunisation of those working in, or visiting, high-risk areas. Certain special precautions are required in non-European areas surrounding the Mediterranean, in Africa, the Middle East, Asia, and South America.

Travellers to areas that have a high incidence of poliomyelitis or tuberculosis should be immunised with the appropriate vaccine; in the case of poliomyelitis previously immunised travellers may be given a booster dose of a preparation containing inactivated poliomyelitis vaccine. BCG immunisation is recommended for travellers aged under 16 years proposing to stay for longer than 3 months (or in close contact with the local population) in countries with an incidence of tuberculosis greater than 40 per 100,000 (list of countries where the incidence of tuberculosis is greater than 40 cases per 100,000 is available from www.gov.uk/phe); it should preferably be given 3 months or more before departure.

Yellow fever immunisation is recommended for travel to the endemic zones of Africa and South America. Many countries require an International Certificate of Vaccination from individuals arriving from, or who have been travelling through, endemic areas; other countries require a certificate from all entering travellers (consult the Department of Health handbook, Health Information for Overseas Travel, www.dh.gov.uk).

Immunisation against meningococcal meningitis is recommended for a number of areas of the world.

Protection against hepatitis A is recommended for travellers to high-risk areas outside Northern and Western Europe, North America, Japan, Australia and New Zealand. Hepatitis A vaccine is preferred and it is likely to be effective even if given shortly before departure; normal immunoglobulin is no longer given routinely but may be indicated in the immunocompromised. Special care must also be taken with food hygiene.

Hepatitis B vaccine is recommended for those travelling to areas of high or intermediate prevalence who intend to remain there for lengthy periods and who may therefore be at increased risk of acquiring infection as the result of medical or dental procedures carried out in those countries. Short-term tourists or business travellers are not generally at increased risk of infection but may put themselves at risk by their sexual behaviour when abroad.

Prophylactic immunisation against rabbies is recommended for travellers to enzootic areas on long journeys or to areas out of reach of immediate medical attention.

Travellers who have not had a tetanus booster in the last 10 years and are visiting areas where medical attention may not be accessible should receive a booster dose of adsorbable diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, even if they have received 5 doses of a tetanus-containing vaccine previously.

Typhoid vaccine is indicated for travellers to countries where typhoid is endemic, but the vaccine is no substitute for personal precautions.

There is no requirement for cholera vaccination as a condition for entry into any country, but oral cholera vaccine should be considered for backpackers and those travelling to situations where the risk is greatest (e.g. refugee camps). Regardless of vaccination, travellers to areas where cholera is endemic should take special care with food hygiene.

Advice on diphtheria, on Japanese encephalitis, and on tick-borne encephalitis is included in Health Information for Overseas Travel.

Food hygiene

In areas where sanitation is poor, good food hygiene is important to help prevent hepatitis A, typhoid, cholera, and other diarrhoeal diseases (including travellers’ diarrhoea). Food should be freshly prepared and hot, and uncooked vegetables (including green salads) should be avoided; only fruits which can be peeled should be eaten. Only suitable bottled water, or tap water that has been boiled or treated with sterilising tablets, should be used for drinking.

Information on health advice for travellers

Health professionals and travellers can find the latest information on immunisation requirements and precautions for avoiding disease while travelling from: www.nathnac.net.

The handbook, Health Information for Overseas Travel (2010), which draws together essential information for healthcare professionals regarding health advice for travellers, can also be obtained from this website.

Immunisation requirements change from time to time, and information on the current requirements for any particular country may be obtained from the embassy or legation of the appropriate country or from:

National Travel Health Network and Centre
UCLH NHS Foundation Trust
3rd Floor Central
250 Euston Road
London, NW1 2PG
Tel: 0845 602 6712
(8:30–11:45 a.m., 1–3:15 p.m. weekdays for healthcare professionals only)
www.nathnac.net

Travel Medicine Team
Health Protection Scotland
Meridian Court
5 Cadogan Street
Glasgow, G2 6QE
Tel: (0141) 300 1130
(2–4 p.m. Monday to Wednesday, 9:30–11:30 a.m. Friday;
for registered TRAVAX users only)
www.travax.nhs.uk

(TRAVAX is free for NHS Scotland users (registration required); subscription fee may be payable for users outside NHS Scotland)

Welsh Assembly Government
Tel (029) 2082 5397
(9 a.m.–5:30 p.m. weekdays)

Department of Health, Social Services and Public Safety
Castle Buildings
Stormont
Belfast, BT4 3SQ
Tel: (028) 9052 2118
(9 a.m.–5 p.m. weekdays)
www.dhsspsni.gov.uk
VACCINES

Vaccines

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE (APRIL 2016)

Following reports of death in neonates who received a live attenuated vaccine after exposure to a tumor necrosis factor alpha (TNF-α) inhibitor in utero, the MHRA has issued the following advice:

- any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible;
- in the case of infants who have been exposed to TNF-α inhibitors and other biological medicines in utero, any live attenuated vaccination should be deferred until the infant is age 6 months, after which time vaccination should be considered.

CONTRA-INDICATIONS

CONTRA-INDICATIONS, FURTHER INFORMATION

Impaired immune response Severely immunosuppressed patients should not be given live vaccines (including those with severe primary immunodeficiency).

CAUTIONS Acute illness - minor illnesses

CAUTIONS, FURTHER INFORMATION

Vaccination may be postponed if the individual is suffering from an acute illness; however, it is not necessary to postpone immunisation in patients with minor illnesses without fever or systemic upset.

Impaired immune response and drugs affecting immune response Immune response to vaccines may be reduced in immunosuppressed patients and there is also a risk of generalised infection with live vaccines.

Specialist advice should be sought for those being treated with high doses of corticosteroids (dose equivalents of prednisolone: adults, at least 40 mg daily for more than 1 week; children, 2 mg/kg (or more than 40 mg) daily for at least 1 week or 1 mg/kg daily for 1 month), or other immunosuppressive drugs, and those being treated for malignant conditions with chemotherapy or generalised radiotherapy. Live vaccines should be postponed until at least 3 months after stopping high-dose systemic corticosteroids and at least 6 months after stopping other immunosuppressive drugs or generalised radiotherapy (at least 12 months after discontinuing immunosuppressants following bone-marrow transplantation).


Predisposition to neurological problems When there is a personal or family history of febrile convulsions, there is an increased risk of these occurring during fever from any cause including immunisation, but this is not a contra-indication to immunisation. In children who have had a seizure associated with fever without neurological deterioration, immunisation is recommended; advice on the management of fever (see Post-immunisation Pyrexia in Infants) should be given before immunisation. When a child has had a convolution not associated with fever, and the neurological condition is not deteriorating, immunisation is recommended.

Children with stable neurological disorders (e.g. spina bifida, congenital brain abnormality, and peri-natal hypoxic-ischaemic encephalopathy) should be immunised according to the recommended schedule.

When there is a still evolving neurological problem, including poorly controlled epilepsy, immunisation should be deferred and the child referred to a specialist. Immunisation is recommended if a cause for the neurological disorder is identified. If a cause is not identified, immunisation should be deferred until the condition is stable.

INTERACTIONS → Appendix 1 (vaccines).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Common or very common Fatigue, fever, gastro-intestinal disturbances, headache, irritability, loss of appetite, lymphangitis, malaise, myalgia
- Very rare Anaphylaxis (can be fatal), angioedema (can be fatal), bronchospasm (can be fatal), hypersensitivity reactions (can be fatal), urticaria (can be fatal)

FREQUENCY NOT KNOWN Arthralgia, asthenia, dizziness, drowsiness, influenza-like symptoms, lymphadenopathy, paraesthesia, rash

SPECIFIC SIDE-EFFECTS

- Common or very common

With intradermal use or intramuscular use or subcutaneous use Induration may develop at the injection site, inflammation, local reactions, pain, redness, sterile abscess may develop at the injection site

SIDE-EFFECTS, FURTHER INFORMATION Occasionally serious adverse reactions can occur—these should always be reported to the CHM.

Post-immunisation pyrexia in infants The parent should be advised that if pyrexia develops after childhood immunisation, and the infant seems distressed, paracetamol can be given. Ibuprofen can be used if paracetamol is unsuitable. The parent should be warned to seek medical advice if the pyrexia persists.

ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a confirmed anaphylactic reaction to a preceding dose of a vaccine containing the same antigens or vaccine component (such as antibacterials in viral vaccines).

PREGNANCY Live vaccines should not be administered routinely to pregnant women because of the theoretical risk of fetal infection but where there is a significant risk of exposure to disease, the need for vaccination usually outweighs any possible risk to the fetus. Termination of pregnancy following inadvertent immunisation is not recommended. There is no evidence of risk from vaccinating pregnant women with inactivated viral or bacterial vaccines or toxoids.

BREAST FEEDING Although there is a theoretical risk of live vaccine being present in breast milk, vaccination is not contra-indicated for women who are breast-feeding when there is significant risk of exposure to disease. There is no evidence of risk from vaccinating women who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids.

DIRECTIONS FOR ADMINISTRATION If alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination to prevent possible inactivation of live vaccines.

When 2 or more live vaccines are required (and are not available as a combined preparation), they can be administered at any time before or after each other at different sites, preferably in a different limb; if more than one injection is to be given in the same limb, they should be administered at least 2.5 cm apart. See also Bacillus Calmette-Guérin vaccine p. 1159.

Vaccines should not be given intravenously. Most vaccines are given by the intramuscular route, although some are given by either the intradermal, deep subcutaneous, or oral route. The intramuscular route should not be used in patients with bleeding disorders.
such as haemophilia or thrombocytopenia, vaccines usually given by the intramuscular route should be given by deep subcutaneous injection instead.

The Department of Health has advised against the use of jet guns for vaccination owing to the risk of transmitting blood borne infections, such as HIV.

Particular attention must be paid to instructions on the use of diluents. Vaccines which are liquid suspensions or are reconstituted before use should be adequately mixed to ensure uniformity of the material to be injected.

**HANDLING AND STORAGE** Care must be taken to store all vaccines under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many vaccines need to be stored at 2–8°C and not allowed to freeze. Vaccines should be protected from light. Reconstituted vaccines and opened multidose vials must be used within the period recommended in the product literature. Unused vaccines should be disposed of by incineration at a registered disposal contractor.

**VACCINES > BACTERIAL AND VIRAL VACCINES, COMBINED**

Diphtheria with haemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus

**INDICATIONS AND DOSE**

Primary immunisation

- **By Intramuscular Injection**
  - Child 2 months-10 years: 0.5 mL every month for 3 doses

**Unlicensed Use** Infanrix-IPV + Hib® not licensed for use in children over 36 months; Pediacel not licensed in children over 4 years. However, the Department of Health recommends that these be used for children up to 10 years.

**SIDE-EFFECTS** Atopic dermatitis · hypotonia · restlessness · sleep disturbances · unusual crying in infants

**SIDE-EFFECTS, FURTHER INFORMATION**

- Side effects of vaccines containing pertussis. The incidence of local and systemic effects is generally lower with vaccines containing acellular pertussis components than with the whole-cell pertussis vaccine used previously. However, compared with primary vaccination, booster doses with vaccines containing acellular pertussis are reported to increase the risk of injection-site reactions (some of which affect the entire limb); local reactions do not contraindicate further doses.

  - The vaccine should not be withheld from children with a history to a preceding dose of:
    - fever, irrespective of severity;
    - persistent crying or screaming for more than 3 hours;
    - severe local reaction, irrespective of extent.

**PREGNANCY** Contra-indicated in pregnant women with a history of encephalopathy of unknown origin within 7 days of previous immunisation with a pertussis-containing vaccine. Contra-indicated in pregnant women with a history of transient thrombocytopenia or neurological complications following previous immunisation against diphtheria or tetanus.

**PRESCRIBING AND DISPENSING INFORMATION** Pregnant women should be vaccinated using low dose vaccines (brands may include Boostrix-IPV® or Repevax®).

Available as part of childhood immunisation schedule from health organisations or ImmForm.

Available for vaccination of pregnant women from ImmForm.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**EXCIPIENTS:** May contain Neomycin, polymyxin b, streptomycin

- Pediacel (sanofi pasteur MSD Ltd)
  - Pediacel vaccine suspension for injection 0.5mL vials | 1 vial [PoS] £32.00

- Infanrix-IPV + Hib (GlaxoSmithKline UK Ltd)
  - Infanrix-IPV + Hib vaccine powder and suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection [PoS] £27.86

**Diphtheria with poliomyelitis and tetanus vaccine**

**INDICATIONS AND DOSE**

Primary immunisation

- **By Intramuscular Injection**
  - Child 10–17 years: 0.5 mL every month for 3 doses
  - Adult: 0.5 mL every month for 3 doses
Booster doses

- **BY INTRAMUSCULAR INJECTION**
  - Child 10–17 years: 0.5 mL for 1 dose, first booster dose—should be given 3 years after primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed), then 0.5 mL for 1 dose, second booster dose—should be given 10 years after first booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed), second booster dose may also be used as first booster dose in those over 10 years who have received only 3 previous doses of a diphtheria-containing vaccine
  - Adult: 0.5 mL for 1 dose, first booster dose—should be given 3 years after primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed), then 0.5 mL for 1 dose, second booster dose—should be given 10 years after first booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed), second booster dose may also be used as first booster dose in those over 10 years who have received only 3 previous doses of a diphtheria-containing vaccine.

**SIDE-EFFECTS** Restlessness · sleep disturbances · unusual crying in infants

**PRESCRIBING AND DISPENSING INFORMATION** Available as part of childhood schedule from health organisations or ImmForm.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Suspension for Injection**
- Revaxis (sanofi pasteur MSD Ltd)
  - Revaxis vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection

**VACCINES**

### Anthrax vaccine

#### INDICATIONS AND DOSE

**Pre-exposure immunisation against anthrax | Post-exposure immunisation**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 1 dose every 3 weeks for 3 doses, followed by 1 dose after 6 months, to be administered in the deltoid region, 1 dose is equivalent to 0.5 mL.

**Booster**

- **BY INTRAMUSCULAR INJECTION**

- Adult: 1 dose every 12 months, to be administered in deltoid region, 1 dose is equivalent to 0.5 mL.


**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Suspension for Injection**
- EXCIPIENTS: May contain Thiomersal
- Anthrax vaccine (Non-proprietary)
  - Anthrax vaccine (alum precipitated sterile filtrate) suspension for injection 0.5mL ampoules | 5 ampoule

### Bacillus Calmette-Guérin vaccine

**DRUG ACTION**

BCG (Bacillus Calmette-Guérin) is a live attenuated strain derived from *Mycobacterium bovis* which stimulates the development of immunity to *M. tuberculosis*.

#### INDICATIONS AND DOSE

**Immunisation against tuberculosis**

- **BY INTRADERMAL INJECTION**
  - Child 1–11 months: 0.05 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.
  - Child 1–17 years: 0.1 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.
  - Adult: 0.1 mL, to be injected in deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.

#### CONTRA-INDICATIONS
Generalised septic skin conditions

#### CAUTIONS

**CAUTIONS, FURTHER INFORMATION**

BCG vaccine can be given simultaneously with another live vaccine, but if they are not given at the same time an interval of 4 weeks should normally be allowed. When BCG is given to infants, there is no need to delay routine primary immunisations. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of regional lymphadenitis.

**SIDE-EFFECTS**

- Rare: Disseminated complications · osteitis · osteomyelitis
- Frequency not known: Prolonged ulceration at the injection site · subcutaneous abscess at the injection site

**PRE-TREATMENT SCREENING**

Apart from children under 6 years, any person being considered for BCG immunisation must first be given a skin test for hypersensitivity to tuberculoprotein (see tuberculin purified protein derivative p. 1145). A skin test is not necessary for a child under 6 years provided that the child has not stayed for longer than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000, the child has not had contact with a person with tuberculosis, and there is no family history of tuberculosis within the last 5 years.

**DIRECTIONS FOR ADMINISTRATION**

**Intradermal injection technique**

Skin is stretched between thumb and forefinger and needle (size 25G or 26G) inserted (bevel upwards) for about 3 mm into superficial layers of dermis (almost parallel with surface). Needle should be short with short bevel (can usually be seen through epidermis during insertion). Tense raised blanched bleb showing tips of hair follicles is sign of correct injection; 7 mm bleb = 0.1 mL injection, 3 mm bleb = 0.05 mL injection; if considerable resistance not felt, needle too deep and should be removed and reinserted before giving more vaccine.

**PRESCRIBING AND DISPENSING INFORMATION**

Available from health organisations or direct from ImmForm www.immform.dh.gov.uk (SSI brand, multidose vial with diluent).
Cholera vaccine

**INDICATIONS AND DOSE**
Immunisation against cholera (for travellers to endemic or epidemic areas on the basis of current recommendations)

- **BY MOUTH**
  - Child 2–5 years: 1 dose every 1–6 weeks for 3 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure
  - Child 6–17 years: 1 dose every 1–6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure
  - Adult: 1 dose every 1–6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure

**Booster**

- **BY MOUTH**
  - Child 2–5 years: A single booster dose can be given within 6 months after primary course, if more than 6 months have elapsed since the last vaccination, the primary course should be repeated
  - Child 6–17 years: A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated
  - Adult: A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated

**CONTRA-INDICATIONS**
Acute gastro-intestinal illness

**SIDE-EFFECTS**
- Rare: Cough, respiratory symptoms, rhinitis
- Very rare: Insomnia, sore throat
- Frequency not known: Abdominal pain and cramps, diarrhoea, nausea, vomiting

**DIRECTIONS FOR ADMINISTRATION**
- In children: Dissolve effervescent sodium bicarbonate granules in a glassful of water or chlorinated water (approximately 150 mL). For children over 6 years, add vaccine suspension to make one dose. For child 2–5 years, discard half (approximately 75 mL) of the solution, then add vaccine suspension to make one dose. Drink within 2 hours. Food, drink, and other oral medicines should be avoided for 1 hour before and after vaccination.
- In adults: Dissolve effervescent sodium bicarbonate granules in a glassful of water or chlorinated water (approximately 150 mL). Add vaccine suspension to make one dose. Drink within 2 hours. Food, drink, and other oral medicines should be avoided for 1 hour before and after vaccination.

**PATIENT AND CARER ADVICE**
Counselling on administration advised. Immunisation with cholera vaccine does not provide complete protection and all travellers to a country where cholera exists should be warned that scrupulous attention to food, water, and personal hygiene is essential.

Haemophilus influenzae type B with meningococcal group C vaccine

**INDICATIONS AND DOSE**

- **Booster dose (for infants who have received primary immunisation with a vaccine containing Haemophilus influenzae type b component) and primary immunisation against Neisseria meningitidis**
  - **BY INTRAMUSCULAR INJECTION**
    - Child 12–13 months: 0.5 mL for 1 dose
    - Immunisation against Neisseria meningitidis in an unimmunised patient
      - **BY INTRAMUSCULAR INJECTION**
        - Child 1–9 years: 0.5 mL for 1 dose

- **Booster dose after recovery from Haemophilus influenzae type b disease (for index cases previously vaccinated, with low Hib antibody concentration or if it is not possible to measure antibody concentration)**
  - **BY INTRAMUSCULAR INJECTION**
    - Child 1–9 years: 0.5 mL for 1 dose

- **Booster dose after recovery from Haemophilus influenzae type b disease (for fully vaccinated index cases with asplenia or splenic dysfunction, if previous dose received over 1 year ago)**
  - **BY INTRAMUSCULAR INJECTION**
    - Child 1–7 years: 0.5 mL for 1 dose
    - Adult: 0.5 mL for 1 dose

- **Booster dose (for patients diagnosed with asplenia, splenic dysfunction or complement deficiency at under 2 years of age)**
  - **BY INTRAMUSCULAR INJECTION**
    - Child 2–17 years: 0.5 mL for 1 dose, this booster dose should be given after the second birthday, this is the second dose of haemophilus influenzae type B vaccine combined with meningococcal group C conjugate vaccine (the first dose is given during the routine immunisation schedule)

  **Booster dose (for patients diagnosed with asplenia, splenic dysfunction or complement deficiency at over 2 years of age)**
  - **BY INTRAMUSCULAR INJECTION**
    - Child 2–17 years: 0.5 mL for 1 dose, this booster dose should be followed 2 months later by one dose of meningococcal A, C, W135, and Y conjugate vaccine (in patients from 11 years of age, this interval can be reduced to one month)
    - Adult: 0.5 mL for 1 dose, this booster dose should be followed 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine

**UNLICENSED USE**
Not licensed for use in patients over 2 years.

**SIDE-EFFECTS**
- Rare: Symptoms of meningitis reported (but no evidence that the vaccine causes meningococcal C meningitis)
- Frequency not known: Atopic dermatitis, hypotonia

**PRESCRIBING AND DISPENSING INFORMATION**
Available as part of the childhood immunisation schedule from ImmForm.
Meningococcal B vaccine (rDNA, component, adsorbed)

**INDICATIONS AND DOSE**

Immunisation against *Neisseria meningitidis*, primary immunisation

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Child 2 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants), for information about the use of paracetamol for prophylaxis of post-immunisation pyrexia, see p. 414.
  - Child 4 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants), for information about the use of paracetamol for prophylaxis of post-immunisation pyrexia, see p. 414.

Immunisation against *Neisseria meningitidis*, primary immunisation booster dose

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Child 12-23 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants)

Immunisation against *Neisseria meningitidis*, primary immunisation (in unimmunised patients)

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Child 6-11 months: 0.5 mL for 2 doses, separated by an interval of at least 2 months; booster dose of 0.5 mL given between 1–2 years of age and at least 2 months after completion of primary immunisation, injected preferably into deltoid region (or anterolateral thigh in infants)
  - Child 12-23 months: 0.5 mL for 2 doses, separated by an interval of at least 2 months; booster dose of 0.5 mL given 12–24 months after completion of primary immunisation, injected preferably into deltoid region (or anterolateral thigh in infants)
  - Child 2-10 years: 0.5 mL for 2 doses, separated by an interval of at least 2 months. Injected preferably into deltoid region (or anterolateral thigh in infants)
  - Child 11-17 years: 0.5 mL for 2 doses, separated by an interval of at least 1 month. Injected preferably into deltoid region
  - Adult: 0.5 mL for 2 doses, separated by an interval of at least 1 month. Injected preferably into deltoid region

**SIDE-EFFECTS**

- **Rare** Kawasaki disease (in children) - symptoms of meningitis reported (but no evidence that the vaccine causes meningococcal C meningitis)
- **Frequency not known** Unusual crying (in children)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Bexsero (GlaxoSmithKline UK Ltd)**
  - Bexsero vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection (Pom) £75.00

Meningococcal groups A with C and W135 and Y vaccine

**INDICATIONS AND DOSE**

**MENVEO®**

Primary immunisation against *Neisseria meningitidis*

- **BY INTRAMUSCULAR INJECTION**
  - Child 13-15 years: 0.5 mL for 1 dose, preferably injected into deltoid region

Immunisation against *Neisseria meningitidis* in an unimmunised patient

- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL for 1 dose, booster dose is not required
  - Adult 18-24 years: 0.5 mL for 1 dose, booster dose is not required

Immunisation against *Neisseria meningitidis* in those at risk of exposure to prevent invasive disease

- **BY INTRAMUSCULAR INJECTION**
  - Child 3-11 months: 0.5 mL every month for 2 doses, dose preferably injected into deltoid region
  - Child 1-7 years: 0.5 mL for 1 dose, dose preferably injected into deltoid region
  - Adult: 0.5 mL for 1 dose, dose preferably injected into deltoid region

Patients attending university for the first time (who have not received the routine meningococcal A, C, W135, and Y conjugate vaccine over the age of 10 years)

- **BY INTRAMUSCULAR INJECTION**
  - Adult 18-24 years: 0.5 mL for 1 dose
NIMENRIX®
Primary immunisation against Neisseria meningitidis
- By intramuscular injection
  - Child 13-15 years: 0.5 mL for 1 dose, to be injected preferably into deltoid region

Immunisation against Neisseria meningitidis in an unimmunised patient
- By intramuscular injection
  - Child 10-17 years: 0.5 mL for 1 dose, booster dose is not required
  - Adult 18-24 years: 0.5 mL for 1 dose, booster dose is not required

Immunisation against Neisseria meningitidis in those at risk of exposure
- By intramuscular injection
  - Child 1-17 years: 0.5 mL for 1 dose, to be injected preferably into deltoid region (or anterolateral thigh in child 12-23 months), then 0.5 mL after 1 year if required for 1 dose, second dose should be considered in those who continue to be at risk of Neisseria meningitidis serogroup A infection
  - Adult: 0.5 mL for 1 dose, to be injected preferably into deltoid region, then 0.5 mL after 1 year if required for 1 dose, second dose should be considered in those who continue to be at risk of Neisseria meningitidis serogroup A infection

Patients attending university for the first time (who have not received the routine meningococcal A, C, W135, and Y conjugate vaccine over the age of 10 years)
- By intramuscular injection
  - Adult 18-24 years: 0.5 mL for 1 dose

- **UNLICENSED USE** Menevo® is not licensed for use in children under 2 years.
- **SIDE-EFFECTS**
  - Rare Symptoms of meningitis reported (but no evidence that the vaccine causes meningococcal C meningitis)

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Powder and solvent for solution for injection**
  - Menevo (GlaxoSmithKline UK Ltd)
    Menevo vaccine powder and solvent for solution for injection 0.5mL vials | 1 vial £30.00
  - Nimenrix (Pfizer Ltd)
    Nimenrix vaccine powder and solvent for solution for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection £30.00

  **Immunisation against pneumococcal infection (in patients who have not been vaccinated or not completed the primary course)**
  - By intramuscular injection
    - Child 12 months-4 years: 0.5 mL for 1 dose, deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants

  **Immunisation against pneumococcal infection, in immunocompromised or asplenic patients or patients with splenic dysfunction (who have not been vaccinated or not completed the primary course)**
  - By intramuscular injection
    - Child 12 months-4 years: 0.5 mL every 2 months for 2 doses, deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants

SYNFLORIX®
Immunisation against pneumococcal infection
- By intramuscular injection
  - Child 6 weeks-4 years: Deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants (consult product literature)

- **UNLICENSED USE** PREVENAR 13® The dose in BNF publications may differ from that in product literature.
- **CONTRA-INDICATIONS** Concomitant use of high potency varicella-zoster vaccine (Zostavax®) with pneumococcal polysaccharide vaccine (in adults)
- **PRESCRIBING AND DISPENSING INFORMATION** PREVENAR 13® Available as part of childhood immunisation schedule from ImForm www.immform.dh.gov.uk.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Suspension for injection**
  - Prevenar (Pfizer Ltd)
    Prevenar 13 vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection £49.10 | 10 pre-filled disposable injection £491.00
  - Synflorix (GlaxoSmithKline UK Ltd)
    Synflorix vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection £27.60

Pneumococcal polysaccharide conjugate vaccine

- **INDICATIONS AND DOSE**

  **PREVENAR 13®**
  Primary immunisation against pneumococcal infection
  (first dose)
  - By intramuscular injection
    - Child 2-17 years: 0.5 mL for 1 dose
    - Adult: 0.5 mL for 1 dose
  Primary immunisation against pneumococcal infection
  (second dose)
  - By intramuscular injection
    - Child 2-4 years: 0.5 mL for 1 dose, dose should be administered after the second birthday or at least 2 months after the final dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed)
    - Child 5-17 years: 0.5 mL for 1 dose
    - Adult: 0.5 mL for 1 dose

- **INDICATIONS AND DOSE**

  **Immunisation against pneumococcal infection**
  - By intramuscular injection, or by subcutaneous injection
    - Child 2-17 years: 0.5 mL for 1 dose
    - Adult: 0.5 mL for 1 dose
  Immunisation in patients at increased risk of pneumococcal disease
  - By intramuscular injection, or by subcutaneous injection
    - Child 2-4 years: 0.5 mL for 1 dose, dose should be administered after the second birthday or at least 2 months after the final dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed)
    - Child 5-17 years: 0.5 mL for 1 dose
    - Adult: 0.5 mL for 1 dose
**Typhoid vaccine**

### Indications and dose

**Immunisation against typhoid fever in children at high risk of typhoid fever**
- **By intramuscular injection**
  - Child 12-23 months: 0.5 mL for 1 dose, dose should be given at least 2 weeks before potential exposure to typhoid infection, response may be suboptimal

**Immunisation against typhoid fever**
- **By intramuscular injection**
  - Child 2-17 years: 0.5 mL for 1 dose, dose should be given at least 2 weeks before potential exposure to typhoid infection
  - Adult: 0.5 mL for 1 dose, should be given at least 2 weeks before potential exposure to typhoid infection
  - **By mouth**
  - Child 6-17 years: 1 capsule every 2 days for 3 doses (on days 1, 3, and 5)
  - Adult: 1 capsule every 2 days for 3 doses (on days 1, 3, and 5)

**Unlicensed use**
- Not licensed for use in children under 2 years.

**Contra-indications**
- With oral use: Acute gastrointestinal illness

**Interactions**
- Oral typhoid vaccine is inactivated by concomitant administration of antibacterials or antimalarials:
  - Antibacterials should be avoided for 3 days before and after oral typhoid vaccination;
  - *Mefloquine* should be avoided for at least 12 hours before or after oral typhoid;
  - For other antimalarials vaccination with oral typhoid vaccine should be completed at least 3 days before the first dose of the antimalarial (except proguanil hydrochloride with atovaquone, which may be given concomitantly).

**Side-effects**
- With oral use: Abdominal cramps, abdominal pain, diarrhoea, nausea, vomiting

**Directions for administration**
- Capsule should be taken once a day after a meal. Swallow as soon as possible after placing in mouth with a cold or lukewarm drink.

**Handling and storage**
- With oral use: It is important to store capsules in a refrigerator.

**Patient and carer advice**
- With oral use: Patients or carers should be given advice on how to administer and store typhoid vaccine capsules.

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant capsule**
- **Cautionary and advisory labels 25**
  - **Vivotif** (PaxVax Ltd)
  - Vivotif vaccine gastro-resistant capsules | 3 capsule | £14.77

**Solution for injection**
- **Typherix** (GlaxoSmithKline UK Ltd)
  - *Salmonella typhi* Vi capsule polysaccharide 50 microgram per 1 mL Typherix 25 micrograms/0.5 mL vaccine solution for injection pre-filled syringes | 1 pre-filled disposable injection | £9.30 | 10 pre-filled disposable injection | £99.32

**Combinations available:** *Hepatitis A with typhoid vaccine*, p. 1165

**Vaccines > Viral vaccines**

### Hepatitis A and B vaccine

The properties listed below are those particular to the combination only. For the properties of the components please consider, hepatitis A vaccine p. 1164, hepatitis B vaccine p. 1165.

**Indications and dose**
- **Ambirix**
  - **Immunisation against hepatitis A and hepatitis B infection (primary course)**
    - **By intramuscular injection**
    - Child 1-15 years: Initially 1 mL for 1 dose, then 1 mL after 6-12 months for 1 dose, the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)
    - Adult: Initially 1 mL every month for 2 doses, then 1 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**Twirnx adult**
- **Immunisation against hepatitis A and hepatitis B infection (primary course)**
  - **By intramuscular injection**
  - Child 16-17 years: Initially 1 mL every month for 2 doses, then 1 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**Immunisation against hepatitis A and hepatitis B infection—accelerated schedule for travellers departing within 1 month**
- **By intramuscular injection**
  - Child 16-17 years: Initially 1 mL for 1 dose, then 1 mL after 7 days for 1 dose, then 1 mL after 14 days for 1 dose, then 1 mL for 1 dose given 12 months after the first dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)
  - Adult: Initially 1 mL for 1 dose, then 1 mL after 7 days for 1 dose, then 1 mL after 14 days for 1 dose, then 1 mL for 1 dose given 12 months after the first dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)
AVAXIM®

Immunisation against hepatitis A and hepatitis B infection (primary course)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-15 years: Initially 0.5 mL every month for 2 doses, then 0.5 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**IMPORANT SAFETY INFORMATION**

Ambirix® and Twinrix® are not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular, or mucous membrane exposure to hepatitis B virus.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - **TWINRIX® PAEDIATRIC** Primary course should be completed with Twinrix® (single component vaccines given at appropriate intervals may be used for booster dose).
  - **AMBIRIX®** Primary course should be completed with Ambirix® (single component vaccines given at appropriate intervals may be used for booster dose).
  - **TWINRIX® ADULT** Primary course should be completed with Twinrix® (single component vaccines given at appropriate intervals may be used for booster dose).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**EXCIPIENTS:** May contain Neomycin

- **Ambirix®** (GlanzSmithKline UK Ltd)
  - Ambirix vaccine suspension for injection 1 mL pre-filled disposable syringes | 1 pre-filled disposable injection | £31.18
- **Twinrix®** (GlanzSmithKline UK Ltd)
  - Twinrix Paediatric vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £20.79
  - Twinrix Adult vaccine suspension for injection 1 mL pre-filled syringes | 1 pre-filled disposable injection | £33.31 | 10 pre-filled disposable injection | £333.13

**AVAXIM®**

Immunisation against hepatitis A and hepatitis B infection (primary course)

- **BY INTRAMUSCULAR INJECTION**
  - Child 16-17 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders; not to be injected into the buttock (vaccine efficacy reduced)

  - Adult: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

  - Child 16-17 years: Initially 1 mL for 1 dose, then 1 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

  - Adult: Initially 1 mL for 1 dose, then 1 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be delayed)

**VAQTA® ADULT**

Immunisation against hepatitis A infection

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 1 mL for 1 dose, then 1 mL after 6–18 months, dose given as booster, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be delayed)

**VAQTA® PAEDIATRIC**

Immunisation against hepatitis A infection

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-17 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–18 months, dose given as booster, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be reduced)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**EXCIPIENTS:** May contain Neomycin

- **Avaxim®** (sanofi pasteur MSD Ltd)
  - Avaxim vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £18.10 | 10 pre-filled disposable injection | £181.00
- **Havrix®** (GlanzSmithKline UK Ltd)
  - Havrix monodose vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £22.14 | 10 pre-filled disposable injection | £221.43
  - Havrix Junior monodose vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £16.77 | 10 pre-filled disposable injection | £167.68
- **VAQTA®** (sanofi pasteur MSD Ltd)
  - VAQTA Adult vaccine suspension for injection 1 mL pre-filled syringes | 1 pre-filled disposable injection | £18.10
  - VAQTA Adult vaccine suspension for injection 1 mL vials | 1 vial | £18.10
  - VAQTA Paediatric vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £14.74
Hepatitis A with typhoid vaccine

The properties listed below are those particular to the combination only. For the properties of the components please consider, hepatitis A vaccine p. 1164, typhoid vaccine p. 1163.

**INDICATIONS AND DOSE**

**HENPATRIX®**

Immunisation against hepatitis A and typhoid infection (primary course)

- **BY INTRAMUSCULAR INJECTION**
  - Child 15-17 years: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines
  - Adult: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines

**VIATIM®**

Immunisation against hepatitis A and typhoid infection (primary course)

- **BY INTRAMUSCULAR INJECTION**
  - Child 16-17 years: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines
  - Adult: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**EXCIPIENTS:** May contain Neomycin

- **Hepatryx** (GlaxoSmithKline UK Ltd)
  - Hepatryx vaccine suspension for injection 1 mL pre-filled syringes | 1 pre-filled disposable injection [Pack] £37.21 | 10 pre-filled disposable injection [Pack] £372.10
- **VIATIM** (sanofi pasteur MSD Ltd)
  - VIATIM vaccine suspension for injection 1 mL pre-filled syringes | 1 pre-filled disposable injection [Pack] £29.80

Hepatitis B vaccine

**INDICATIONS AND DOSE**

**ENERGIRX B®**

Immunisation against hepatitis B infection

- **BY INTRAMUSCULAR INJECTION**
  - Child 1 month-15 years: 10 micrograms for 1 dose, then 10 micrograms after 1 month for 1 dose, followed by 10 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
  - Child 16-17 years: 20 micrograms for 1 dose, then 20 micrograms after 1 month for 1 dose, followed by 20 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
  - Adult: 20 micrograms for 1 dose, then 20 micrograms after 1 month for 1 dose, followed by 20 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (accelerated schedule)

- **BY INTRAMUSCULAR INJECTION**
  - Neonate: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), this dose should not be given to neonates born to hepatitis B surface antigen positive mother.
  - Child 1 month-15 years: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
  - Child 16-17 years: 20 micrograms every month for 3 doses, followed by 20 micrograms after 10 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
  - Adult: 20 micrograms every month for 3 doses, followed by 20 micrograms after 10 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection, alternative accelerated schedule

- **BY INTRAMUSCULAR INJECTION**
  - Child 11-15 years: 20 micrograms for 1 dose, followed by 20 micrograms after 6 months, this schedule is not suitable if high risk of infection between doses or if compliance with second dose uncertain, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (accelerated schedule in exceptional cases, e.g. for travellers departing within 1 month)

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 20 micrograms for 1 dose, then 20 micrograms after 7 days for 1 dose, followed by 20 micrograms after 14 days for 1 dose, followed by 20 micrograms for 1 dose, to be given 12 months after the first dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (in renal insufficiency, including haemodialysis patients)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1 month-15 years: 10 micrograms every month for 2 doses, followed by 10 micrograms after 5 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
  - Child 16-17 years: 40 micrograms every month for 3 doses, followed by 40 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
  - Adult: 40 micrograms every month for 3 doses, followed by 40 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
Immunisation against hepatitis B infection (in renal insufficiency, including haemodialysis patients (accelerated schedule))

► BY INTRAMUSCULAR INJECTION

- Child 1 month–15 years: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is a preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 20 micrograms every month for 3 doses, followed by 20 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

HBVAXPRO®

Immunisation against hepatitis B infection

► BY INTRAMUSCULAR INJECTION

- Neonate: 5 micrograms for 1 dose, followed by 5 micrograms after 1 month for 1 dose, then 5 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), dose not to be used for neonate born to hepatitis B surface antigen positive mother.
- Child 1 month–15 years: 5 micrograms for 1 dose, followed by 5 micrograms after 1 month for 1 dose, then 5 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; anterolateral thigh is preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced)
- Child 16–17 years: 40 micrograms every month for 2 doses, followed by 40 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in older children; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 40 micrograms every month for 2 doses, followed by 40 micrograms after 5 months for 1 dose, booster doses may be required in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (in renal insufficiency, including pre-haemodialysis and haemodialysis patients)

► BY INTRAMUSCULAR INJECTION

- Child 15–17 years: 20 micrograms every month for 3 doses, followed by 20 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 20 micrograms every month for 3 doses, followed by 20 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
- Chronic haemodialysis patients

► BY INTRAMUSCULAR INJECTION

- Child 16–17 years: 40 micrograms every month for 2 doses, followed by 40 micrograms after 5 months for 1 dose, booster doses may be required in those with low antibody concentration, deltoid muscle is preferred site of injection in older children; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 40 micrograms every month for 2 doses, followed by 40 micrograms after 5 months for 1 dose, booster doses may be required in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Suspension for injection

EXCIPIENTS: May contain Thiomersal

- Engerix B (GlaxoSmithKline UK Ltd)
  - Hepatitis B virus surface antigen 20 microgram per 1 ml
  - Engerix B 20micrograms/1ml vaccine suspension for injection vials | 1 vial (PoM) £12.34 | 10 vial (PoM) £123.41
  - Engerix B 10micrograms/0.5ml vaccine suspension for injection pre-filled syringes | 1 pre-filled disposable injection (PoM) £3.67
  - Engerix B 20micrograms/1ml vaccine suspension for injection pre-filled syringes | 1 pre-filled disposable injection (PoM) £12.99 | 10 pre-filled disposable injection (PoM) £129.92
Human papillomavirus vaccines

- **INDICATIONS AND DOSE**

**CERVARIX®**

**Prevention of premalignant genital lesions and cervical cancer**

- **BY INTRAMUSCULAR INJECTION**
  - Child 9–14 years (female): 0.5 mL for 1 dose, followed by 0.5 mL after 5–7 months for 1 dose, if second dose administered earlier than 5 months after the first, a third dose should be administered, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose or if the girl is then aged 15 years or more.
  - Child 15–17 years (female): 0.5 mL for 1 dose, followed by 0.5 mL after 1–2.5 months for 1 dose, then 0.5 mL after 5–12 months from the first dose for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.
  - Adult (female): 0.5 mL for 1 dose, followed by 0.5 mL after 1–2.5 months for 1 dose, then 0.5 mL after 5–12 months from the first dose for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**GARDASIL®**

**Prevention of premalignant genital (cervical, vulvar, and vaginal) and anal lesions, cervical and anal cancers, and genital warts**

- **BY INTRAMUSCULAR INJECTION**
  - Child 9–13 years (female): 0.5 mL for 1 dose, followed by 0.5 mL after 6 months for 1 dose, if the second dose is administered earlier than 6 months after the first dose, a third dose should be administered, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.
  - Child 14–17 years (female): 0.5 mL for 1 dose, followed by 0.5 mL for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 mL for 1 dose, third dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.
  - Adult (female): 0.5 mL for 1 dose, followed by 0.5 mL for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 mL for 1 dose, second dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**Prevention of premalignant genital (cervical, vulvar, and vaginal) and anal lesions, cervical and anal cancers, and genital warts (alternative schedule)**

- **BY INTRAMUSCULAR INJECTION**
  - Child 9–13 years (female): 0.5 mL for 1 dose, followed by 0.5 mL for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 mL for 1 dose, third dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**PREGNANCY**

Not known to be harmful, but vaccination should be postponed until completion of pregnancy.

**PRESCRIBING AND DISPENSING INFORMATION**

To avoid confusion, prescribers should specify the brand to be dispensed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Cervarix (GlaxoSmithKline UK Ltd)**
  - Cervarix vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £80.50
- **Gardasil (sanofi pasteur MSD Ltd)**
  - Gardasil vaccine suspension for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection | £86.50

Influenza vaccine

- **INDICATIONS AND DOSE**

**Annual immunisation against seasonal influenza (for children who have not received seasonal influenza vaccine previously)**

- **BY INTRAMUSCULAR INJECTION**
  - Child 6 months–9 years: 0.5 mL for 1 dose, followed by 0.5 mL after at least 4 weeks for 1 dose
  - **BY INTRanasal ADMINISTRATION**
  - Adult: 0.5 mL for 1 dose
  - **BY INTRAderal INJECTION**
  - Adult 18–59 years: 9 micrograms for 1 dose, dose to be injected into deltoid region
  - Adult 60 years and over: 15 micrograms for 1 dose, dose to be injected into deltoid region
  - **BY INTRanasal ADMINISTRATION**
  - Child 2–17 years: 0.1 mL for 1 dose, dose to be administered into each nostril

**UNLICENSED USE**

Some products containing inactivated influenza vaccine (surface antigen) are not licensed for use in children under 4 years—check product literature.

**FLUVIRIN®**

Not licensed for use in children under 4 years.

**FLUARIX TETRA®**

Not licensed for use in children under 3 years of age.
OPTAFLU® Not licensed for use in children and adolescents under 18 years.

- CONTRA-INDICATIONS Preparations marketed by Pfizer, or CSL Bioteherapies in child under 5 years— increased risk of febrile convulsions
- FLUENZ TETRA® Active wheezing - concomitant use with antiviral therapy for influenza - severe asthma
- CONTRA-INDICATIONS, FURTHER INFORMATION
  - Concomitant use with antivirals Avoid antivirals for at least 2 weeks after immunisation; avoid immunisation for at least 48 hours after stopping the antiviral.
- ENZIRA® Child under 5—increased risk of febrile convulsions
- CAUTIONS Increased risk of fever in child 5—9 years with preparations marketed by Pfizer or CSL Bioteherapies—use alternative influenza vaccine if available
- ENZIRA® Child 5—9 years (increased risk of fever)—use alternative influenza vaccine if available
- SIDE-EFFECTS
  - GENERAL SIDE-EFFECTS
  - Uncommon Epistaxis
  - Frequency not known Febrile convulsions • transient thrombocytopenia • vasculitis (in adults)
  - SPECIFIC SIDE-EFFECTS
    - With intranasal use Rhinorrhea
  - ALLERGY AND CROSS-SENSITIVITY Individuals with a history of egg allergy can be immunised with either an egg free influenza vaccine, if available, or an influenza vaccine with an ovalbumin content less than 120 nanograms/mL (facilities should be available to treat anaphylaxis). Vaccines with an ovalbumin content more than 120 nanograms/mL or where content is not stated should not be used in individuals with egg allergy. If an influenza vaccine containing ovalbumin is being considered in those with a history of anaphylaxis to egg or egg allergy with uncontrolled asthma, these individuals should be referred to a specialist in hospital.
  - PREGNANCY Inactivated vaccines not known to be harmful.
  - FLUENZ TETRA® Avoid in pregnancy.
  - BREAST FEEDING Inactivated vaccines not known to be harmful.
  - FLUENZ TETRA® Avoid in breast-feeding.
  - PRESCRIBING AND DISPENSING INFORMATION
  - FLUARIK TETRA® Ovalbumin content less than 100 nanograms/mL.
  - PATIENT AND CARER ADVICE
  - FLUENZ TETRA® Avoid close contact with severely immunocompromised patients for 1—2 weeks after vaccination.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Suspension for injection
    - EXCIPIENTS: May contain Gelatin, kanamycin, neomycin penicillins, polymyxin b, thiomersal
      - Influenza vaccine (Non-proprietary)
        - Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PO) £5.00—£6.59 | 10 pre-filled disposable injection (PO) £55.90
        - Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes | 10 pre-filled disposable injection (PO) £61.50
        - Agrippal (Sequoris Ltd)
          - Agrippal vaccine suspension for injection 0.5ml pre-filled syringes | 10 pre-filled disposable injection (PO) £58.50
        - Enzira (Pfizer Ltd)
          - Enzira vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PO) £5.25 | 10 pre-filled disposable injection (PO) £52.50

  - Fluarix Tetra (GlawoSmithkline UK Ltd)
    - Fluarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PO) £9.90 | 10 pre-filled disposable injection (PO) £99.40
  - Imuvac (BGP Products Ltd)
    - Imuvac vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PO) £6.59 | 10 pre-filled disposable injection (PO) £65.90
  - Influvac Sub-unit (BGP Products Ltd)
    - Influvac Sub-unit vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PO) £5.22 | 10 pre-filled disposable injection (PO) £52.20
  - Intanza (sanofi pasteur MSD Ltd)
    - Intanza 150microgram strain vaccine suspension for injection 0.1ml pre-filled syringes | 1 pre-filled disposable injection (PO) £9.05 | 10 pre-filled disposable injection (PO) £90.50
  - Optafu (Novartis Vaccines and Diagnostics Ltd)
    - Optafu vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PO) £6.59

- Spray
  - EXCIPIENTS: May contain Gelatin, gentamicin
    - FluMist Quadrivalent (AstraZeneca UK Ltd)
      - FluMist Quadrivalent vaccine nasal suspension 0.2ml unit dose | 10 unit dose (PO) £180.00
    - Fluarix Tetra (AstraZeneca UK Ltd)
      - Fluarix Tetra vaccine nasal suspension 0.2ml unit dose | 10 unit dose (PO) £180.00

Japanese encephalitis vaccine

- INDICATIONS AND DOSE
  - Immunisation against Japanese encephalitis
    - BY INTRAMUSCULAR INJECTION
      - Child 2 months—2 years: 0.25 mL every 28 days for 2 doses, anterolateral thigh is preferred site of injection in infants, the subcutaneous route may be used for patients with bleeding disorders
      - Child 3—17 years: 0.5 mL every 28 days for 2 doses, deltoid muscle is preferred site in older children; anterolateral thigh is preferred in infants, the subcutaneous route may be used for patients with bleeding disorders
      - Adult: 0.5 mL every 28 days for 2 doses, deltoid muscle is preferred site of injection, the subcutaneous route may be used for patients with bleeding disorders
    - Booster dose
      - BY INTRAMUSCULAR INJECTION
        - Adult: 0.5 mL after 1—2 years, deltoid muscle is preferred site of injection, the subcutaneous route may be used for patients with bleeding disorders, for those at continued risk, the booster dose should be given 1 year after completing the primary course

- SIDE-EFFECTS
  - Uncommon Cough (in children) • migraine (in adults) • vertigo (in adults)
  - Rare Dyspnoea (in adults) • neuritis (in adults) • palpitation (in adults) • tachycardia (in adults) • thrombocytopenia (in adults)
  - PREGNANCY Although manufacturer advises avoid because of limited information, miscarriage has been associated with Japanese encephalitis virus infection acquired during the first 2 trimesters of pregnancy.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - Japanese encephalitis vaccine (Non-proprietary)
      - Japanese encephalitis GCV vaccine solution for injection 1ml vials | 1 vial no price available
      - Japanese encephalitis GCV vaccine solution for injection 20ml vials | 1 vial no price available
      - Japanese encephalitis GCV vaccine solution for injection 10ml vials | 1 vial no price available
Measles, mumps and rubella vaccine, live

**INDICATIONS AND DOSE**

Primary immunisation against measles, mumps, and rubella (first dose)
- By intramuscular injection, or by deep subcutaneous injection
- Child 12-13 months: 0.5 mL for 1 dose

Primary immunisation against measles, mumps, and rubella (second dose)
- By intramuscular injection, or by deep subcutaneous injection
- Child 40 months-5 years: 0.5 mL for 1 dose

Rubella immunisation (in seronegative women, susceptible to rubella and in unimmunised, seronegative women, post-partum)
- By intramuscular injection, or by deep subcutaneous injection
- Females of childbearing potential: (consult product literature or local protocols)

Children presenting for pre-school booster, who have not received the primary immunisation (first dose)
- Immunisation for patients at school-leaving age or at entry into further education, who have not completed the primary immunisation course

Control of measles
- Where measles is endemic or epidemic, who have not completed the primary immunisation
- By intramuscular injection, or by deep subcutaneous injection
- Child 6 months-17 years: (consult product literature or local protocols)
- Adult: (consult product literature or local protocols)

**SIDE-EFFECTS**

- Frequency of side effects
- Post-vaccination aseptic meningitis was reported (rarely and with complete recovery) following vaccination with MMR vaccine containing Urabe mumps vaccine, which has now been discontinued; no cases have been confirmed in association with the currently used Jeryl Lynn mumps vaccine.
- Children with post-vaccination symptoms are not infectious.
- Frequency of side effects Adverse reactions are considerably less frequent after the second dose of MMR vaccine than after the first.

**UNLICENSED USE**

Not licensed for use in children under 9 months.

**IMPORTANT SAFETY INFORMATION**

MMR VACCINATION AND BOWEL DISEASE OR AUTISM

Reviews undertaken on behalf of the CSM, the Medical Research Council, and the Cochrane Collaboration, have not found any evidence of a link between MMR vaccination and bowel disease or autism. The Chief Medical Officers have advised that the MMR vaccine is the safest and best way to protect children against measles, mumps, and rubella. Information (including fact sheets and a list of references) may be obtained from www.dh.gov.uk/immunisation.

**ALLERGY AND CROSS-SENSITIVITY**

MMR vaccine can be given safely even when the child has had an anaphylactic reaction to food containing egg. Dislike of eggs, refusal to eat egg, or confirmed anaphylactic reactions to egg-containing food is not a contra-indication to MMR vaccination. Children with a confirmed anaphylactic reaction to the MMR vaccine should be assessed by a specialist.

**CONCEPTION AND CONTRACEPTION**

Exclude pregnancy before immunisation. Avoid pregnancy for at least 1 month after vaccination.

**PRESCRIBING AND DISPENSING INFORMATION**

Available as part of childhood immunisation schedule from health organisations or ImmForm www.immform.dh.gov.uk.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

**EXCIPIENTS:** May contain Neomycin
- Priorix (GlaxoSmithKline UK Ltd) Priorix vaccine powder and solvent for solution for injection 0.5ml vials 1 vial £7.64

**Powder and solvent for suspension for injection**

**EXCIPIENTS:** May contain Gelatin, neomycin
- M-M-RVAXPRO (sanofi pasteur MSD Ltd) M-M-RVAXPRO vaccine powder and solvent for suspension for injection 0.5ml pre-filled syringes 1 1 pre-filled disposable injection £11.00
Rabies vaccine

- **INDICATIONS AND DOSE**
  - **Pre-exposure prophylaxis**
    - **BY INTRAMUSCULAR INJECTION**
      - Child: 1 mL for 2 doses (on days 0 and 7), followed by 1 mL for 1 dose (on day 28), to be administered in deltoid region or anterolateral thigh in infants, for those at continuous risk, measure plasma-concentration of antirabies antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL, final dose may be given from day 21, if insufficient time before travel.
      - Adult: 1 mL for 2 doses (on days 0 and 7), followed by 1 mL for 1 dose (on day 28), to be administered in deltoid region, for those at continuous risk, measure plasma-concentration of antirabies antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL, final dose may be given from day 21, if insufficient time before travel.
  - **Pre-exposure prophylaxis booster dose (for patients at frequent risk of exposure)**
    - **BY INTRAMUSCULAR INJECTION**
      - Child: 1 mL after 1 year for 1 dose, to be given 1 year after primary course is completed, then 1 mL every 3–5 years, to be administered in deltoid region or anterolateral thigh in infants, the frequency of booster doses may alternatively be determined according to plasma-concentration of antirabies antibodies.
      - Adult: 1 mL for 1 dose, to be given 1 year after primary course is completed, then 1 mL every 3–5 years, to be administered in deltoid region, the frequency of booster doses may alternatively be determined according to plasma-concentration of antirabies antibodies.
  - **Pre-exposure prophylaxis booster dose (for patients at infrequent risk of exposure)**
    - **BY INTRAMUSCULAR INJECTION**
      - Child: 1 mL for 1 dose, to be given 10 years after primary course is completed, administered in deltoid region or anterolateral thigh in infants.
      - Adult: 1 mL for 1 dose, to be given 10 years after primary course is completed, administered in deltoid region.
  - **Post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine)**
    - **BY INTRAMUSCULAR INJECTION**
      - Child (administered on expert advice): 1 mL for 1 dose, followed by 1 mL after 3–7 days for 1 dose, to be administered in deltoid region or anterolateral thigh in infants, rabies immunoglobulin is not necessary.
      - Adult (administered on expert advice): 1 mL for 1 dose, followed by 1 mL after 3–7 days for 1 dose, to be administered in deltoid region, rabies immunoglobulin is not necessary.
  - **Post-exposure treatment for unimmunised individuals (or those whose prophylaxis is possibly incomplete)**
    - **BY INTRAMUSCULAR INJECTION**
      - Child (administered on expert advice): 1 mL 5 times a month for 1 month, doses should be given on days 0, 3, 7, 14, and the fifth dose is given between day 28–30, to be administered in deltoid region or anterolateral thigh in infants, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine, the immunisation course can be discontinued if it is proved that the individual was not at risk.
      - Adult (administered on expert advice): 1 mL 5 times a month for 1 month, doses should be given on days 0, 3, 7, 14, and the fifth dose is given between day 28–30, to be administered in deltoid region, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine, the immunisation course can be discontinued if it is proved that the individual was not at risk.

- **SIDE-EFFECTS** Paresis
- **PREGNANCY** Because of the potential consequences of untreated rabies exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis. Immunisation against rabies is indicated during pregnancy if there is substantial risk of exposure to rabies and rapid access to post-exposure prophylaxis is likely to be limited.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder and solvent for solution for injection**
    - EXCIPIENTS: May contain Neomycin.
    - Rabipur vaccine powder and solvent for solution for injection 1 mL vial £3.45
    - Rabipur vaccine powder and solvent for suspension for injection 1 mL vial £3.90

Rotavirus vaccine

- **DRUG ACTION** Rotavirus vaccine is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection.

- **INDICATIONS AND DOSE**
  - **Immunisation against gastro-enteritis caused by rotavirus**
    - **BY MOUTH**
      - Child 6–23 weeks: 1.5 mL for 2 doses separated by an interval of at least 4 weeks, first dose must be given between 6–14 weeks of age; course should be completed before 24 weeks of age (preferably before 16 weeks).

- **CONTRA-INDICATIONS** History of intussusception · predisposition to intussusception · severe combined immunosuppression

**CONTRA-INDICATIONS, FURTHER INFORMATION**
- Immunosuppression With the exception of severe combined immunodeficiency, rotavirus vaccine is not contra-indicated in immunosuppressed patients—benefit from vaccination is likely to outweigh the risk, if there is any doubt, seek specialist advice.

**CAUTIONS** Diarrhoea (postpone vaccination) · immunosuppressed close contacts · vomiting (postpone vaccination)

**CAUTIONS, FURTHER INFORMATION** The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; however, vaccination of those with immunosuppressed close contacts may protect the contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus.
 Tick-borne encephalitis vaccine, inactivated

**INDICATIONS AND DOSE**

**Initial immunisation against tick-borne encephalitis**

- **By intramuscular injection**
  - Child 1-15 years: 0.25 mL for 1 dose, followed by 0.25 mL after 1-3 months for 1 dose, then 0.25 mL after further 5-12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, dose to be administered in deltoid region or anterolateral thigh in infants, in immunocompromised patients (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
  - Child 16-17 years: 0.5 mL for 1 dose, followed by 0.5 mL after 1-3 months for 1 dose, then 0.5 mL after further 5-12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, dose to be administered in deltoid region, in immunocompromised patients (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
  - Adult: 0.5 mL for 1 dose, followed by 0.5 mL after 1-3 months for 1 dose, then 0.5 mL after further 5-12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, dose to be administered in deltoid region, in immunocompromised patients (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
  - Elderly: 0.5 mL for 1 dose, followed by 0.5 mL after 1-3 months for 1 dose, then 0.5 mL after further 5-12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, dose to be administered in deltoid region, antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved

**Immunisation against tick-borne encephalitis, booster doses**

- **By intramuscular injection**
  - Child 1-17 years: First dose to be given within 3 years after initial course completed and then every 3-5 years, dose to be administered in deltoid region or anterolateral thigh in infants
  - Adult: First dose to be given within 3 years after initial course completed and then every 3-5 years, dose to be administered in deltoid region (consult product literature)

**ALLERGY AND CROSS-SENSITIVITY** Individuals with evidence of previous anaphylactic reaction to egg should not be given tick-borne encephalitis vaccine.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Exipients:** May contain Gentamicin, neomycin
  - **TicoVac** (Masta Ltd)
    - TicoVac Junior vaccine suspension for injection 0.25ml pre-filled syringes | 1 pre-filled disposable injection (£28.00)
    - TicoVac vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (£32.00)

Varicella-zoster vaccine

**INDICATIONS AND DOSE**

**VARILRIX®**

**Prevention of varicella infection (chickenpox)**

- **By subcutaneous injection, or by intramuscular injection**
  - Child 1-17 years: 0.5 mL every 4–6 weeks for 2 doses, to be administered preferably into the deltoid region
  - Adult: 0.5 mL every 4–6 weeks for 2 doses, to be administered preferably into the deltoid region

**VARIVAX®**

**Prevention of varicella infection (chickenpox)**

- **By subcutaneous injection, or by intramuscular injection**
  - Child 1-12 years: 0.5 mL for 2 doses, interval of at least 4 weeks between each dose, to be administered into the deltoid region (or higher anterolateral thigh in young children)
  - Child 13-17 years: 0.5 mL every 4–8 weeks for 2 doses, to be administered preferably into the deltoid region
  - Adult: 0.5 mL every 4–8 weeks for 2 doses, to be administered preferably into the deltoid region

**Prevention of varicella infection (chickenpox) in children with asymptomatic HIV infection**

- **By subcutaneous injection, or by intramuscular injection**
  - Child 1-12 years: 0.5 mL every 12 weeks for 2 doses, to be administered into the deltoid region (or higher anterolateral thigh in young children)

**ZOSTAVAX®**

**Prevention of herpes zoster (shingles)**

- **By subcutaneous injection**
  - Adult 70-79 years: 0.65 mL for 1 dose, to be administered preferably into the deltoid region

**CAUTIONS** Post-vaccination close contact with susceptible individuals

**CAUTIONS, FURTHER INFORMATION**

Rarely, the varicella–zoster virus vaccine has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:

- varicella–susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy.

Healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with patients until the lesions have crusted. Those who develop a localised rash after vaccination should cover the lesions and be allowed to continue working unless in contact with patients at high risk of severe varicella.
Administration with MMR vaccine
Varicella–zoster and MMR vaccines can be given on the same day or separated by a 4-week minimum interval. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of the vaccine given second may be considered.

SIDE-EFFECTS
- Rare
- Frequency not known

CONCEPTION AND CONTRACEPTION
Avoid pregnancy for 3 months after vaccination.

PRESCRIBING AND DISPENSING INFORMATION
ZOSTAVAX® Advice in the BNF may differ from that in product literature.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
EXCIPIENTS: May contain Neomycin
- Varilrix (GlaxoSmithKline UK Ltd)
  Varilrix vaccine powder and solvent for solution for injection 0.5ml vials | 1 vial £5.51

Powder and solvent for suspension for injection
EXCIPIENTS: May contain Gelatin, neomycin
- Varivax (sanofi pasteur MSD Ltd)
  Varivax vaccine powder and solvent for suspension for injection 0.5ml vials | 1 vial £4.28
- Zostavax (sanofi pasteur MSD Ltd)
  Zostavax vaccine powder and solvent for suspension for injection 0.65ml pre-filled syringes | 1 pre-filled disposable injection £99.96

Yellow fever vaccine, live

INDICATIONS AND DOSE
Immunisation against yellow fever
- BY DEEP SUBCUTANEOUS INJECTION
  - Child 6–8 months (administered on expert advice): Infants under 9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (consult product literature or local protocols)
  - Child 9 months–17 years: 0.5 mL for 1 dose
  - Adult: 0.5 mL for 1 dose

CONTRA-INDICATIONS
- Children under 6 months - history of thymus dysfunction
- Individuals over 60 years — greater risk of adverse effects

CAUTIONS, FURTHER INFORMATION
- Administration with MMR vaccine
  Yellow fever and MMR vaccines should not be administered on the same day; there should be a 4-week minimum interval between the vaccines. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of MMR may be considered.

SIDE-EFFECTS
- Neurotropic disease - viscerotropic disease

SIDE-EFFECTS, FURTHER INFORMATION
- Vaccine-associated adverse effects
  - Very rare adverse effects, such as viscerotropic disease (yellow-fever vaccine-associated viscerotropic disease, YEL-AVD), a syndrome which may include metabolic acidosis, muscle and liver cirrhosis, and multi-organ failure. Neurological disorders (yellow fever vaccine-associated neurotropic disease, YEL-AND) such as encephalitis have also been reported. These very rare adverse effects usually occur after the first dose of yellow fever vaccine in those with no previous immunity.

ALLERGY AND CROSS-SENSITIVITY
- Yellow fever vaccine should only be considered under the guidance of a specialist in individuals with evidence of previous anaphylactic reaction to egg.

PREGNANCY
- Live yellow fever vaccine should not be given during pregnancy because there is a theoretical risk of fetal infection. Pregnant women should be advised not to travel to areas at high risk of yellow fever. If exposure cannot be avoided during pregnancy, then the vaccine should be given if the risk from disease in the mother outweighs the risk to the fetus from vaccination.

BREAST FEEDING
- Avoid; seek specialist advice if exposure to virus cannot be avoided.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for suspension for injection
- Stamaril (sanofi pasteur MSD Ltd)
  Stamaril vaccine powder and solvent for suspension for injection 0.5ml vials | 1 vial £33.10
Chapter 15
Anaesthesia

Contents

General anaesthesia

Overview

Several different types of drug are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation or with an intravenously administered drug; anaesthesia is maintained with an intravenous or inhalational anaesthetic. Analgesics, usually short-acting opioids, are also used. The use of neuromuscular blocking drugs necessitates intermittent positive-pressure ventilation. Following surgery, anticholinesterases can be given to reverse the effects of neuromuscular blocking drugs; specific antagonists can be used to reverse central and respiratory depression caused by some drugs used in surgery. A local topical anaesthetic can be used to reduce pain at the injection site.

Individual requirements vary considerably and the recommended doses are only a guide. Smaller doses are indicated in ill, shocked, or debilitated patients and in significant hepatic impairment, while robust individuals may require larger doses. The required dose of induction agent may be less if the patient has been premedicated with a sedative agent or if an opioid analgesic has been used.

Intravenous anaesthetics

Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout surgery. Intravenous anaesthetics nearly all produce their effect in one arm-brain circulation time. Extreme care is required in surgery of the mouth, pharynx, or larynx where the airway may be difficult to maintain (e.g. in the presence of a tumour in the pharynx or larynx).

To facilitate tracheal intubation, induction is usually followed by a neuromuscular blocking drug or a short-acting opioid.

The doses of all intravenous anaesthetic drugs should be titrated to effect (except when using ‘rapid sequence induction’); lower doses may be required in premedicated patients.

Total intravenous anaesthesia

This is a technique in which major surgery is carried out with all drugs given intravenously. Respiration can be spontaneous, or controlled with oxygen-enriched air. Neuromuscular blocking drugs can be used to provide relaxation and prevent reflex muscle movements. The main problem to be overcome is the assessment of depth of anaesthesia. Target Controlled Infusion (TCI) systems can be used to titrate intravenous anaesthetic infusions to predicted plasma-drug concentrations in ventilated adult patients.

Drugs used for intravenous anaesthesia

Propofol p. 1175, the most widely used intravenous anaesthetic, can be used for induction or maintenance of anaesthesia in adults and children, but it is not commonly used in neonates. Propofol is associated with rapid recovery and less hangover effect than other intravenous anaesthetics. Propofol can also be used for sedation during diagnostic procedures and sedation in adults in intensive care.

Thiopental sodium p. 316 is a barbiturate that is used for induction of anaesthesia, but has no analgesic properties. Induction is generally smooth and rapid, but dose-related cardiovascular and respiratory depression can occur. Awakening from a moderate dose of thiopental sodium is rapid because the drug redistributes into other tissues, particularly fat. However, metabolism is slow and sedative effects can persist for 24 hours. Repeated doses have a cumulative effect and recovery is much slower.

Etomidate p. 1177 is an intravenous agent associated with rapid recovery without a hangover effect. Etomidate causes less hypotension than thiopental sodium and propofol during induction. It produces a high incidence of extraneous muscle movements, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

Ketamine p. 1189 is used rarely. Ketamine causes less hypotension than thiopental sodium and propofol during induction. It is used mainly for paediatric anaesthesia, particularly when repeated administration is required (such as for serial burns dressings); recovery is relatively slow and there is a high incidence of extraneous muscle movements. The main disadvantage of ketamine is the high incidence of hallucinations, nightmares, and other transient psychotic effects; these can be reduced by a benzodiazepine such as diazepam p. 321 or midazolam p. 318.

Inhalational anaesthetics

Inhalational anaesthetics include gases and volatile liquids. Gaseous anaesthetics require suitable equipment for storage and administration. Volatile liquid anaesthetics are administered using calibrated vaporisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times. Higher concentrations of oxygen (greater than 30%) are usually required during inhalational anaesthesia when nitrous oxide p. 1177 is being administered.
Anaesthesia

Volatile liquid anaesthetics

Volatile liquid anaesthetics can be used for induction and maintenance of anaesthesia, and following induction with an intravenous anaesthetic.

Isofluorane p. 1177 is a volatile liquid anaesthetic. Heart rhythm is generally stable during isoflurane anaesthesia, but heart-rate can rise, particularly in younger patients. Systemic arterial pressure and cardiac output can fall, owing to a decrease in systemic vascular resistance. Muscle relaxation occurs and the effects of muscle relaxant drugs are potentiated. Isoflurane is the preferred inhalational anaesthetic for use in obstetrics.

Desflurane p. 1177 is a rapid acting volatile liquid anaesthetic; it is reported to have about one-fifth the potency of isoflurane. Emergence and recovery from anaesthesia are particularly rapid because of its low solubility. Desflurane is not recommended for induction of anaesthesia as it is irritant to the upper respiratory tract.

Sevoflurane p. 1178 is a rapid acting volatile liquid anaesthetic and is more potent than desflurane. Emergence and recovery are particularly rapid, but slower than desflurane. Sevoflurane is non-irritant and is therefore often used for inhalational induction of anaesthesia; it has little effect on heart rhythm compared with other volatile liquid anaesthetics.

Nitrous oxide

Nitrous oxide is used for maintenance of anaesthesia and, in sub-anaesthetic concentrations, for analgesia. For anaesthesia, nitrous oxide is commonly used in a concentration of 50 to 66% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents. Nitrous oxide is unsatisfactory as a sole anaesthetic owing to lack of potency, but is useful as part of a combination of drugs since it allows a significant reduction in dosage.

For analgesia (without loss of consciousness), a mixture of nitrous oxide and oxygen containing 50% of each gas (Entonox™, Equanox™) is used. Self-administration using a demand valve is popular in obstetric practice, for changing painful dressings, as an aid to postoperative physiotherapy, and in emergency ambulances.

Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intra-ocular gas injection.

Malignant hyperthermia

Malignant hyperthermia is a rare but potentially lethal complication of anaesthesia. It is characterised by a rapid rise in temperature, increased muscle rigidity, tachycardia, and acidosis. The most common triggers of malignant hyperthermia are the volatile anaesthetics. Suxamethonium chloride p. 1181 has also been implicated, but malignant hyperthermia is more likely if it is given following a volatile anaesthetic. Volatile anaesthetics and suxamethonium chloride should be avoided during anaesthesia in patients at high risk of malignant hyperthermia.

Dantrolene sodium p. 1191 is used in the treatment of malignant hyperthermia.

Sedation, anaesthesia, and resuscitation in dental practice

Overview

Sedation for dental procedures should be limited to conscious sedation. Diazepam p. 321 and temazepam p. 451 are effective anxiolytics for dental treatment in adults.

For details of sedation, anaesthesia, and resuscitation in dental practice see A Conscious Decision: A review of the use of general anaesthesia and conscious sedation in primary dental care; report by a group chaired by the Chief Medical Officer and Chief Dental Officer, July 2000 and associated documents. Further details can also be found in Standards for Conscious Sedation in the Provision of Dental Care; report of an Intercollegiate Advisory Committee for Sedation in Dentistry, 2015 www.rcseng.ac.uk/dental-faculties/fds/publications-guidelines/standards-for-conscious-sedation-in-the-provision-of-dental-care

Surgery and long-term medication

Overview

The risk of losing disease control on stopping long-term medication before surgery is often greater than the risk posed by continuing it during surgery. It is vital that the anaesthetist knows about all drugs that a patient is (or has been) taking.

Patients with adrenal atrophy resulting from long-term corticosteroid use may suffer a precipitous fall in blood pressure unless corticosteroid cover is provided during anaesthesia and in the immediate postoperative period. Anaesthetists must therefore know whether a patient is, or has been, receiving corticosteroids (including high-dose inhaled corticosteroids).

Other drugs that should normally not be stopped before surgery include antiepileptics, antiparkinsonian drugs, antipsychotics, anxiolytics, bronchodilators, cardiovascular drugs (but see potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor antagonists), glaucoma drugs, immunosuppressants, drugs of dependence, and thyroid or antithyroid drugs. Expert advice is required for patients receiving antivirals for HIV infection. See general advice on surgery in diabetic patients in Insulins and anti-diabetic drugs p. 627, Diabetes and surgery.

Patients taking antiplatelet medication or an oral anticoagulant present an increased risk for surgery. In these circumstances, the anaesthetist and surgeon should assess the relative risks and decide jointly whether the antiplatelet or the anticoagulant drug should be stopped or replaced with heparin (unfractionated) p. 125 or low molecular weight heparin therapy.

Drugs that should be stopped before surgery include combined oral contraceptives, see Contraceptives, hormonal p. 723; for advice on hormone replacement therapy, see Sex hormones p. 686. MAOIs can have important interactions with some drugs used during surgery, such as pethidine hydrochloride p. 434. Tricyclic antidepressants need not be stopped, but there may be an increased risk of arrhythmias and hypotension (and dangerous interactions with vasopressor drugs); therefore, the anaesthetist should be informed if they are not stopped. Lithium should be stopped 24 hours before major surgery but the normal dose can be continued for minor surgery (with careful monitoring of fluids and electrolytes). Potassium-sparing diuretics may need to be withheld on the morning of surgery because hyperkalaemia may develop if renal perfusion is impaired or if there is tissue damage. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists can
be associated with severe hypotension after induction of anaesthesia; these drugs may need to be discontinued 24 hours before surgery. Herbal medicines may be associated with adverse effects when given with anaesthetic drugs and consideration should be given to stopping them before surgery.

**ANAESTHETICS, GENERAL** > **INTRAVENOUS ANAESTHETICS**

**Etomidate**

- **INDICATIONS AND DOSE**
  - **Induction of anaesthesia**
    - By slow intravenous injection
      - Adult: 150–300 micrograms/kg (max. per dose 60 mg), to be administered over 30–60 seconds (60 seconds in patients in whom hypotension might be hazardous)
      - Elderly: 150–200 micrograms/kg (max. per dose 60 mg), to be administered over 30–60 seconds (60 seconds in patients in whom hypotension might be hazardous)

**IMPORTANT SAFETY INFORMATION**

Etomidate should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- **CAUTIONS**
  - Acute circulatory failure (shock) • Acute porphyrias p. 930 (avoid) • Adrenal insufficiency • Cardiovascular disease • Elderly • Fixed cardiac output • Hypovolaemia

- **INTERACTIONS**
  - Appendix 1 (anaesthetics, general).

- **SIDE-EFFECTS**
  - Common or very common
    - Apnoea • Hyperventilation • Hypotension • Nausea • Rash • Stridor • Vomiting
  - Uncommon
    - Arrhythmias • Cough • Hiccups • Hypersalivation • Hypertension • Phlebitis
  - Frequency not known
    - AV block • Cardiac arrest • Excessive muscle movement (high incidence) • Pain on injection • Respiratory depression • Seizures • Shivering • Stevens-Johnson syndrome

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Pain on injection Can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction.
  - Excessive muscle movement Excessive muscle movements can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

- **PREGNANCY**
  - May depress neonatal respiration if used during delivery.

- **BREAST FEEDING**
  - Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

- **HEPATIC IMPAIRMENT**
  - Reduce dose in liver cirrhosis.

- **DIRECTIONS FOR ADMINISTRATION**
  - To be administered over 30–60 seconds (60 seconds in patients in whom hypotension might be hazardous).

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - **EXCIPIENTS:** May contain Propylene glycol
      - Hypnomidate (Janssen-Cilag Ltd)
        - Etomidate 2 mg per 1 ml Hypnomidate 20mg/10ml solution for injection ampoules | 5 ampoule £6.90
    - **Emulsion for injection**
      - Etomidate-Lipuro (B Braun Medical Ltd)
        - Etomidate 2 mg per 1 ml Etomidate-Lipuro 20mg/10ml emulsion for injection ampoules | 10 ampoule £15.62

**Propofol**

- **INDICATIONS AND DOSE**
  - **Induction of anaesthesia using 0.5% or 1% injection**
    - By slow intravenous injection, or by intravenous infusion
  - Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response, for debilitated patients use dose for 55 years and over
  - Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response

  - **Induction of anaesthesia using 2% injection**
    - By intravenous infusion
  - Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response. For debilitated patients use dose for 55 years and over
  - Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response

  - **Maintenance of anaesthesia using 1% injection**
    - Initially by intravenous infusion
  - Adult: Usual dose 4–12 mg/kg/hour, alternatively (by slow intravenous injection) 25–50 mg, dose may be repeated according to response, for debilitated patients use dose for elderly
  - Elderly: Usual dose 3–6 mg/kg/hour, alternatively (by slow intravenous injection) 25–50 mg, dose may be repeated according to response

  - **Maintenance of anaesthesia using 2% injection**
    - By intravenous infusion
  - Adult: Usual dose 4–12 mg/kg/hour, for debilitated patients use dose for elderly
  - Elderly: Usual dose 3–6 mg/kg/hour

  - **Sedation of ventilated patients in intensive care using 1% or 2% injection**
    - By continuous intravenous infusion
  - Adult: Usual dose 0.3–4 mg/kg/hour, adjusted according to response

  - **Induction of sedation for surgical and diagnostic procedures using 0.5% or 1% injection**
    - By slow intravenous injection
  - Adult: Initially 0.5–1 mg/kg, to be administered over 1–5 minutes, dose and rate of administration adjusted according to desired level of sedation and response

  - **Maintenance of sedation for surgical and diagnostic procedures using 0.5% injection**
    - Initially by intravenous infusion
  - Adult: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by continued →
Anaesthesia

RENAL IMPAIRMENT

Propofol infusion syndrome

Extraneous muscle movement

Bradycardia

Frequency not known

SIDE-EFFECTS, FURTHER INFORMATION

Bradyarrhythmias - hypotension - tachycardia - transient anaphylaxis

SIDE-EFFECTS

CAUTIONS Acute circulatory failure (shock) - cardiac impairment - cardiovascular disease - elderly - epilepsy - fixed cardiac output - hypotension - hypervolaemia - raised intracranial pressure - respiratory impairment

INTERACTIONS Appendix 1 (anaesthetics, general).

SIDE-EFFECTS

Common or very common Headache - hypotension - tachycardia - transient anaphylaxis

Uncommon Phlebitis - thrombosis

Rare Anaphylaxis - arrhythmia - convulsions (onset can be delayed) - delayed recovery from anaesthesia - euphoria

Very rare Discoloration of urine - pancreatitis - pulmonary oedema - sexual disinhibition

Frequency not known Bradyarrhythmias - pain on intravenous injection - propofol infusion syndrome - significant extraneous muscle movements

SIDE-EFFECTS, FURTHER INFORMATION

Bradyarrhythmias - hypotension - tachycardia - transient anaphylaxis

Extraneous muscle movement

Pain on injection

Propofol infusion syndrome

Pregnancy

Breast feeding

Hepatic impairment

Renal impairment

MONITORING REQUIREMENTS

Monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days.

DIRECTIONS FOR ADMINISTRATION

Shake before use; microbiological filter not recommended; may be administered via a Y-piece close to injection site or administered with Glucose 5% or Sodium chloride 0.9% 0.5% emulsion for injection or intermittent infusion; may be administered undiluted, or diluted with Glucose 5% or Sodium chloride 0.9%; dilute to a concentration not less than 1 mg/ml. 1% emulsion for injection or infusion; may be administered undiluted, or diluted with Glucose 5% (Diprivan®) or Propofol-Lipuro® or Sodium chloride 0.9% (Propofol-Lipuro®) only; dilute to a concentration not less than 2 mg/ml; use within 6 hours of preparation. 2% emulsion for infusion; do not dilute.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Emulsion for injection

Diprivan (AstraZeneca UK Ltd)

Propofol 10 mg per 1 ml Diprivan 1% emulsion for injection 20ml ampoules | 5 ampoule £15.36 (Hospital only)

Propofol-Lipuro (B.Braun Melsungen AG)

Propofol 5 mg per 1 ml Propofol-Lipuro 0.5% emulsion for injection 20ml ampoules | 5 ampoule £14.71

Emulsion for infusion

Diprivan (AstraZeneca UK Ltd)

Propofol 10 mg per 1 ml Diprivan 1% emulsion for infusion 50ml pre-filled syringes | 1 pre-filled disposable injection £10.68

Propofol 20 mg per 1 ml Diprivan 2% emulsion for infusion 50ml pre-filled syringes | 1 pre-filled disposable injection £15.16

ANAESTHETICS, GENERAL > VOLATILE LIQUID ANAESTHETICS

Volatile halogenated anaesthetics

IMPORTANT SAFETY INFORMATION

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

CONTRA-INDICATIONS

Susceptibility to malignant hyperthermia

CAUTIONS Can trigger malignant hyperthermia - raised intracranial pressure (can increase cerebrospinal pressure)

SIDE-EFFECTS

Common or very common Arrhythmias - cardiorespiratory depression - hypotension

Frequency not known Convulsions - mood changes (that can last several days)

ALLERGY AND CROSS-SENSITIVITY

Can cause hepatotoxicity in those sensitised to halogenated anaesthetics.

DIRECTIONS FOR ADMINISTRATION

Volatile liquid anaesthetics are administered using calibrated vapourisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the...
carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks
Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of driving or undertaking skilled tasks afterwards. For a short general anaesthetic, the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking **alcohol** should also be emphasised.

### Desflurane

**INDICATIONS AND DOSE**

**Induction of anaesthesia (but not recommended)**
- **BY INHALATION**
  - Adult: 4–11%, to be inhaled through specifically calibrated vaporiser

**Maintenance of anaesthesia (in nitrous oxide-oxygen)**
- **BY INHALATION**
  - Adult: 2–6%, to be inhaled through a specifically calibrated vaporiser

**INTERACTIONS** → Appendix 1 (anaesthetics, general).

**SIDE-EFFECTS** Apnoea, breath-holding, cough, increased secretions, laryngospasm

**PREGNANCY** May depress neonatal respiration if used during delivery.

**BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks
Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking **alcohol** should also be emphasised.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Inhalation vapour**
- **Desflurane (Non-proprietary)**
  - Desflurane 1 ml per 1 ml | 240 ml [P]
  - Desflurane volatile liquid | 250 ml [P]
  - no price available (Hospital only)

### Isoflurane

**INDICATIONS AND DOSE**

**Induction of anaesthesia (in oxygen or nitrous oxide-enriched air)**
- **BY INHALATION**
  - Adult: 2.5–8.5%, to be inhaled through a specifically calibrated vaporiser

**Maintenance of anaesthesia (in oxygen or oxygen-enriched air)**
- **BY INHALATION**
  - Adult: 2.5–8.5%, to be inhaled through a specifically calibrated vaporiser

**INTERACTIONS** → Appendix 1 (anaesthetics, general).

**SIDE-EFFECTS** Apnoea, breath-holding, cough, increased secretions, laryngospasm

**PREGNANCY** May depress neonatal respiration if used during delivery.

**BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks
Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking **alcohol** should also be emphasised.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Inhalation vapour**
- **Isoflurane (Non-proprietary)**
  - Isoflurane 1 ml per 1 ml | 250 ml [P] £35.29 (Hospital only)
  - Isoflurane volatile liquid | 250 ml [P] £47.50 (Hospital only)
  - AErrane (Baxter Healthcare Ltd)
    - Isoflurane 1 ml per 1 ml | 250 ml [P] no price available (Hospital only)

### Nitrous oxide

**INDICATIONS AND DOSE**

**Maintenance of anaesthesia in conjunction with other anaesthetic agents**
- **BY INHALATION**
  - Adult: 50–66%, to be administered using suitable anaesthetic apparatus in oxygen

**Anaesthesia**
- **BY INHALATION**
  - Adult: Up to 50%, to be administered using suitable anaesthetic apparatus in oxygen, adjusted according to the patient’s needs

**IMPORTANT SAFETY INFORMATION**

Nitrous oxide should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

**CAUTIONS** Entrapped air following recent underwater dive, pneumothorax, presence of intracranial air after head injury, recent intra-ocular gas injection

**CAUTIONS, FURTHER INFORMATION**

Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intra-ocular gas injection.

**INTERACTIONS** → Appendix 1 (anaesthetics, general).
Sevoflurane

- **INDICATIONS AND DOSE**
  - **Induction of anaesthesia (in oxygen or nitrous oxide-oxygen)**
    - **By Inhalation**
      - Adult: Initially 0.5–1 %, then increased to up to 8 %, increased gradually, according to response, to be administered using specifically calibrated vaporiser
  - **Maintenance of anaesthesia (in oxygen or nitrous oxide-oxygen)**
    - **By Inhalation**
      - Adult: 0.5–3 %, adjusted according to response, to be administered using specifically calibrated vaporiser

- **CAUTIONS** Susceptibility to QT-interval prolongation

- **INTERACTIONS** → Appendix 1 (anaesthetics, general).
  - Sevoflurane can interact with carbon dioxide absorbents to form compound A, a potentially nephrotoxic vinyl ether. However, in spite of extensive use, no cases of sevoflurane-induced permanent renal injury have been reported and the carbon dioxide absorbents used in the UK produce very low concentrations of compound A, even in low-flow anaesthetic systems.

- **SIDE-EFFECTS** Cardiac arrest - dystonia - leucopenia - torsade de pointes - urinary retention

- **PREGNANCY** May depress neonatal respiration if used during delivery.

- **BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

- **MEDICINAL FORMS**
  - Inhalation vapour
    - Sevoflurane (Non-proprietary)
      - Sevoflurane 1 ml per 1 ml: Sevoflurane volatile liquid | 250 ml (Pres No 1175)

1 Anaesthesia adjuvants

**Pre-medication and peri-operative drugs**

**Drugs that affect gastric pH**

Regurgitation and aspiration of gastric contents (Mendelson’s syndrome) can be an important complication of general anaesthesia, particularly in obstetrics and during emergency surgery, and requires prophylaxis against acid aspiration. Prophylaxis is also needed in those with gastroesophageal reflux disease and in circumstances where gastric emptying may be delayed.

A H₂-receptor antagonist can be used before surgery to increase the pH and reduce the volume of gastric fluid. It does not affect the pH of fluid already in the stomach and this limits its value in emergency procedures; an oral H₂-receptor antagonist can be given 1–2 hours before the procedure. Antacids are frequently used to neutralise the acidity of the fluid already in the stomach; ‘clear’ (non-particulate) antacids such as sodium citrate p. 721 are preferred.

**Antimuscarinic drugs**

Antimuscarinic drugs are used (less commonly nowadays) as premedicants to dry bronchial and salivary secretions which are increased by intubation, upper airway surgery, or some inhalational anaesthetics. They are also used before or with neostigmine p. 583 to prevent bradycardia, excessive salivation, and other muscarinic actions of neostigmine. They also prevent bradycardia and hypotension associated with drugs such as propofol p. 1175 and suxamethonium chloride p. 1181.

Atropine sulfate p. 1179 is now rarely used for premedication but still has an emergency role in the
treatment of vagotonic side-effects. Atropine sulfate may have a role in acute arrhythmias after myocardial infarction. Hyoscine hydrobromide p. 409 reduces secretions and also provides a degree of amnesia, sedation, and anti-emesis. Unlike atropine sulfate it may produce bradycardia rather than tachycardia.

Glycopyronium bromide p. 1180 reduces salivary secretions. When given intravenously it produces less tachycardia than atropine sulfate. It is widely used with neostigmine for reversal of non-depolarising neuromuscular blocking drugs.

Phenothiazines do not effectively reduce secretions when used alone.

**Sedative drugs**

Fear and anxiety before a procedure (including the night before) can be minimised by using a sedative drug, usually a benzodiazepine. Premedication may also augment the action of anaesthetics and provide some degree of pre-operative amnesia. The choice of drug depends on the individual, the nature of the procedure, the anaesthetic to be used, and other prevailing circumstances such as outpatients, obstetrics, and availability of recovery facilities. The choice also varies between elective and emergency procedures.

Premedics can be given the night before major surgery; a further, smaller dose may be required before surgery. Alternatively, the first dose may be given on the day of the procedure.

**Benzodiazepines**

Benzodiazepines possess useful properties for premedication including relief of anxiety, sedation, and amnesia; short-acting benzodiazepines taken by mouth are the most common premedicants. Benzodiazepines are also used in intensive care units for sedation, particularly in those receiving assisted ventilation. Flumazenil p. 1213 is used to antagonise the effects of benzodiazepines.

Diazepam p. 321 is used to produce mild sedation with amnesia. It is a long-acting drug with active metabolites and a second period of drowsiness can occur several hours after its administration. Peri-operative use of diazepam in children is not recommended; its effect and timing of administration. Peri-operative use of diazepam in children is not recommended; its effect and timing of administration depend on the severity of poisoning.

Diazepam is relatively insoluble in water and preparations formulated in organic solvents are painful on intravenous injection and give rise to a high incidence of venous thrombosis (which may not be noticed for several days after the injection). Intramuscular injection of diazepam is painful and absorption is erratic. An emulsion formulated for intravenous injection is less irritating and reduces the risk of venous thrombosis; it is not suitable for intramuscular injection.

Temazepam p. 451 is given by mouth for premedication and has a shorter duration of action and a more rapid onset than oral diazepam; anxiolytic and sedative effects last about 90 minutes although there may be residual drowsiness.

Lorazepam p. 317 produces more prolonged sedation than temazepam and it has marked amnesic effects.

Midazolam p. 318 is a water-soluble benzodiazepine that is often used in preference to intravenous diazepam; recovery is faster than from diazepam, but may be significantly longer in the elderly, in patients with a low cardiac output, or after repeated dosing. Midazolam is associated with profound sedation when high doses are given intravenously or when it is used with certain other drugs.

**Other drugs for sedation**

Dexmedetomidine p. 1190 and clonidine hydrochloride p. 136 are alpha₂-adrenergic agonists with sedative properties. Dexmedetomidine is licensed for the sedation of patients receiving intensive care who need to remain responsive to verbal stimulation. Clonidine hydrochloride [unlicensed indication] can be used by mouth or by intravenous injection as a sedative agent when adequate sedation cannot be achieved with standard treatment.

**Antagonists for central and respiratory depression**

Respiratory depression is a major concern with opioid analgesics and it may be treated by artificial ventilation or be reversed by naloxone hydrochloride p. 1214. Naloxone hydrochloride will immediately reverse opioid-induced respiratory depression but the dose may have to be repeated because of the short duration of action of naloxone hydrochloride; however, naloxone hydrochloride will also antagonise the analgesic effect.

Flumazenil is a benzodiazepine antagonist for the reversal of the central sedative effects of benzodiazepines after anaesthetic and similar procedures. Flumazenil has a shorter half-life and duration of action than diazepam or midazolam so patients may become resedated.

Doxapram hydrochloride p. 280 is a central and respiratory stimulant but is of limited value in anaesthesia.

**ANTIMUSCARINICS**

**Atropine sulfate**

- **INDICATIONS AND DOSE**
  - Bradycardia due to acute massive overdose of beta-blockers
    - **BY INTRAVENOUS INJECTION**
      - Child: 40 micrograms/kg (max. per dose 3 mg)
      - Adult: 3 mg
  - Treatment of poisoning by organophosphorus insecticide or nerve agent (in combination with pralidoxime chloride)
    - **BY INTRAVENOUS INJECTION**
      - Child: 20 micrograms/kg every 5–10 minutes (max. per dose 2 mg) until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished, frequency of administration dependent on the severity of poisoning
      - Adult: 2 mg every 5–10 minutes until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished, frequency of administration dependent on the severity of poisoning
  - Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm
    - **BY MOUTH**
      - Adult: 0.6–1.2 mg daily, dose to be taken at night
  - Premedication
    - **BY INTRAVENOUS INJECTION**
      - Child 12-17 years: 300–600 micrograms, to be administered immediately before induction of anaesthesia
      - Adult: 300–600 micrograms, to be administered immediately before induction of anaesthesia
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
      - Child 12-17 years: 300–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia
      - Adult: 300–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia
  - **Intra-operative bradycardia**
    - **BY INTRAVENOUS INJECTION**
      - Child 12-17 years: 300–600 micrograms, larger doses may be used in emergencies
      - Adult: 300–600 micrograms, larger doses may be used in emergencies
Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block

- **BY INTRAVENOUS INJECTION**
- Child 12–17 years: 0.6–1.2 mg
- Adult: 0.6–1.2 mg

Excessive bradycardia associated with beta-blocker use

- **BY INTRAVENOUS INJECTION**
- Adult: 0.6–2.4 mg in divided doses (max. per dose 600 micrograms)

Bradycardia following myocardial infarction (particularly if complicated by hypotension)

- **BY INTRAVENOUS INJECTION**
- Adult: 500 micrograms every 3–5 minutes; maximum 3 mg per course

**UNLICENSED USE** Not licensed for use in children under 12 years for intra-operative bradycardia or by intravenous route for premedication.

### IMPORTANT SAFETY INFORMATION

Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by, or under the direct supervision of, personnel experienced in their use.

- **PREGNANCY** Not known to be harmful; manufacturer advises caution.
- **BREAST FEEDING** May suppress lactation; small amount present in milk—manufacturer advises caution.
- **MONITORING REQUIREMENTS**
  - Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block. Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may result; close monitoring of the patient is necessary.

- **LESS SUITABLE FOR PRESCRIBING** Atropine tablets less suitable for prescribing. Any clinical benefit as a gastro-intestinal antispasmodic is outweighed by atropinic side-effects.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - With intramuscular use or intravenous use or subcutaneous use Prescription medicine restriction does not apply where administration is for saving life in emergency.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution containing the same drug.

**Tablet**

- **Atropine sulfate (Non-proprietary)**
  - Atropine sulfate 600 microgram Atropine 600microgram tablets | 28 tablet £52.92 DT price = £49.53

**Solution for injection**

- **Atropine sulfate (Non-proprietary)**
  - Atropine sulfate 100 microgram per 1 ml Atropine 500micrograms/5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £7.40–£13.00 | 10 pre-filled disposable injection £69.00–£130.00
  - Atropine sulfate 1 mg per 1 ml Atropine 1mg/1ml solution for injection ampoules | 10 ampoule £68.72–£72.77 DT price = £70.75
  - Atropine sulfate 200 microgram per 1 ml Atropine 1mg/5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £7.08–£13.00 | 10 pre-filled disposable injection £69.00–£130.00
  - Atropine sulfate 300 microgram per 1 ml Atropine 3mg/10ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £7.08–£13.00 DT price = £7.29 | 10 pre-filled disposable injection £69.00–£130.00
  - Atropine sulfate 400 microgram per 1 ml Atropine 400micrograms/1ml solution for injection ampoules | 10 ampoule £74.14–£78.94 DT price = £76.54

**Glycopyrronium bromide**

(Glycopyrrolate)

**INDICATIONS AND DOSE**

Premedication at induction

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS**
- Adult: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms)

Intra-operative bradycardia

- **BY INTRAVENOUS INJECTION**
- Adult: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms), repeated if necessary

Control of muscarinic side-effects of neostigmine in reversal of non-depolarising neuromuscular block

- **BY INTRAVENOUS INJECTION**
- Adult: 10–15 micrograms/kg, alternatively, 200 micrograms per 1 mg of neostigmine to be administered

Bowel colic in palliative care | Excessive respiratory secretions in palliative care

- **BY SUBCUTANEOUS INJECTION**
- Adult: 200 micrograms every 4 hours and when required, hourly use is occasionally necessary, particularly in excessive respiratory secretions

- **BY SUBCUTANEOUS INFUSION**
- Adult: 0.6–1.2 mg/24 hours

**IMPORTANT SAFETY INFORMATION**

Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by, or under the direct supervision of, personnel experienced in their use.

**PRESCRIBING AND DISPENSING INFORMATION**

Palliative care

For further information on the use of glycopyrronium bromide in palliative care, see www.palliativedrugs.com/formulary/en/glycopyrronium.html.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Glycopyrronium bromide (Non-proprietary)**
  - Glycopyrronium bromide 200 microgram per 1 ml Glycopyrronium bromide 200micrograms/1ml solution for injection ampoules | 10 ampoule £14.00 DT price = £10.88
  - Glycopyrronium bromide 600micrograms/3ml solution for injection ampoules | 3 ampoule £8.00–£9.75 | 10 ampoule £11.50

Combinations available: Neostigmine with glycopyrronium bromide, p. 1185

### 1.1 Neuromuscular blockade

**Neuromuscular blockade**

Neuromuscular blocking drugs

Neuromuscular blocking drugs used in anaesthesia are also known as muscle relaxants. By specific blockade of the
neuromuscular junction they enable light anaesthesia to be used with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube. Their action differs from the muscle relaxants used in musculoskeletal disorders that act on the spinal cord or brain.

Patients who have received a neuromuscular blocking drug should always have their respiration assisted or controlled until the drug has been inactivated or antagonised. They should also receive sufficient concomitant inhalational or intravenous anaesthetic or sedative drugs to prevent awareness.

**Non-depolarising neuromuscular blocking drugs**

Non-depolarising neuromuscular blocking drugs (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction and their action can be reversed with anticholinesterases such as neostigmine p. 983. Non-depolarising neuromuscular blocking drugs can be divided into the aminosteroid group, comprising pancuronium bromide p. 1183, rocuronium bromide p. 1184, and vecuronium bromide p. 1184, and the benzylisoquinolinium group, comprising atracurium besilate p. 1182, cisatracurium p. 1183, and mivacurium p. 1183.

Non-depolarising neuromuscular blocking drugs have a slower onset of action than suxamethonium chloride below. These drugs can be classified by their duration of action as short-acting (15–30 minutes), intermediate-acting (30–40 minutes), and long-acting (60–120 minutes), although duration of action is dose-dependent. Drugs with a shorter or intermediate duration of action, such as atracurium besilate and vecuronium bromide, are more widely used than those with a longer duration of action, such as pancuronium bromide.

Non-depolarising neuromuscular blocking drugs have no sedative or analgesic effects and are not considered to trigger malignant hyperthermia.

For patients receiving intensive care and who require tracheal intubation and mechanical ventilation, a non-depolarising neuromuscular blocking drug is chosen according to its onset of effect, duration of action, and side-effects. Rocuronium bromide, with a rapid onset of effect, may facilitate intubation. Atracurium besilate or cisatracurium may be suitable for long-term neuromuscular blockade since their duration of action is not dependent on elimination by the liver or the kidneys.

Atracurium besilate, a mixture of 10 isomers, is a benzylisoquinolinium neuromuscular blocking drug with an intermediate duration of action. It undergoes non-enzymatic metabolism which is independent of liver and kidney function, thus allowing its use in patients with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release; histamine release can be minimised by administering slowly or in divided doses over at least 1 minute.

Cisatracurium is a single isomer of atracurium besilate. It is more potent and has a slightly longer duration of action than atracurium besilate and provides greater cardiovascular stability because cisatracurium lacks histamine-releasing effects.

Mivacurium, a benzylisoquinolinium neuromuscular blocking drug, has a short duration of action. It is metabolised by plasma cholinesterase and muscle paralysis is prolonged in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release can occur, particularly with rapid injection.

Pancuronium bromide, an aminosteroid neuromuscular blocking drug, has a long duration of action and is often used in patients receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

Rocuronium bromide exerts an effect within 2 minutes and has the most rapid onset of any of the non-depolarising neuromuscular blocking drugs. It is an aminosteroid neuromuscular blocking drug with an intermediate duration of action. It is reported to have minimal cardiovascular effects; high doses produce mild vagolytic activity.

Vercuronium bromide, an aminosteroid neuromuscular blocking drug, has an intermediate duration of action. It does not generally produce histamine release and lacks cardiovascular effects.

**Depolarising neuromuscular blocking drugs**

Suxamethonium chloride has the most rapid onset of action of any of the neuromuscular blocking drugs and is ideal if fast onset and brief duration of action are required, e.g. with tracheal intubation. Unlike the non-depolarising neuromuscular blocking drugs, its action cannot be reversed and recovery is spontaneous; anticholinesterases such as neostigmine potentiate the neuromuscular block.

Suxamethonium chloride should be given after anaesthetic induction because paralysis is usually preceded by painful muscle fasciculations. While tachycardia occurs with single use, bradycardia may occur with repeated doses in adults and with the first dose in children. Premedication with atropine reduces bradycardia as well as the excessive salivation associated with suxamethonium chloride use.

Prolonged paralysis may occur in dual block, which occurs with high or repeated doses of suxamethonium chloride and is caused by the development of a non-depolarising block following the initial depolarising block. Individuals with myasthenia gravis are resistant to suxamethonium chloride but can develop dual block resulting in delayed recovery. Prolonged paralysis may also occur in those with low or atypical plasma cholinesterase. Assisted ventilation should be continued until muscle function is restored.

**NEUROMUSCULAR BLOCKING DRUGS › DEPOLARISING**

### Suxamethonium chloride (sucinylcholine chloride)

- **DRUG ACTION** Suxamethonium acts by mimicking acetylcholine at the neuromuscular junction but hydrolysis is much slower than for acetylcholine; depolarisation is therefore prolonged, resulting in neuromuscular blockade.

- **INDICATIONS AND DOSE**

  **Neuromuscular blockade (short duration) during surgery and intubation**

  - BY INTRAVENOUS INJECTION
  - Adult: 1–1.5 mg/kg

  - **UNLICENSED USE** Doses of suxamethonium in BNF may differ from those in product literature.

- **IMPORTANT SAFETY INFORMATION**

  Should only be administered by, or under the direct supervision of, personnel experienced in its use.

- **CONTRA-INDICATIONS** Duchenne muscular dystrophy · family history of malignant hyperthermia · hyperkalaemia · low plasma-cholinesterase activity (including severe liver disease) · major trauma · neurological disease involving acute wasting of major muscle · personal or family history of congenital myotonic disease · prolonged immobilation of the musculature (risk of hyperkalaemia) · severe burns
**NEUROMUSCULAR BLOCKING DRUGS**

### Non-depolarising neuromuscular blocking drugs

**IMPORTANT SAFETY INFORMATION**

Non-depolarising neuromuscular blocking drugs should only be administered by, or under direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

- **CAUTIONS** Burns (resistance can develop, increased doses may be required) - cardiovascular disease (reduce rate of administration) - electrolyte disturbances (response unpredictable) - fluid disturbances (response unpredictable) - hypothermia (activity prolonged, lower doses required) - myasthenia gravis (activity prolonged, lower doses required) - neuromuscular disorders (response unpredictable)

- **INTERACTIONS** Appendix 1 (muscle relaxants).

- **ALLERGY AND CROSS-SENSITIVITY** Allergic cross-reactivity between neuromuscular blocking drugs has been reported; caution is advised in cases of hypersensitivity to these drugs.

- **PREGNANCY** Non-depolarising neuromuscular blocking drugs are highly ionised at physiological pH and are therefore unlikely to cross the placenta in significant amounts.

- **BREAST FEEDING** Non-depolarising neuromuscular blocking drugs are ionised at physiological pH and are unlikely to be present in milk in significant amounts. Breast-feeding may be resumed once the mother has recovered from neuromuscular block.

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**Atracurium besilate**

(Atracurium besylate)

- **INDICATIONS AND DOSE**
  - **Neuromuscular blockade (short to intermediate duration)**
    - **for surgery and intubation**
      - **INITIALLY BY INTRAVENOUS INJECTION**
        - **Adult**: Initially 300–600 micrograms/kg, then (by intravenous injection) 100–200 micrograms/kg as required, alternatively (by intravenous injection) initially 300–600 micrograms/kg, followed by (by intravenous infusion) 300–600 micrograms/kg/hour
  - **Neuromuscular blockade during intensive care**
    - **INITIALLY BY INTRAVENOUS INJECTION**
      - **Adult**: Initially 300–600 micrograms/kg, initial dose is optional, then (by intravenous infusion) 270–1770 micrograms/kg/hour; (by intravenous infusion) usual dose 650–780 micrograms/kg/hour

- **DOSES AT EXTREMES OF BODY-WEIGHT**
  - To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- **SIDE-EFFECTS**
  - **Very rare** Anaphylactoid reactions
  - **Frequency not known** Acute myopathy (after prolonged use in intensive care) - bronchospasm - hypotension - seizures - skin flushing - tachycardia

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for injection
- Suxamethonium chloride (Non-proprietary)
  - Suxamethonium chloride 50 mg per 1 ml: Suxamethonium chloride 100mg/2ml solution for injection ampoules 10 ampoule £28.80–£50.00
  - Anectine (GlaxoSmithKline UK Ltd)
  - Suxamethonium chloride 50 mg per 1 ml: Anectine 100mg/2ml solution for injection ampoules 5 ampoule £3.57

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**Atracurium besilate 50 mg per 1 ml**

Atracurium besilate 50 mg/5ml solution for injection ampoules 5 ampoule £17.50; 10 ampoule £35.00

**Tracrium (GlaxoSmithKline UK Ltd)**

Tracrium 50 mg/5ml solution for injection ampoules 5 ampoule £8.28

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Atracurium besilate (Non-proprietary)
  - Atracurium besilate 10 mg per 1 ml: Atracurium besilate 250mg/25ml solution for injection vials 1 vial £16.50
  - Atracurium besilate 25mg/2.5ml solution for injection ampoules 5 ampoule £9.25
  - Atracurium besilate 50mg/5ml solution for injection ampoules 5 ampoule £17.50; 10 ampoule £35.00
  - Tracrium (GlaxoSmithKline UK Ltd)
  - Atracurium besilate 10 mg per 1 ml: Tracrium 250mg/25ml solution for injection vials 2 vial £25.81
  - Tracrium 25mg/2.5ml solution for injection ampoules 5 ampoule £8.28
  - Tracrium 50mg/5ml solution for injection ampoules 5 ampoule £15.02

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**Non-depolarising**

- **Neuromuscular blocking drugs**
- **INDICATIONS AND DOSE**
- **DIRECTIONS FOR ADMINISTRATION**
- **SIDE-EFFECTS**
- **INTERACTIONS**
- **ALLERGY AND CROSS-SENSITIVITY**

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**Anaesthesia adjuvants**

**DEPOLARISING INTERACTIONS CAUTIONS**

Non-depolarising

- **MEDICINAL FORMS**
- **HEPATIC IMPAIRMENT**
- **BREAST FEEDING**
- **ALLERGY AND CROSS-SENSITIVITY**
- **Bradycardia**
- **SIDE-EFFECTS, FURTHER INFORMATION**
- **Bradycardia**

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**Suxamethonium chloride 50 mg per 1 ml**

Suxamethonium chloride 50 mg per 1 ml: Suxamethonium chloride 100mg/2ml solution for injection ampoules 10 ampoule £28.80–£50.00

**Atracurium injection/infusion, Genus**

- **Atracurium besilate (Non-proprietary)**
- **Solution for injection**
- **DOSAGE**
  - **Adult:** Initially 300–600 micrograms/kg, then (by intravenous injection) 100–200 micrograms/kg as required, alternatively (by intravenous injection) initially 300–600 micrograms/kg, followed by (by intravenous infusion) 300–600 micrograms/kg/hour

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**Bradycardia**

- **Frequency not known** Bradycardia (may occur with repeated doses) - hypertension - hypotension - rhabdomyolysis - tachycardia (occurs with single use)

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**TRACHEAL INTUBATION**

- **Adult:** Initially 300–600 micrograms/kg, then (by intravenous injection) 100–200 micrograms/kg as required, alternatively (by intravenous injection) initially 300–600 micrograms/kg, followed by (by intravenous infusion) 300–600 micrograms/kg/hour

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**Atracurium besilate 10 mg per 1 ml**

Atracurium besilate 10 mg/5ml solution for injection ampoules 5 ampoule £17.50; 10 ampoule £35.00

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**Bradycardia**

- **Frequency not known** Bradycardia (may occur with repeated doses) - hypertension - hypotension - rhabdomyolysis - tachycardia (occurs with single use)

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**Atracurium besilate 50 mg per 1 ml**

Atracurium besilate 50 mg/5ml solution for injection ampoules 5 ampoule £17.50; 10 ampoule £35.00

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**Atracurium besilate 250 mg per 1 ml**

Atracurium besilate 250mg/25ml solution for injection vials 1 vial £16.50

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**Atracurium besilate 25 mg per 1 ml**

Atracurium besilate 25mg/2.5ml solution for injection ampoules 5 ampoule £9.25

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**Atracurium besilate 50 mg per 1 ml**

Atracurium besilate 50mg/5ml solution for injection ampoules 5 ampoule £17.50; 10 ampoule £35.00
Cisatracurium

**INDICATIONS AND DOSE**

Neuromuscular blockade (intermediate duration) during surgery and intubation

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 150 micrograms/kg, then (by intravenous injection) maintenance 30 micrograms/kg every 20 minutes, alternatively (by intravenous infusion) initially 180 micrograms/kg/hour, then (by intravenous infusion) maintenance 60–120 micrograms/kg/hour, maintenance dose administered after stimulation.

Neuromuscular blockade (intermediate duration) during intensive care

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 150 micrograms/kg, initial dose is optional, then (by intravenous infusion) 180 micrograms/kg/hour, adjusted according to response; (by intravenous infusion) usual dose 30–600 micrograms/kg/hour.

**SIDE-EFFECTS**

Acute myopathy (after prolonged use in intensive care) - bradycardia.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Nimbex®, Nimbex Forte®), give continuously in Glucose 5% or Sodium Chloride 0.9%; solutions of 2 mg/mL and 5 mg/mL may be infused undiluted; alternatively dilute with infusion fluid to a concentration of 0.1–2 mg/mL.

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**INDICATIONS AND DOSE**

Neuromuscular blockade (long duration) during surgery and intubation

- **BY INTRAVENOUS INJECTION**
  - Adult: Initially 100 micrograms/kg, then 20 micrograms/kg as required.

Neuromuscular blockade (long duration) during intensive care

- **BY INTRAVENOUS INJECTION**
  - Adult: Initially 100 micrograms/kg, initial dose is optional, then 60 micrograms/kg every 60–90 minutes.

**SIDE-EFFECTS**

Acute myopathy (after prolonged use in intensive care) - hypertension - tachycardia

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute to a concentration of 500 micrograms/mL; may also be given undiluted. Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In asthma, cardiovascular disease or in those sensitive to reduced arterial blood pressure, give over 60 seconds.

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**SIDE-EFFECTS**

Burns (low plasma cholinesterase activity; dose titration required) - elderly

**SIDE-EFFECTS**

- Very rare: Anaphylactoid reactions
- Frequency not known: Bronchospasm - hypotension - skin flushing - tachycardia

**HEPATIC IMPAIRMENT**

Reduce dose in severe impairment.

**RENAI IMPAIRMENT**

Clinical effect prolonged in renal failure—reduce dose according to response.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Mivacron (GlaxoSmithKline UK Ltd)
  - Mivacurium (as Mivacurium chloride) 2 mg per 1 mL
    - Mivacron 10 mg/5 mL solution for injection ampoules | 5 ampoule £55.00
    - Mivacron 20 mg/10 mL solution for injection ampoules | 5 ampoule £22.57

**Mivacron**

**INDICATIONS AND DOSE**

Neuromuscular blockade (short duration) during surgery and intubation

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 70–250 micrograms/kg; (by intravenous injection) maintenance 100 micrograms/kg every 15 minutes, alternatively (by intravenous infusion) maintenance 8–10 micrograms/kg/minute, (by intravenous infusion) adjusted in steps of 1 microgram/kg/minute every 3 minutes if required; (by intravenous infusion) usual dose 6–7 micrograms/kg/minute.

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.
Rocuronium bromide

**INDICATIONS AND DOSE**

Neuromuscular blockade (intermediate duration) during surgery and intubation

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 600 micrograms/kg; (by intravenous injection) maintenance 150 micrograms/kg, alternatively (by intravenous infusion) maintenance 300–600 micrograms/kg/hour, adjusted according to response.
  - Elderly: Initially 600 micrograms/kg; (by intravenous injection) maintenance 75–100 micrograms/kg, alternatively (by intravenous infusion) maintenance up to 400 micrograms/kg/hour, adjusted according to response.

**RENAL IMPAIRMENT**

Very rare

**SIDE-EFFECTS**

- Very rare Anaphylactoid reactions
- Frequency not known Acute myopathy (after prolonged use in intensive care) - bronchospasm - hypotension - skin flushing - tachycardia

**HEPATIC IMPAIRMENT**

Reduce dose.

**RENAI IMPAIRMENT**

Reduce maintenance dose; prolonged paralysis.

**DIRECTIONS FOR ADMINISTRATION**

For continuous intravenous infusion or via drip tubing, may be diluted with Glucose 5% or Sodium Chloride 0.9%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Rocuronium bromide (Non-proprietary) Rocuronium bromide 10 mg per 1 ml Rocuronium bromide 50mg/5ml solution for injection ampoules | 10 ampoule £24.00
  - Rocuronium bromide 50mg/5ml solution for injection vials | 10 vial £28.00–£30.00
  - Rocuronium bromide 100mg/10ml solution for injection vials | 10 vial £57.00–£57.90
- Esmeron (Merck Sharp & Dohme Ltd) Esmeron 10 mg per 1 ml Esmeron 50mg/5ml solution for injection vials | 10 vial £28.92 (Hospital only)
  - Esmeron 100mg/10ml solution for injection vials | 10 vial £57.85 (Hospital only)

<table>
<thead>
<tr>
<th>Rocuronium bromide 10 mg per 1 ml</th>
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<td>Esmeron 50mg/5ml solution for injection vials</td>
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<td>Esmeron 100mg/10ml solution for injection vials</td>
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**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal bodyweight.

**Vecuronium bromide**

**INDICATIONS AND DOSE**

Neuromuscular blockade (intermediate duration) during surgery and intubation

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 80–100 micrograms/kg; (by intravenous injection) maintenance 20–30 micrograms/kg, adjusted according to response, max. 100 micrograms/kg in caesarian section, alternatively (by intravenous infusion) maintenance 0.8–1.4 micrograms/kg/minute, adjusted according to response.

**SIDE-EFFECTS**

- Very rare Anaphylactoid reactions
- Frequency not known Acute myopathy (after prolonged use in intensive care) - bronchospasm - hypotension - skin flushing - tachycardia

**HEPATIC IMPAIRMENT**

Use with caution in significant impairment.

**RENAI IMPAIRMENT**

Use with caution.

**DIRECTIONS FOR ADMINISTRATION**

Reconstitute each vial with 5 mL Water for Injections to give 2 mg/mL solution; alternatively reconstitute with up to 10 mL Glucose 5% or Sodium Chloride 0.9% or Water for Injections—unsuitable for further dilution if not reconstituted with Water for Injections. For continuous intravenous infusion, dilute reconstituted solution to a concentration up to 40 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; reconstituted solution can also be given via drip tubing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- Norcuron (Merck Sharp & Dohme Ltd) Vecuronium bromide 10 mg Norcuron 10mg powder and solvent for solution for injection vials | 10 vial £33.73 (Hospital only)

1.2 Neuromuscular blockade reversal

**Neuromuscular blockade reversal**

**Drugs for reversal of neuromuscular blockade**

**Anticholinesterases**

Anticholinesterases reverse the effects of the non-depolarising (competitive) neuromuscular blocking drugs such as pancuronium bromide but they prolong the action of the depolarising neuromuscular blocking drug succinylcholine chloride.

- Neostigmine is used specifically for reversal of non-depolarising (competitive) blockade. It acts within one minute of intravenous injection and its effects last for 20 to 30 minutes; a second dose may then be necessary.
- Glycopyronium bromide p. 1180 or alternatively atropine sulfate p. 1179, given before or with neostigmine, prevent bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

**Other drugs for reversal of neuromuscular blockade**

Sugammadex p. 1185 is a modified gamma cyclodextrin that can be used for rapid reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide. In
practice, sugammadex is used mainly for rapid reversal of neuromuscular blockade in an emergency.

**ANTICHOLINESTERASES**

Neostigmine with glycopyrronium bromide

The properties listed below are those particular to the combination only. For the properties of the components please consider, neostigmine p. 983, glycopyrronium bromide p. 1180.

- **INDICATIONS AND DOSE**
  - Reversal of non-depolarising neuromuscular blockade
    - **BY INTRAVENOUS INJECTION**
    - Adult: 1–2 mL, repeated if necessary, alternatively 0.02 mL/kilogram, repeated if necessary; maximum 2 mL per course

- **DIRECTIONS FOR ADMINISTRATION** For intravenous injection, give over 10–30 seconds.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - Neostigmine with glycopyrronium bromide (Non-proprietary)
      - Glycopyrronium bromide 500 microgram per 1 mL, Neostigmine methylsulfate 2.5 mg per 1 mL Neostigmine 2.5mg/1mL / Glycopyrronium bromide 500micrograms/1mL solution for injection ampoules | 10 ampoule £11.50

ANTIDOTES AND CHELATORS

Sugammadex

- **INDICATIONS AND DOSE**
  - Routine reversal of neuromuscular blockade induced by rocuronium or vecuronium
    - **BY INTRAVENOUS INJECTION**
    - Adult: Initially 2–4 mg/kg, then 4 mg/kg if required, administered if recurrence of neuromuscular blockade occurs; consult product literature for further details
  - Immediate reversal of neuromuscular blockade induced by rocuronium
    - **BY INTRAVENOUS INJECTION**
    - Adult: 16 mg/kg (consult product literature)

**IMPORTANT SAFETY INFORMATION**

Should only be administered by, or under the direct supervision of, personnel experienced in its use.

- **CAUTIONS**
  - Cardiovascular disease (recovery may be delayed) - elderly (recovery may be delayed) - pre-existing coagulation disorders - recurrence of neuromuscular blockade— monitor respiratory function until fully recovered - use of anticoagulants (unrelated to surgery) - wait 24 hours before re-administering rocuronium - wait 24 hours before re-administering vecuronium
- **INTERACTIONS** Appendix 1 (sugammadex).
- **SIDE-EFFECTS** Bradycardia - bronchospasm - cardiac arrest - hypersensitivity reactions
- **PREGNANCY** Use with caution—no information available.
- **RENA L IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) Decisions
    - The Scottish Medicines Consortium, has advised (February 2013) that sugammadex (Bridion®) is accepted for restricted use within NHS Scotland for the routine reversal of neuromuscular blockade in high-risk patients only, or where prompt reversal of neuromuscular block is required.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **ELECTROLYTES:** May contain Sodium
    - Bridion (Merck Sharp & Dohme Ltd)
      - Sugammadex (as Sugammadex sodium) 100 mg per 1 ml Bridion 500mg/5ml solution for injection vials | 10 vial £149.00 (Hospital only)
      - Bridion 200mg/2ml solution for injection vials | 10 vial £596.40 (Hospital only)

1.3 Peri-operative analgesia

**Peri-operative analgesia**

Non-opioid analgesics

Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastro-intestinal motility, and do not affect coagulation, they may be useful alternatives or adjuncts to opioids for the relief of postoperative pain. NSAIDs may be inadequate for the relief of severe pain. Acetaminophen p. 989, diclofenac sodium p. 993, diclofenac potassium p. 992, flurbiprofen p. 998, ibuprofen p. 999, ketoprofen p. 1002, paracetamol p. 414, parecoxib p. 1187, and ketorolac trometamol p. 1186, are licensed for postoperative use. Diclofenac and paracetamol can be given by injection as well as by mouth. Diclofenac sodium can be given by intravenous infusion for the treatment or prevention of postoperative pain. Intramuscular injections of diclofenac sodium and ketoprofen are rarely used; they are given deep into the gluteal muscle to minimise pain and tissue damage. Ketorolac trometamol is less irritant on intramuscular injection but has been reported; it can also be given by intravenous injection.

Suppositories of diclofenac sodium and ketoprofen may be effective alternatives to the parenteral use of these drugs.

Opioid analgesics

Opioid analgesics are now rarely used as premedicants; they are more likely to be administered at induction. Pre-operative use of opioid analgesics is generally limited to those patients who require control of existing pain. See general notes on opioid analgesics and their use in postoperative pain.

See the management of opioid-induced respiratory depression in Pre-medication and peri-operative drugs p. 1178.

Intra-operative analgesia

Opioid analgesics given in small doses before or with induction reduce the dose requirement of some drugs used during anaesthesia.

 Alfentanil p. 1187, fentanyl p. 424, and remifentanil p. 1188 are particularly useful because they act within 1–2 minutes and have short durations of action. The initial doses of alfentanil or fentanyl are followed either by successive intravenous injections or by an intravenous infusion; prolonged infusions increase the duration of effect. Repeated intra-operative doses of alfentanil or fentanyl should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive. Alfentanil, fentanyl, and remifentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by
nonspecific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression. Remifentanil should not be given by intravenous injection intraoperatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanil.

**ANAESTHETICS, LOCAL**

### Bupivacaine with fentanyl

The properties listed below are those particular to the combination only. For the properties of the components please consider, bupivacaine hydrochloride p. 1193, fentanyl p. 424.

#### INDICATIONS AND DOSE

**During labour (once epidural block established)**

- **BY CONTINUOUS LUMBAR EPIDURAL INFUSION**
  - Adult: 10–18.75 mg/hour, dose of bupivacaine to be administered, maximum 400 mg bupivacaine in 24 hours and 16–30 micrograms/hour, dose of fentanyl to be administered, maximum 720 micrograms fentanyl in 24 hours

**Postoperative pain (once epidural block established)**

- **BY CONTINUOUS EPIDURAL INFUSION**
  - Adult: 4–18.75 mg/hour, dose of bupivacaine to be administered, maximum 400 mg bupivacaine in 24 hours and 8–30 micrograms/hour, dose of fentanyl to be administered, maximum 720 micrograms fentanyl in 24 hours, to be administered by thoracic, upper abdominal or lower abdominal epidural infusion

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Solution for infusion**

- **Bufyl (AMCo)**
  - Bupivacaine hydrochloride 1 mg per 1 ml, Fentanyl 2 microgram per 1 ml Bufyl 1mg/ml and 2micrograms/ml 500ml infusion bags | 10 bag (£9.20) (Hospital only) [CD2]
  - Bufyl 1mg/ml and 2micrograms/ml 500ml infusion bags | 20 bag (£17.00) (Hospital only) [CD2]
  - Bupivacaine hydrochloride 1.25 mg per 1 ml, Fentanyl (as Fentanyl citrate) 2 microgram per 1 ml Bufyl 1.25mg/ml and 2micrograms/ml 500ml infusion bags | 20 bag (£18.00) (Hospital only) [CD2]
  - Bufyl 1.25mg/ml and 2micrograms/ml 500ml infusion bags | 10 bag (£9.20) (Hospital only) [CD2]

**ANAALGESICS**

### Ketorolac trometamol

#### INDICATIONS AND DOSE

**Short-term management of moderate to severe acute postoperative pain only**

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
  - Adult (body-weight up to 50 kg): Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 60 mg per day
  - Adult (body-weight 50 kg and above): Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 60 mg per day

- **CONTRA-INDICATIONS**
  - Active or history of gastrointestinal bleeding, active or history of gastrointestinal ulceration, coagulation disorders, complete or partial syndrome of nasal polyps, confirmed or suspected cerebrovascular bleeding, dehydration, following operations with high risk of haemorrhage or incomplete haemostasis, haemorrhagic diatheses, history of gastrointestinal perforation, hypovolaemia, severe heart failure

- **CAUTIONS**
  - Allergic disorders, cardiac impairment (NSAIDs may impair renal function), cerebrovascular disease, coagulation defects, connective-tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), heart failure, ischaemic heart disease, peripheral arterial disease, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated), uncontrolled hypertension

- **INTERACTIONS** → Appendix 1 (NSAIDs).

#### SIDE-EFFECTS

- **Rare**
  - Alveolitis · aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · hepatic damage · interstitial fibrosis associated with NSAIDs can lead to renal failure · pancreatitis · papillary necrosis associated with NSAIDs can lead to renal failure · pulmonary eosinophilia · Stevens-Johnson syndrome · toxic epidermal necrolysis

- **Frequency not known**
  - Abnormal dreams · angioedema · asthma · blood disorders · bradycardia · bronchospasm · chest pain · colitis (induction of or exacerbation of) · confusion · convulsions · Crohn’s disease (induction of or exacerbation of) · depression · diarrhoea · dizziness · drowsiness · dry mouth · dyspnoea · euphoria · fluid retention (rarely precipitating congestive heart failure) · flushing · gastro-intestinal bleeding · gastro-intestinal discomfort · gastro-intestinal disturbances · gastro-intestinal ulceration · haemorrhagia · hallucinations · headache · hearing disturbances · hyperkalaemia · hyperkinesia · hypersensitivity reactions · hypertension · hyponatraemia · insomnia · malaise · myalgia · nausea · nervousness · optic neuritis · pain at injection site · pallor · palpitation · paraesthesia · photosensitivity · psychosis · purpura · raised blood pressure · rashes · renal failure (especially in patients with pre-existing renal impairment) · sweating · taste disturbances · thirst · tinnitus · urinary frequency · vertigo · visual disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- **ALLERGY AND CROSS-SENSITIVITY**
  - Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION**
  - Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY**
  - Avoid until the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
**Parecoxib**

- **DRUG ACTION** Parecoxib is a selective inhibitor of cyclooxygenase-2.

- **INDICATIONS AND DOSE**
  - **Short-term management of acute postoperative pain**
    - **BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
      - Adult: Initially 40 mg, then 20–40 mg every 6–12 hours as required for up to 3 days; maximum 80 mg per day
      - Elderly (body-weight up to 50 kg): Initially 20 mg; maximum 40 mg per day

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding • active gastro-intestinal ulceration • cerebral vascular disease • inflammatory bowel disease • ischaemic heart disease • mild to severe heart failure • peripheral arterial disease

- **CAUTIONS** Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • dehydration • elderly (risk of serious side-effects and fatalities) • following coronary artery bypass graft surgery • history of cardiac failure • hypertension • left ventricular dysfunction • oedema • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated)

- **INTERACTIONS** → Appendix 1 (NSAIDs).

- **SIDE-EFFECTS**
  - Common or very common • Alveolar osteitis • flatulence • hypoaesthesia • hypokalaemia • hypotension • postoperative anaemia • sweating
  - Uncommon • Anorexia • arthralgia • bradycardia • cardiovascular events • ecchymosis • hyperglycaemia • malaise • pulmonary embolism
  - Rare • Alveolitis • aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • hepatic damage • interstitial fibrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances
  - Frequency not known • Angioedema • blood disorders • blood pressure may be raised • bronchospasm • circulatory collapse • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • rashes • renal failure (especially in patients with pre-existing renal impairment) • tachycardia • tinnitus • vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**
- **Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 987.

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID. Contra-indicated in patients with a history of allergic drug reactions including sulfonamide hypersensitivity.

- **CONCEPTION AND CONCEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Avoid—present in milk.

- **HEPATIC IMPAIRMENT** Halve dose in moderate impairment (max. 40 mg daily). Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions** The Scottish Medicines Consortium (SMC) has advised (January 2003) that parecoxib is not recommended for use within NHS Scotland.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - Ketorolac tromethamol (Non-proprietary) Ketorolac tromethamol 30 mg per 1 ml Ketorolac 30mg/1ml solution for injection ampoules | 6 ampoule (Pom) £6.56
  - Toradol (AstraZeneca UK Ltd) Ketorolac tromethamol 30 mg per 1 ml Toradol 30mg/1ml solution for injection ampoules | 5 ampoule (Pom) £5.36

**ALGESICS ▶ OPIOIDS**

- **Alfentanil**

  - **INDICATIONS AND DOSE**
    - **Spontaneous respiration: analgesia and enhancement of anaesthesia for short procedures**
      - **BY INTRAVENOUS INJECTION**
        - Adult: Initially up to 500 micrograms, dose to be administered over 30 seconds; supplemental doses 250 micrograms
**Assisted ventilation: analgesia and enhancement of anaesthesia for short procedures**
- **BY INTRAVENOUS INJECTION**
  - Adult: Initially 30–50 micrograms/kg, supplemental doses 15 micrograms/kg
- **Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia for longer procedures**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 50–100 micrograms/kg, dose to be administered over 10 minutes or as a bolus, followed by maintenance 30–60 micrograms/kg/hour
- **Assisted ventilation: analgesia and suppression of respiratory activity during intensive care for up to 4 days**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 2 mg/hour, adjusted according to response; usual dose 0.5–10 mg/hour, alternatively initially 5 mg in divided doses, to be administered over 10 minutes; dose used for more rapid initial control, reduce rate of administration if hypotension or bradycardia occur; additional doses of 0.5–1 mg may be given by intravenous injection during short painful procedures

**DOSES AT EXTREMES OF BODY-WEIGHT**
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**
- Repeated intra-operative doses: Repeated intra-operative doses of alfentanil should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive.

**SIDE-EFFECTS**
- **Common or very common** Hypertension - myoclonic movements
- **Uncommon** Arrhythmias - hiccup - laryngospasm
- **Rare** Epistaxis
- **Frequency not known** Cardiac arrest - convulsions - cough - muscle rigidity - pyrexia

**SIDE-EFFECTS, FURTHER INFORMATION**
- Muscle rigidity: Alfentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

**BREAST FEEDING**
Present in milk — withhold breastfeeding for 24 hours.

**RENAI IMPAIRMENT**
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**DIRECTIONS FOR ADMINISTRATION**
5 mg/mL injection to be diluted before use. For continuous or intermittent intravenous infusion dilute in Glucose 5% or Sodium Chloride 0.9%.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. No licensed medicines identified.

**Alfentanil**

- **INDICATIONS AND DOSE**
  - **Premedication**
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Adult: 0.5–1 mL
  - **LESS SUITABLE FOR PRESCRIBING** Hydrobromide with papaveretum is less suitable for prescribing.

**Rapifen**

- **INDICATIONS AND DOSE**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds, if patient is to be intubated more than 8 minutes after start of intravenous infusion, initial bolus intravenous injection dose is not necessary
  - **Analgesia and enhancement of anaesthesia at induction with or without initial bolus dose**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 30–60 micrograms/kg/hour, if patient is to be intubated more than 8 minutes after start of intravenous infusion, initial bolus intravenous injection dose is not necessary
  - **Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia (initial bolus injection)**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds
  - **Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia with or without initial bolus dose**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 3–120 micrograms/kg/hour, dose to be administered according to anaesthetic technique and adjusted according to response, in light anaesthesia additional doses can be given by intravenous injection every 2–5 minutes during the intravenous infusion

**Spontaneous respiration: analgesia and enhancement of anaesthesia during maintenance of anaesthesia**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 2.4 micrograms/kg/hour, adjusted according to response; usual dose 1.5–6 micrograms/kg/hour

**Papaveretum with hyoscine hydrobromide**
The properties listed below are those particular to the combination only. For the properties of the components please consider, papaveretum p. 434, hyoscine hydrobromide p. 409.
**Assisted ventilation: analgesia and sedation in intensive-care patients (for max 3 days)**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 6–9 micrograms/kg/hour, then adjusted in steps of 1.5 micrograms/kg/hour, allow at least 5 minutes between dose adjustments; usual dose 0.36–44.4 micrograms/kg/hour, if an infusion rate of 12 micrograms/kg/hour does not produce adequate sedation add another sedative (consult product literature for details)

**Assisted ventilation: additional analgesia during stimulating or painful procedures in intensive-care patients**

- **BY INTRAVENOUS INFUSION**
  - Adult: Usual dose 15–45 micrograms/kg/hour, maintain infusion rate of at least 6 micrograms/kg/hour for at least 5 minutes before procedure and adjust every 2–5 minutes according to requirements

**Cardiac surgery**

- Adult: (consult product literature)

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- ** UNLICENSED USE** Remifentanil doses in BNF may differ from those in product literature.
- ** CONTRA-INDICATIONS** Analgesia in conscious patients
- ** SIDE-EFFECTS**
  - Common or very common Hypertension
  - Uncommon Hypoxia
  - Rare Asystole
  - Frequency not known AV block · convulsions

**SIDE-EFFECTS, FURTHER INFORMATION**

- Muscle rigidity Alfentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.
- Respiratory depression In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by non-specific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression.

- ** PREGNANCY** No information available.
- ** BREAST FEEDING** Avoid breast-feeding for 24 hours after administration—present in milk in animal studies.
- ** RENAL IMPAIRMENT** No dose adjustment necessary in renal impairment.
- ** DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Ultiva®), give continuously in Glucose 5% or Sodium Chloride 0.9% or Water for Injections; reconstitute with infusion fluid to a concentration of 1 mg/mL then dilute further to a concentration of 20–250 micrograms/mL. (50 micrograms/mL recommended for general anaesthesia, 20–50 micrograms/mL recommended when used with target controlled infusion (TCI) device).

- ** PRESCRIBING AND DISPENSING INFORMATION** Remifentanil should not be given by intravenous injection intra-operatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanil.

- ** MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- Remifentanil (Non-proprietary)
  - Remifentanil (as Remifentanyl hydrochloride) 1 mg Remifentanil 1mg powder for concentrate for solution for injection vials | 5 vial (Pow) £25.58–£25.60 (Hospital only) [G2]

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**Remifentanil (as Remifentanyl hydrochloride) 2 mg** Remifentanil 2mg powder for concentrate for solution for injection vials | 5 vial (Pow) £51.13–£51.15 (Hospital only) [G2]

**Remifentanil (as Remifentanyl hydrochloride) 5 mg** Remifentanil 5mg powder for concentrate for solution for injection vials | 5 vial (Pow) £127.75–£127.90 (Hospital only) [G2]

**Ultiva** (GlaxoSmithKline UK Ltd)

- Remifentanil (as Remifentanyl hydrochloride) 1 mg Ultiva 1mg powder for solution for injection vials | 5 vial (Pow) £25.58 (Hospital only) [G2]

- Remifentanil (as Remifentanyl hydrochloride) 2 mg Ultiva 2mg powder for solution for injection vials | 5 vial (Pow) £51.15 (Hospital only) [G2]

- Remifentanil (as Remifentanyl hydrochloride) 5 mg Ultiva 5mg powder for solution for injection vials | 5 vial (Pow) £127.88 (Hospital only) [G2]

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## 1.4 Peri-operative sedation

### Conscious sedation for clinical procedures

**Overview**

Sedation of patients during diagnostic and therapeutic procedures is used to reduce fear and anxiety, to control pain, and to minimise excessive movement. The choice of sedative drug will depend upon the intended procedure; some procedures are safer and more successful under anaesthesia. The patient should be monitored carefully; monitoring should begin as soon as the sedative is given or when the patient becomes drowsy, and should be continued until the patient wakes up.

**ANAESTHETICS, GENERAL › NMDA RECEPTOR ANTAGONISTS**

### Ketamine

- **INDICATIONS AND DOSE**
  - **Induction and maintenance of anaesthesia for short procedures**
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: Initially 6.5–13 mg/kg, adjusted according to response, a dose of 10 mg/kg usually produces 12–25 minutes of surgical anaesthesia
    - **BY INTRAVENOUS INJECTION**
      - Adult: Initially 1–4.5 mg/kg, adjusted according to response, to be administered over at least 60 seconds, a dose of 2 mg/kg usually produces 5–10 minutes of surgical anaesthesia
  - **Diagnosis manoeuvres and procedures not involving intense pain**
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: Initially 4 mg/kg
  - **Induction and maintenance of anaesthesia for long procedures**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 0.5–2 mg/kg, using an infusion solution containing 1 mg/ml; maintenance 10–45 micrograms/kg/minute, adjusted according to response

**IMPORTANT SAFETY INFORMATION**

Ketamine should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.
HYPNOTICS, SEDATIVES AND ANXIOLYTICS

NON-BENZODIAZEPINE HYPNOTICS AND SEDATIVES

Dexmedetomidine

INDICATIONS AND DOSE

Maintenance of sedation during intensive care

BY INTRAVENOUS INFUSION

Adult: 0.7 microgram/kg/hour, adjusted according to response; usual dose 0.2–1.4 micrograms/kg/hour

CONTRA-INDICATIONS

Acute cerebrovascular disorders - second- or third-degree AV block (unless pacemaker fitted) - uncontrolled hypotension

CAUTIONS

Abrupt withdrawal after prolonged use - bradycardia - ischaemic heart disease - malignant hyperthermia - severe cerebrovascular disease (especially at higher doses) - severe neurological disorders - spinal cord injury

SIDE-EFFECTS

Common or very common Agitation - blood pressure changes - bradycardia - changes in blood sugar - dry mouth - hyperthermia - myocardial infarction - myocardial ischaemia - nausea - tachycardia - vomiting

Uncommon Abdominal distension - AV block - decreased cardiac output - dyspnoea - hallucination - hypoalbuiminaemia - metabolic acidosis - thirst

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

BREAST FEEDING

Manufacturer advises avoid unless potential benefit outweighs risk—present in milk in animal studies.

HEPATIC IMPAIRMENT

Dose reduction may be required. Manufacturer advises caution.

MONITORING REQUIREMENTS

Monitor cardiac function.

Monitor respiratory function in non-intubated patients.

DIRECTIONS FOR ADMINISTRATION

To be diluted before use. For intravenous infusion given continuously in Glucose 5% or Sodium chloride 0.9%, dilute to a concentration of 4 micrograms/mL.

MEDIcular FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for infusion

> Dexdor (Orion Pharma (UK) Ltd)

Dexmedetomidine (as Dexmedetomidine hydrochloride)

100 microgram per 1 ml

Dexdor 1mg/10ml concentrate for solution for infusion vials | 4 vial (Pom) £313.20 (Hospital only)

Dexdor 400micrograms/4ml concentrate for solution for infusion vials | 4 vial (Pom) £125.28 (Hospital only)

Dexdor 200micrograms/2ml concentrate for solution for infusion ampoules | 5 ampoule (Pom) £78.30 (Hospital only) | 25 ampoule (Pom) £391.50 (Hospital only)

> MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

> Ketamine (Non-proprietary)

Ketamine (as Ketamine hydrochloride) 10 mg per 1 ml

Ketamin 50mg/5ml solution for injection ampoules | 10 ampoule (Pom) no price available (CD)

Ketamine (as Ketamine hydrochloride) 50 mg per 1 ml

Ketamine 100mg/2ml solution for injection ampoules | 10 ampoule (Pom) no price available (CD)

Ketalar (Pfizer Ltd)

Ketamine (as Ketamine hydrochloride) 10 mg per 1 ml Ketalar 200mg/20ml solution for injection vials | 1 vial (Pom) £5.06 (Hospital only) (CD)

Ketamine (as Ketamine hydrochloride) 50 mg per 1 ml Ketalar 500mg/10ml solution for injection vials | 1 vial (Pom) £8.77 (Hospital only) (CD)

Ketalar (Hydromorphone hydrochloride) 100 mg per 1 ml Ketalar 1g/10ml solution for injection vials | 1 vial (Pom) £16.10 (Hospital only) (CD)
2 Malignant hyperthermia

MUSCLE RELAXANTS  DIRECTLY ACTING

Dantrolene sodium

- **DRUG ACTION** Acts on skeletal muscle cells by interfering with calcium efflux, thereby stopping the contractile process.

- **INDICATIONS AND DOSE**
  - **Malignant hyperthermia**
    - **BY RAPID INTRAVENOUS INJECTION**
    - Adult: Initially 2–3 mg/kg, then 1 mg/kg, repeated if necessary; maximum 10 mg/kg per course
  - **Chronic severe spasticity of voluntary muscle**
    - **BY MOUTH**
    - Adult: Initially 25 mg daily, then increased to up to 100 mg 4 times a day, dose increased at weekly intervals; usual dose 75 mg 3 times a day

- **SIDE-EFFECTS**
  - **Common or very common**
    - With oral use Abdominal pain, anorexia, asthenia, chills, diarrhea (withdraw if severe, discontinue treatment if recurs on re-introduction), dizziness, drowsiness, fatigue, fever, headache, hepatotoxicity, nausea, pericarditis, pleural effusion, rash, respiratory depression, seizures, speech disturbances, visual disturbances, vomiting
  - **Uncommon**
    - With oral use Confusion, constipation, crystalluria, depression, dysphagia, dyspnoea, erratic blood pressure, exacerbation of cardiac insufficiency, haematuria, increased sweating, increased urinary frequency, insomnia, nervousness, tachycardia, urinary incontinence, urinary retention
  - **Frequency not known**
    - With intravenous use Dizziness, erythema, hepatotoxicity, injection-site reactions, pulmonary oedema, rash, swelling, thrombophlebitis, weakness

- **FURTHER INFORMATION**
  - Hepatotoxicity Potentially life-threatening hepatotoxicity reported—discontinue if abnormal liver function tests or symptoms of liver disorder; re-introduce only if complete reversal of hepatotoxicity.

- **PREGNANCY**
  - With intravenous use Use only if potential benefit outweighs risk.
  - With oral use Avoid use in chronic spasticity—embryotoxic in animal studies.

- **BREAST FEEDING**
  - With intravenous use Present in milk—use only if potential benefit outweighs risk.
  - With oral use Present in milk—manufacturer advises avoid use in chronic spasticity.

- **HEPATIC IMPAIRMENT**
  - Avoid—may cause severe liver damage (injection may be used in an emergency for malignant hyperthermia).

- **MONITORING REQUIREMENTS**
  - With oral use Test liver function before and at intervals during therapy.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - With oral use Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.
  - Hepatotoxicity
    - With oral use Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **CAPSULE**
  - **CAUTIONARY AND ADVISORY LABELS 2**
  - **Dantrium** (Norgine Pharmaceuticals Ltd)
    - Dantrolene sodium 25 mg
      - Dantrium 25mg capsules 100 capsule 16.87 DT price = £16.87
      - Dantrium 25mg capsules 160 capsule 43.07 DT price = £43.07
    - **Powder for solution for injection**
      - Dantrium (Norgine Pharmaceuticals Ltd)
        - Dantrolene sodium 20 mg
          - Dantrium Intravenous 20mg powder for solution injection vials 12 vial 836 (Hospital only)
          - 36 vial 1,836.00 (Hospital only)

Local anaesthesia

Local anaesthesia

Local anaesthetic drugs

The use of local anaesthetics by injection or by application to mucous membranes to produce local analgesia is discussed in this section.

Local anaesthetic drugs act by causing a reversible block to conduction along nerve fibres. They vary widely in their potency, toxicity, duration of action, stability, solubility in water, and ability to penetrate mucous membranes. These factors determine their application, e.g. topical (surface), infiltration, peripheral nerve block, intravenous regional anaesthesia (Bier’s block), plexus, epidural (extradural), or spinal (intrathecal or subarachnoid) block. Local anaesthetics may also be used for postoperative pain relief, thereby reducing the need for analgesics such as opioids.

Bupivacaine hydrochloride p. 1193 has a longer duration of action than other local anaesthetics. It has a slow onset of action, taking up to 30 minutes for full effect. It is often used in lumbar epidural blockade and is particularly suitable for continuous epidural analgesia in labour, or for postoperative pain relief. It is the principal drug used for spinal anaesthesia. Hyperbaric solutions containing glucose may be used for spinal block.

Chloroprocaine hydrochloride p. 1195, a para-aminobenzoic acid ester, is used for spinal anaesthesia in adults where the planned procedure should not exceed 40 minutes.
Levobupivacaine p. 1196, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine hydrochloride, but is thought to have fewer adverse effects.

Lidocaine hydrochloride p. 1197 is effectively absorbed from mucous membranes and is a useful surface anaesthetic in concentrations up to 10%. Except for surface anaesthesia and dental anaesthesia, solutions should not usually exceed 1% in strength. The duration of the block (with adrenaline/epinephrine p. 211) is about 30 minutes.

Prilocaine hydrochloride p. 1201 is a local anaesthetic of low toxicity which is similar to lidocaine hydrochloride. A hyperbaric solution of prilocaine hydrochloride (containing glucose) may be used for spinal anaesthesia.

Ropivacaine hydrochloride p. 1202 is an amide-type local anaesthetic agent similar to bupivacaine hydrochloride. It is less cardiotoxic than bupivacaine hydrochloride, but also less potent.

Tetracaine p. 1203, a para-aminobenzoic acid ester, is an effective local anaesthetic for topical application; a 4% gel is indicated for anaesthesia before venepuncture or venous cannulation. It is rapidly absorbed from mucous membranes and should never be applied to inflamed, traumatised, or highly vascular surfaces. It should never be used to provide anaesthesia for bronchoscopy or cystoscopy because lidocaine hydrochloride is a safer alternative.

**Administration by injection**

The dose of local anaesthetic depends on the injection site and the procedure used. In determining the safe dosage, it is important to take account of the rate of absorption and excretion, and of the potency. The patient’s age, weight, physique, and clinical condition, and the vascularity of the administration site and the duration of administration, must also be considered.

Uptake of local anaesthetics into the systemic circulation determines their duration of action and produces toxicity.

NHS Improvement has advised (September 2016) that, prior to administration, all injectable medicines must be drawn directly from their original ampoule or container into a syringe and should never be decanted into gallipots or open containers. This is to avoid the risk of medicines being confused with other substances, e.g. skin disinfectants, and to reduce the risk of contamination.

Great care should be taken to avoid accidental intravascular injection; local anaesthetic injections should be given slowly in order to detect inadvertent intravascular administration. When prolonged analgesia is required, a long-acting local anaesthetic is preferred to minimise the likelihood of cumulative systemic toxicity. Local anaesthesia around the oral cavity may impair swallowing and therefore increases the risk of aspiration.

Epidural anaesthesia is commonly used during surgery, often combined with general anaesthesia, because of its protective effect against the stress response of surgery. It is often used when good postoperative pain relief is essential.

**Use of vasoconstrictors**

Local anaesthetics cause dilatation of blood vessels. The addition of a vasoconstrictor such as adrenaline/epinephrine to the local anaesthetic preparation diminishes local blood flow, slowing the rate of absorption and thereby prolonging the anaesthetic effect. Great care should be taken to avoid inadvertent intravenous administration of a preparation containing adrenaline/epinephrine, and it is not advisable to give adrenaline/epinephrine with a local anaesthetic injection in digits or appendages because of the risk of ischaemic necrosis.

Adrenaline/epinephrine must be used in a low concentration when administered with a local anaesthetic. Care must also be taken to calculate a safe maximum dose of local anaesthetic when using combination products.

In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline/epinephrine with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline/epinephrine should be used.

**Dental anaesthesia**

Lidocaine hydrochloride is widely used in dental procedures; it is most often used in combination with adrenaline/epinephrine. Lidocaine hydrochloride 2% combined with adrenaline/epinephrine 1 in 80 000 (12.5 micrograms/mL) is a safe and effective preparation; there is no justification for using higher concentrations of adrenaline/epinephrine.

The amide-type local anaesthetics articaine and mepivacaine hydrochloride p. 1200 are also used in dentistry; they are available in cartridges suitable for dental use. Mepivacaine hydrochloride is available with or without adrenaline/epinephrine and articaine is available with adrenaline.

In patients with severe hypertension or unstable cardiac rhythm, mepivacaine hydrochloride without adrenaline/epinephrine may be used. Alternatively, prilocaine hydrochloride with or without felypressin can be used but there is no evidence that it is any safer. Felypressin can cause coronary vasoconstriction when used at high doses; limit dose in patients with coronary artery disease.

**Toxicity**

For management of toxicity see Severe local anaesthetic-induced cardiovascular toxicity below.

### Severe local anaesthetic-induced cardiovascular toxicity

**Overview**

After injection of a bolus of local anaesthetic, toxicity may develop at any time in the following hour. In the event of signs of toxicity during injection, the administration of the local anaesthetic must be stopped immediately.

Cardiovascular status must be assessed and cardiopulmonary resuscitation procedures must be followed.

In the event of local anaesthetic-induced cardiac arrest, standard cardiopulmonary resuscitation should be initiated immediately. Lidocaine must not be used as anti-arrhythmic therapy.

If the patient does not respond rapidly to standard procedures, 20% lipid emulsion such as Intralipid® [unlicensed indication] should be given intravenously at an initial bolus dose of 1.5 mL/kg over 1 minute, followed by an infusion of 15 mL/kg/hour. After 5 minutes, if cardiovascular stability has not been restored or circulation deteriorates, give a maximum of two further bolus doses of 1.5 mL/kg over 1 minute, 5 minutes apart, and increase the infusion rate to 30 mL/kg/hour. Continue infusion until cardiovascular stability and adequate circulation are restored or maximum cumulative dose of 12 mL/kg is given.

Standard cardiopulmonary resuscitation must be maintained throughout lipid emulsion treatment.

Propofol is not a suitable alternative to lipid emulsion.

Further advice on ongoing treatment should be obtained from the National Poisons Information Service.

Detailed treatment algorithms and accompanying notes are available at www.toxbase.org or can be found in the Association of Anaesthetists of Great Britain and Ireland safety guideline, Management of Severe Local Anaesthetic Toxicity and Management of Severe Local Anaesthetic Toxicity – Accompanying notes.
Adrenaline with articaine hydrochloride
(Carticaine hydrochloride with epinephrine)

- **INDICATIONS AND DOSE**
  - **Infiltration anaesthesia in dentistry**
  - **BY REGIONAL ADMINISTRATION**
  - Adult: Consult expert dental sources

- **DOSES AT EXTREMES OF BODY-WEIGHT**
  - To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- **CONTRA-INDICATIONS**
  - Application to damaged skin.
  - Application to the middle ear (may cause ototoxicity).
  - Complete heart block.
  - Injection into inflected tissues.
  - Injection into inflamed tissues.
  - Preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia.

- **CAUTIONS**
  - Arrhythmias.
  - Arteriosclerosis.
  - Cardiovascular disease.
  - Cerebrovascular disease.
  - Cor pulmonale.
  - Debilitated patients (consider dose reduction).
  - Diabetes mellitus.
  - Elderly (consider dose reduction).
  - Epilepsy.
  - Hypercalcemia.
  - Hyperreflexia.
  - Hypertension.
  - Hyperthyroidism.
  - Hypokalaemia.
  - Hypovolaemia.
  - Impaired cardiac conduction.
  - Impaired respiratory function.
  - Ischaemic heart disease.
  - Myasthenia gravis.
  - Obstructive cardiomyopathy.
  - Occulsive vascular disease.
  - Organic brain damage.
  - Phaeochromocytoma.
  - Prostate disorders.
  - Psychoneurosis.
  - Severe angina.
  - Shock.
  - Susceptibility to angle-closure glaucoma.

- **CAUTIONS, FURTHER INFORMATION**
  - Use of vasoconstrictors.
  - In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline should be used.

- **INTERACTIONS**
  - Appendix 1 (sympathomimetics).

- **SIDE-EFFECTS**
  - Angina.
  - Angle-closure glaucoma.
  - Anorexia.
  - Anxiety.
  - Arrhythmias.
  - Blurred vision.
  - Cardiac arrest.
  - Cold extremities.
  - Confusion.
  - Convulsions.
  - Difficulty in micturition.
  - Dizziness.
  - Drowsiness.
  - Dry mouth.
  - Dysphonia.
  - Feeling of inebriation.
  - Headache.
  - Hyperglycaemia.
  - Hypersalivation.
  - Hypertension (risk of cerebral haemorrhage).
  - Hypokalaemia.
  - Insomnia.
  - Lightheadedness.
  - Metabolic acidosis.
  - Methaemoglobinemia.
  - Muscle twitching.
  - Mydriasis.
  - Myocardial depression (resulting in hypotension and bradycardia).
  - Nausea.
  - Numberness of the tongue and perioral region.
  - Pallor.
  - Palpitation.
  - Paraesthesia (including sensations of hot and cold).
  - Peripheral vasodilatation (resulting in hypotension and bradycardia).
  - Psychosis.
  - Pulmonary oedema.
  - Severe hypertension (risk of cerebral haemorrhage).
  - Twitching.

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Toxic effects.
  - Hypersensitivity and cross-sensitivity.

- **ALLERGY AND CROSS-SENSITIVITY**
  - Hypersensitivity and cross-sensitivity.

- **PREGNANCY**
  - Use only if potential benefit outweighs risk.

- **BREAST FEEDING**
  - Avoid breast-feeding for 48 hours after administration.

- **HEPATIC IMPAIRMENT**
  - Use with caution.

- **RENAI IMPAIRMENT**
  - Manufacturers advise use with caution in severe impairment.

- **MONITORING REQUIREMENTS**
  - Consider monitoring blood pressure and ECG (advised with systemic adrenaline/epinephrine).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- EXCIPIENTS: May contain Sulphites.
- Septanest (Septodont Ltd)
  - Adrenaline (as Adrenaline acid tartrate) 10 microgram per 1 ml.
  - Articaine hydrochloride 40 mg per 1 ml.
  - Septanest 1 in 100,000 solution for injection cartridges | 50 cartridge (POM) no price available.
- Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml.
  - Articaine hydrochloride 40 mg per 1 ml.
  - Septanest 1 in 200,000 solution for injection cartridges | 50 cartridge (POM) no price available.

Bupivacaine hydrochloride

- **INDICATIONS AND DOSE**
  - **Surgical anaesthesia, lumbar epidural block**
  - **BY REGIONAL ADMINISTRATION**
  - Adult: 75–150 mg, dose administered using a 5 mg/mL (0.5%) solution.

- **Surgical anaesthesia, field block**
  - **BY REGIONAL ADMINISTRATION**
  - Adult: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution.

continued →
Surgical anaesthesia, thoracic epidural block
► BY THORACIC EPIDURAL
► Adult: 12.5–50 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

Surgical anaesthesia, caudal epidural block
► BY REGIONAL ADMINISTRATION
► Adult: 50–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

Surgical anaesthesia, major nerve block
► BY REGIONAL ADMINISTRATION
► Adult: 50–175 mg, dose administered using 5 mg/mL (0.5%) solution

Acute pain, intra-articular block
► BY INTRA-ARTICULAR INJECTION
► Adult: Up to 100 mg, dose administered using a 2.5 mg/mL (0.25%) solution; when co-administered with bupivacaine by another route, total max. 150 mg

Acute pain, thoracic epidural block
► BY CONTINUOUS EPIDURAL INFUSION
► Adult: 6.3–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

Acute pain, labour
► BY CONTINUOUS EPIDURAL INFUSION
► Adult: 6.25–12.5 mg/hour, dose administered using a 1.25 mg/mL (0.125%) solution; maximum 400 mg per day

Acute pain, lumbar epidural block
► INITIALLY BY LUMBAR EPIDURAL
► Adult: 15–37.5 mg, then (by lumbar epidural) 15–37.5 mg, repeated when required at intervals of at least 30 minutes, dose administered by intermittent injection using a 2.5 mg/mL (0.25%) solution, alternatively (by continuous epidural infusion) 12.5–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

Acute pain, field block
► BY REGIONAL ADMINISTRATION
► Adult: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) solution

MARCAIN HEAVY®

Intrathecal anaesthesia for surgery
► BY INTRATECAL INJECTION
► Adult: 10–20 mg

DOSES AT EXTREMES OF BODY-WEIGHT
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

IMPORTANT SAFETY INFORMATION
The licensed doses stated may not be appropriate in some settings and expert advice should be sought.
Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

CONTRA-INDICATIONS Application to the middle ear (can cause ototoxicity) • avoid injection into infected tissues • avoid injection into inflamed tissues • complete heart block • preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) • should not be applied to damaged skin

CONTRA-INDICATIONS, FURTHER INFORMATION
Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

CAUTIONS Cardiovascular disease • cerebral atheroma • debilitated patients (consider dose reduction) • elderly (consider dose reduction) • epilepsy • hypertension • hypotension • hypovolaemia • impaired cardiac conduction • impaired respiratory function • myasthenia gravis • myocardial depression may be more severe and more resistant to treatment • shock

INTERACTIONS → Appendix 1 (bupivacaine).

SIDE-EFFECTS Arrhythmias • blurred vision • cardiac arrest • convulsions • dizziness • drowsiness • feeling of inebriation • headache • lightheadedness • muscle twitching • myocardial depression (resulting in hypotension and bradycardia) • nausea • numbness of the tongue and perioral region • paraesthesia (including sensations of hot and cold) • peripheral vasodilatation (resulting in hypotension and bradycardia) • restlessness • tinnitus • transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) • tremors • vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Toxic effects Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection.
Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection.
The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

ALLERGY AND CROSS-SENSITIVITY
Hypersensitivity and cross-sensitivity Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

PREGNANCY Use lower doses for intrathecal use during late pregnancy. Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block.

BREAST FEEDING Amount too small to be harmful.

HEPATIC IMPAIRMENT Use with caution in severe impairment.

RENAL IMPAIRMENT Use with caution in severe impairment.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion, solution for infusion

Solution for injection
► Bupivacaine hydrochloride (Non-proprietary)
Bupivacaine hydrochloride 2.5 mg per 1 ml Bupivacaine 0.25% solution for injection 10ml Sure-Amp ampoules | 20 ampoule | £17.50
Bupivacaine hydrochloride 5 mg per 1 ml Bupivacaine 0.5% solution for injection 10ml Sure-Amp ampoules | 20 ampoule | £18.30
Bupivacaine 50mg/10ml (0.5%) solution for injection ampoules | 10 ampoule | no price available
► Marcain (AstraZeneca UK Ltd)
Bupivacaine hydrochloride 2.5 mg per 1 ml Marcain 0.25% solution for injection 10ml Polyamp Steripack ampoules | 5 ampoule | £7.92
Bupivacaine with adrenaline

The properties listed below are those particular to the combination only. For the properties of the components please consider, bupivacaine hydrochloride p. 1193, adrenaline/epinephrine p. 211.

● INDICATIONS AND DOSE

Surgical anaesthesia
▶ BY LUMBAR EPIDURAL, OR BY LOCAL INFILTRATION, OR BY CAUDAL EPIDURAL
Adult: (consult product literature)

Acute pain management
▶ BY LUMBAR EPIDURAL, OR BY LOCAL INFILTRATION
Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION
Adrenaline/epinephrine must be used in a low concentration when administered with a local anaesthetic. The total dose of adrenaline should not exceed 500 micrograms and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected.

● CAUTIONS

CAUTIONS, FURTHER INFORMATION
In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline should be used.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
▶ Bupivacaine with adrenaline (Non-proprietary)
Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml, Bupivacaine hydrochloride 5 mg per 1 ml Bupivacaine 25mg/10ml (0.25%) / Adrenaline (base) 50micrograms/10ml (1 in 200,000) solution for injection ampoules | 10 ampoule (£0.40)
Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml, Bupivacaine hydrochloride anhydrous 2.5 mg per 1 ml Carbostesin-adrenaline 0.25% / 100micrograms/20ml (1 in 200,000) solution for injection ampoules | 1 ampoule (£0.27)
Carbostesin-adrenaline 0.25% / 25micrograms/5ml (1 in 200,000) solution for injection ampoules | 1 ampoule (£0.27)
anesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepipvacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Avoid—no information available.

- **BREAST FEEDING** Avoid—no information available.

- **HEPATIC IMPAIRMENT** Use with caution in severe impairment.

- **RENAL IMPAIRMENT** Use with caution in severe impairment.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection

- Chloroprocaine hydrochloride 10 mg per 1 ml Ampres (AMCo) solution for injection ampoules | 10 ampoule (£0.50) £87.50

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### Levobupivacaine

#### INDICATIONS AND DOSE

**Acute postoperative pain**

- BY CONTINUOUS EPIDURAL INFUSION
  - Adult: 12.5–18.75 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

**Acute labour pain**

- BY LUMBAR EPIDURAL
  - Adult: 15–25 mg, repeated at intervals of at least 15 minutes, dose administered using a 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

**Surgical anaesthesia, peripheral nerve block**

- BY REGIONAL ADMINISTRATION
  - Adult: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, peribulbar nerve block**

- BY REGIONAL ADMINISTRATION
  - Adult: 37.5–112.5 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia for caesarean section**

- BY LUMBAR EPIDURAL
  - Adult: 75–150 mg, to be given over 15–20 minutes, dose administered using a 5 mg/mL (0.5%) solution

**Surgical anaesthesia**

- BY LUMBAR EPIDURAL
  - Adult: 50–150 mg, to be given over 5 minutes, dose administered using a 5 mg/mL (0.5%) or 7.5 mg/mL (0.75%) solution

- BY INTRATHECAL INJECTION
  - Adult: 15 mg, dose administered using a 5 mg/mL (0.5%) solution

- BY LOCAL INFILTRATION
  - Adult: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) solution

### DOSES AT EXTREMES OF BODY-WEIGHT

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

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**IMPORTANT SAFETY INFORMATION**

The licensed doses stated may not be appropriate in some settings and expert advice should be sought.

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Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

- **CONTRA-INDICATIONS** Application to the middle ear (can cause ototoxicity) · avoid injection into infected tissues · avoid injection into inflamed tissues · complete heart block · preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) · should not be applied to damaged skin

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

- **CAUTIONS** Cardiovascular disease · debilitated patients (consider dose reduction) · elderly (consider dose reduction) · epilepsy · hypovolaemia · impaired cardiac conduction · impaired respiratory function · myasthenia gravis · shock

- **INTERACTIONS** → Appendix 1 (levobupivacaine).

**SIDE-EFFECTS**

**Anaemia** · arrhythmias · blurred vision · cardiac arrest · convulsions · dizziness · drowsiness · feeling of inebriation · headache · lightheadedness · muscle twitching · myocardial depression (resulting in hypotension and bradycardia) · nausea · numbness of the tongue and perioral region · paraesthesia (including sensations of hot and cold) · peripheral vasodilatation (resulting in hypotension and bradycardia) · pyrexia · restlessness · sweating · tinnitus · transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) · tremors · vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- Toxic effects: Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection.

  Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection.

  The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- **ALLERGY AND CROSS-SENSITIVITY**

  Hypersensitivity and cross-sensitivity Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepipvacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

  - **PREGNANCY** Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block. Avoid if possible in the first trimester—toxicity in animal studies. May cause fetal distress syndrome. Do not use for paracervical block in obstetrics. Do not use 7.5 mg/mL strength in obstetrics.

  - **BREAST FEEDING** Amount too small to be harmful.

  - **HEPATIC IMPAIRMENT** Use with caution.

  - **DIRECTIONS FOR ADMINISTRATION** For 1.25 mg/mL concentration dilute standard solutions with sodium chloride 0.9%.
Prescribing and dispensing information

Levbupivacaine is an isomer of bupivacaine.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- **Chirocaine (AbbVie Ltd)**
  - Levobupivacaine (as Levobupivacaine hydrochloride) 2.5 mg per 1 ml Chirocaine 25mg/10ml solution for injection ampoules | 10 ampoule £14.11 (Hospital only)
  - Levobupivacaine (as Levobupivacaine hydrochloride) 5 mg per 1 ml Chirocaine 50mg/10ml solution for injection ampoules | 10 ampoule £16.15 (Hospital only)
  - Levobupivacaine (as Levobupivacaine hydrochloride) 7.5 mg per 1 ml Chirocaine 75mg/10ml solution for injection ampoules | 10 ampoule £24.23 (Hospital only)
  - Levobupivacaine (as Levobupivacaine hydrochloride) 1.25 mg per 1 ml Chirocaine 125mg/100ml infusion bags | 12 bag £174.22

Infusion

- **Chirocaine (AbbVie Ltd)**
  - Levobupivacaine (as Levobupivacaine hydrochloride) 1.25 mg per 1 ml Chirocaine 125mg/100ml infusion bags | 12 bag £174.22

Indications for injection

- **Infiltration anaesthesia**
  - Adult: Dose to be given according to patient’s weight and nature of procedure; max 200 mg, maximum dose 500 mg if given in solutions containing adrenaline

Doses at extremes of body-weight

- When used by local infiltration To avoid excessive dosage in obese patients, weight-based doses for non-emergency indications may need to be calculated on the basis of ideal body-weight.

Intravenous regional anaesthesia and nerve block

- **By regional administration**
  - Adult: Seek expert advice

Pain relief (in anal fissures, haemorrhoids, pruritus ani, pruritus vulvae, herpes zoster, or herpes labialis)

- **To the skin using ointment**
  - Adult: Apply 1–2 mL as required, avoid long-term use

Sore nipples from breast-feeding

- **To the skin using ointment**
  - Adult: Apply using gauze and wash off immediately before next feed

LMX®

Anaesthesia before venous cannulation or venepuncture

- **To the skin**
  - Child 1-2 months: Apply up to 1 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 60 minutes, remove cream with gauze and perform procedure after approximately 5 minutes
  - Child 3-11 months: Apply up to 1 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 4 hours, remove cream with gauze and perform procedure after approximately 5 minutes
  - Child 1-7 years: Apply 1–2.5 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 5 hours, remove cream with gauze and perform procedure after approximately 5 minutes

Solution for injection

- **XYLOCAINE®**
  - Postherpetic neuralgia
    - **To the skin**
    - Adult: Apply once daily for up to 12 hours, followed by a 12-hour plaster-free period; discontinue if no response after 4 weeks, to be applied to intact, dry, non-hairy, non-irritated skin, up to 3 plasters may be used to cover large areas; plasters may be cut

Dosing during delivery in obstetrics

- **To the skin**
  - Adult: Up to 20 doses

Important safety information

- When used by local infiltration
  - The licensed doses stated may not be appropriate in some settings and expert advice should be sought. Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

Contra-indications

- When used by regional administration
  - All grades of atrioventricular block - application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intraneuronal regional anaesthesia (Bier’s block) - severe myocardial depression - should not be applied to damaged skin - sino-atrial disorders

Contra-indications, further information

- When used by regional administration
  - Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

Caution

- When used by regional administration
  - Acute porphyria (consider infusion with glucose for its antiporphyrinoic effects) - congestive cardiac failure (consider lower dose) - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - post cardiac surgery (consider lower dose) - shock

Interactions

- Appendix 1 (lidocaine)

Side-effects

- When used by regional administration
  - Common or very common
    - Bradycardia (may lead to cardiac arrest) - confusion - convulsions - dizziness (particularly if injection too rapid) - drowsiness (particularly if injection too rapid) - hypotension (may lead to cardiac arrest) - paraesthesia (particularly if injection too rapid) - respiratory depression

- Rare
  - When used by regional administration
    - Anaphylaxis

Lidoaaine hydrochloride

(Lignocaine hydrochloride)

**Indications and dose**

Infiltration anaesthesia

- **By local infiltration**
  - Adult: Dose to be given according to patient’s weight and nature of procedure; max 200 mg, maximum dose 500 mg if given in solutions containing adrenaline

Doses at extremes of body-weight

- When used by local infiltration To avoid excessive dosage in obese patients, weight-based doses for non-emergency indications may need to be calculated on the basis of ideal body-weight.

Intravenous regional anaesthesia and nerve block

- **By regional administration**
  - Adult: Seek expert advice

Pain relief (in anal fissures, haemorrhoids, pruritus ani, pruritus vulvae, herpes zoster, or herpes labialis)

- **To the skin using ointment**
  - Adult: Apply 1–2 mL as required, avoid long-term use

Sore nipples from breast-feeding

- **To the skin using ointment**
  - Adult: Apply using gauze and wash off immediately before next feed

LMX®

Anaesthesia before venous cannulation or venepuncture

- **To the skin**
  - Child 1-2 months: Apply up to 1 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 60 minutes, remove cream with gauze and perform procedure after approximately 5 minutes
  - Child 3-11 months: Apply up to 1 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 4 hours, remove cream with gauze and perform procedure after approximately 5 minutes
  - Child 1-7 years: Apply 1–2.5 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 5 hours, remove cream with gauze and perform procedure after approximately 5 minutes

- Adult: Apply 1–2.5 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 5 hours, remove cream with gauze and perform procedure after approximately 5 minutes

VERSATIS®

Postherpetic neuralgia

- **To the skin**
  - Adult: Apply once daily for up to 12 hours, followed by a 12-hour plaster-free period; discontinue if no response after 4 weeks, to be applied to intact, dry, non-hairy, non-irritated skin, up to 3 plasters may be used to cover large areas; plasters may be cut

XYLOCAINE®

During delivery in obstetrics

- **To the skin**
  - Adult: Up to 20 doses
FREQUENCY NOT KNOWN
- When used by regional administration: transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma); arthrinamas, blurred vision, cardiac arrest, feeling of inebriation, headache, hypoglycaemia (following intrathecal or extradural administration); methaemoglobinaemia; muscle twitching, myocardial depression (resulting in hypotension and bradycardia); nausea; numbness of the tongue and perioral region; nystagmus; peripheral vasodilatation (resulting in hypotension and bradycardia); rash; restlessness; tinnitus; tremors; vomiting.

SIDE-EFFECTS, FURTHER INFORMATION
- Topical application: A single application of a topical lidocaine preparation does not generally cause systemic side-effects.
- Toxic effects
  - When used by regional administration: Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.
- Methaemoglobinaemia
  - When used by regional administration: Methaemoglobinaemia can be treated with an intravenous injection of methylthioninium chloride.

ALLERGY AND CROSS-SENSITIVITY
- Hypersensitivity and cross-sensitivity: Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

PREGNANCY
- Crosses the placenta but not known to be harmful in animal studies—use if benefit outweighs risk. When used as a local anaesthetic, large doses can cause fetal bradycardia; if given during delivery can also cause neonatal respiratory depression, hypotonia, or bradycardia after paracervical or epidural block.

BREAST FEEDING
- Present in milk but amount too small to be harmful.

HEPATIC IMPAIRMENT
- Caution—increased risk of side-effects.

RENAL IMPAIRMENT
- Possible accumulation of lidocaine and active metabolite; caution in severe impairment.

MONITORING REQUIREMENTS
- With systemic use: Monitor ECG and have resuscitation facilities available.

PROFESSION SPECIFIC INFORMATION
- Dental practitioners’ formulary: Lidocaine ointment 5% may be prescribed. Spray may be prescribed as Lidocaine Spray 10%

NATIONAL FUNDING/ACCESS DECISIONS
- VERSATIS®
- Scottish Medicines Consortium (SMC) Decisions: The Scottish Medicines Consortium has advised (July 2008) that Versatis® is accepted for restricted use within NHS Scotland for the treatment of postherpetic neuralgia in patients who are intolerant of first-line systemic therapies or when they have been ineffective.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection.

Solution for injection
- Lidocaine hydrochloride (Non-proprietary)
  - Lidocaine hydrochloride 5 mg per 1 ml
    - Lidocaine 50 mg/10 ml (0,5%) solution for injection ampoules | 10 ampoule (POM) £7.00
    - Lidocaine hydrochloride 10 mg per 1 ml
      - Lidocaine 100 mg/10 ml (1%) solution for injection Mini-Plasco ampoules | 20 ampoule (POM) £10.89
  - Lidocaine 100 mg/10 ml (1%) solution for injection ampoules | 10 ampoule (POM) £4.40 DT price = £4.01
  - Lidocaine 100 mg/10 ml (1%) solution for injection Sure-Amp ampoules | 20 ampoule (POM) £8.00
  - Lidocaine hydrochloride 20 mg per 1 ml
    - Lidocaine 100 mg/5 ml (2%) solution for injection ampoules | 10 ampoule (POM) £2.40- £3.80 DT price = £2.41
    - Lidocaine 400 mg/20 ml (2%) solution for injection vials | 10 vial (POM) £19.50
    - Lidocaine 200 mg/10 ml (2%) solution for injection ampoules | 10 ampoule (POM) £14.52
    - Lidocaine 40 mg/2 ml (2%) solution for injection ampoules | 10 ampoule (POM) £4.00 DT price = £4.11
    - Lidocaine 100 mg/5 ml (1%) solution for injection Sure-Amp ampoules | 20 ampoule (POM) £6.00
    - Lidocaine hydrochloride 40 mg per 1 ml
      - Lidocaine 200 mg/5 ml (4%) solution for injection ampoules | 10 ampoule (POM) £2.98 DT price = £2.98
      - Lidocaine 40 mg/2 ml (2%) solution for injection ampoules | 10 ampoule (POM) £14.90 DT price = £14.90

Spray
- Xylocaine (AstraZenica UK Ltd)
  - Lidocaine 10 mg per actuation Xylocaine 10 mg/dose spray | 50 ml | £6.29

Cream
- EXCIPIENTS: May contain Benzyl alcohol, propylene glycol
- LMX 4 (Fernendale Pharmaceuticals Ltd)
  - Lidocaine 40 mg per 1 gram LMX 4 cream | 5 gram (P) £2.98 DT price = £2.98
  - Lidocaine 40 mg/2 ml (2%) solution for injection ampoules | 10 ampoule (POM) £14.90 DT price = £14.90

Ointment
- Lidocaine hydrochloride (Non-proprietary)
  - Lidocaine hydrochloride 50 mg per 1 gram
    - Lidocaine 5% ointment | 15 gram | £6.50 DT price = £6.18

Medicated plaster
- EXCIPIENTS: May contain Hydroxybenzoates (parabens), propylene glycol
- Versatis (Grunenthal Ltd)
  - Lidocaine 50 mg per 1 gram Versatis 5% medicated plasters | 30 plaster (POM) £72.40 DT price = £72.40

Lidocaine with adrenaline
The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride, p. 1197, adrenaline/epinephrine p. 211.

INDICATIONS AND DOSE
Local anaesthesia
- BY LOCAL INFILTRATION
- Adult: Dosed according to the type of nerve block required (consult product literature)
The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride, p. 1197, prilocaine hydrochloride p. 1201.

**Lidocaine with prilocaine**

Anaesthesia before minor skin procedures including venepuncture

**To the skin**

- Child 1–2 months: Apply up to 1 g for maximum 1 hour before procedure, to be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 1 dose per day
- Child 3–11 months: Apply up to 2 g for maximum 4 hours before procedure, to be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 2 doses per day
- Child 1–11 years: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 2 doses per day
- Child 12–17 years: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca)
- Adult: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing

Anaesthesia on genital skin before injection of local anaesthetics

**To the skin**

- Adult: Apply for 15 minutes (in adult men) and 60 minutes (in adult women), to be applied under occlusive dressing

Anaesthesia before surgical treatment of lesions on genital mucosa

**To the skin**

- Adult: Apply up to 10 g, to be applied 5–10 minutes before procedure

Anaesthesia before cervical curettage

**To the skin**

- Adult: Apply 10 g in lateral vaginal fornices for 10 minutes

Anaesthesia before mechanical cleansing or debridement of leg ulcer

**To the skin**

- Adult: Apply up to 10 g for 30–60 minutes, to be applied under occlusive dressing

**Patient and carer advice**

- Use in child less than 37 weeks corrected gestational age

 Medicines for Children leaflet: EMLA cream for local anaesthesia [www.medicinesforchildren.org.uk/emla-cream-for-local-anaesthesia](http://www.medicinesforchildren.org.uk/emla-cream-for-local-anaesthesia)
CONTRA-INDICATIONS

MEDICINAL FORMS

Lidocaine with prilocaine (Non-proprietary)
Lidocaine 25 mg per 1 gram, Prilocaine 25 mg per 1 gram
5 % g / 70mg / 70mg/gram | 15 gram [P] £2.29
30 gram [P] £12.99

Denela (Teva UK Ltd)
Lidocaine 25 mg per 1 gram, Prilocaine 25 mg per 1 gram
5 % cream | 5 gram [P] £12.99
25 gram [P] £14.75
30 gram [P] £12.30

Emla (AstraZeneca UK Ltd)
Lidocaine 25 mg per 1 gram, Prilocaine 25 mg per 1 gram
5 % cream | 5 gram [P] £2.25
25 gram [P] £11.70
30 gram [P] £12.30

Contra-indications

Side-effects

Injection site

Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

Caution

Cardiovascular disease · children (consider dose reduction) · debilitated patients (consider dose reduction) · elderly (consider dose reduction) · epilepsy · hypovolaemia · impaired cardiac conduction · impaired respiratory function · myasthenia gravis · shock

Side-effects

Arrhythmias · blurred vision · cardiac arrest · convulsions · dizziness · drowsiness · feeling of inebriation · headache · lightheadedness · muscle twitching · myocardial depression (resulting in hypotension and bradycardia) · nausea · numbness of the tongue and perioral region · paraesthesia (including sensations of hot and cold) · peripheral vasodilatation (resulting in hypotension and bradycardia) · restlessness · tinnitus · transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) · tremors · vomiting

Further information

Toxic effects

Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection.

Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection.

The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

Allergy and cross-sensitivity

Hypersensitivity and cross-sensitivity

Reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, methylpracaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

Pregnancy

Use with caution in early pregnancy.

Breastfeeding

Use with caution.

Hepatic impairment

Use with caution; increased risk of side-effects in severe impairment.

Renal impairment

Use with caution; increased risk of side-effects.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Scandonest plain (Deproco UK Ltd)
Mepivacaine hydrochloride 30 mg per 1 ml Scandonest plain 3% solution for injection 2.2ml cartridges | 50 cartridge [Box] no price available

Lidocaine with tetracaine

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride, p. 1197, tetracaine p. 1203.

INDICATIONS AND DOSE

Anaesthesia before dermatological procedures and venepuncture

To the skin

Adult: Apply 1 mm layer using a spatula 30 minutes before procedure, then peel off immediately before procedure; max. application area 400 cm², application time of 60 minutes indicated for certain procedures, such as laser-assisted tattoo removal and laser leg vein ablation.

INDICATIONS AND DOSE

Infiltration anaesthesia and nerve block in dentistry

Child 3-17 years: Consult expert dental sources

Adult: Consult expert dental sources

Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

EXCIPIENTS: May contain Hydroxybenzoates (parabens)

Pliaglis (Galderma (UK) Ltd)
Lidocaine 70 mg, Tetracaine 70 mg Pliaglis 70mg/g / 70mg/g cream | 15 gram [P] £22.95

Mepivacaine hydrochloride

INDICATIONS AND DOSE

Infiltration anaesthesia and nerve block in dentistry

Child 3-17 years: Consult expert dental sources

Adult: Consult expert dental sources

Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

Important safety information

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

CONTRA-INDICATIONS

Application to the middle ear (can cause ototoxicity) · avoid injection into infected tissues · avoid injection into inflamed tissues · complete heart block · preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) · should not be applied to damaged skin

CONTRA-INDICATIONS, FURTHER INFORMATION

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
Mepivacaine with adrenaline

The properties listed below are those particular to the combination only. For the properties of the components please consider, mepivacaine hydrochloride p. 1200, adrenaline/epinephrine p. 211.

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion anaesthesia and nerve block in dentistry</td>
</tr>
<tr>
<td>▶ BY LOCAL INFUSION</td>
</tr>
<tr>
<td>▶ Adult: (consult product literature)</td>
</tr>
</tbody>
</table>

### IMPORTANT SAFETY INFORMATION

Adrenaline/epinephrine must be used in a low concentration when administered with a local anaesthetic. The total dose of adrenaline should not exceed 500 micrograms and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Sulfites

« Scandostan special (Deproco UK Ltd)

Adrenaline 10 microgram per 1 ml Mepivacaine hydrochloride 20 mg per 1 ml Scandostan special 2% solution for injection 2.2ml cartridges | 50 cartridge [Pom] no price available

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### Prilocaine hydrochloride

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CITANEST 1% (b)</td>
</tr>
<tr>
<td>Infusion anaesthesia</td>
</tr>
<tr>
<td>▶ BY REGIONAL ADMINISTRATION</td>
</tr>
<tr>
<td>▶ Adult: 100–200 mg/minute, alternatively may be given in incremental doses; dose adjusted according to site of administration and response, and in elderly and debilitated patients (smaller doses may be required); maximum 400 mg per course</td>
</tr>
</tbody>
</table>

**PRILOTEKAL**

Spinal anaesthesia

▶ BY INTRATHecal INJECTION

Adult: Usual dose 40–60 mg (max. per dose 80 mg), dose may need to be reduced in elderly or debilitated patients, or in late pregnancy

### DOSES AT EXTREMES OF BODY-WEIGHT

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

### IMPORTANT SAFETY INFORMATION

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

### CONTRA-INDICATIONS

Acquired methaemoglobinaemia • anaemia • application to the middle ear (can cause ototoxicity) • avoid injection into infected tissues • avoid injection into inflamed tissues • complete heart block • congenital methaemoglobinaemia • preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) • should not be applied to damaged skin

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### CONTRA-INDICATIONS, FURTHER INFORMATION

> Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

### CAUTIONS

Acute porphyrias p. 930 • cardiovascular disease • debilitated patients (consider dose reduction) • elderly (consider dose reduction) • epilepsy • hypovolaemia • impaired cardiac conduction • impaired respiratory function • myasthenia gravis • severe or untreated hypertension • shock

### INTERACTIONS

> Appendix 1 (prilocaine). Caution with concomitant use of drugs that cause methaemoglobinaemia.

### SIDE-EFFECTS

Arrhythmias • blurred vision • cardiac arrest • convulsions • dizziness • drowsiness • feeling of inebriation • headache • hypertension • lightheadedness • methaemoglobinaemia (with high doses) • muscle twitching • myocardial depression (resulting in hypotension and bradycardia) • nausea • numbness of the tongue and perioral region • paraesthesia (including sensations of hot and cold) • peripheral vasodilatation (resulting in hypotension and bradycardia) • restlessness • tinnitus • transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) • tremors • vomiting

### SIDE-EFFECTS, FURTHER INFORMATION

> Toxic effects Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection.

The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

Methaemoglobinaemia Methaemoglobinaemia can be treated with an intravenous injection of methylthioninium chloride.

### ALLERGY AND CROSS-SENSITIVITY

> Hypersensitivity and cross-sensitivity Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

### PREGNANCY

Use lower doses for intrathecal use during late pregnancy. Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block. Avoid paracervical or pudendal block in obstetrics (neonatal methaemoglobinaemia reported).

### BREAST FEEDING

Present in milk but not known to be harmful.

### HEPATIC IMPAIRMENT

Lower doses may be required for intrathecal anaesthesia. Use with caution.

### RENAL IMPAIRMENT

Lower doses may be required for intrathecal anaesthesia. Use with caution.

### NATIONAL FUNDING/ACCESS DECISIONS

**PRILOTEKAL**

Scottish Medicines Consortium (SMC) Decisions

> With intrathecal use The Scottish Medicines Consortium has advised (December 2010) that prilocaine 2% hyperbaric solution for injection (Prilotekal®) is accepted for
restricted use within NHS Scotland for use in spinal anaesthesia in ambulatory surgery settings.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Citarest** (AstraZeneca UK Ltd)
  - Prilocaine hydrochloride 10 mg per 1 ml Citanest 1% solution for injection 50ml vials | 1 vial (PSt) £5.06
- **Priletekal** (AMCo)
  - Prilocaine hydrochloride 20 mg per 1 ml Priletekal 100mg/5ml hyperbaric solution for injection ampoules | 10 ampoule (PSt) £78.75

### Prilocaine with felypressin

The properties listed below are those particular to the combination only. For the properties of the components please consider, prilocaine hydrochloride p. 1201.

**INDICATIONS AND DOSE**

**Dental anaesthesia**
- **BY REGIONAL ADMINISTRATION**
- Adult: Consult expert dental sources for specific advice

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Citarest with Octapressin** (Dentsply Ltd)
  - Felypressin 0.3 unit per 1 ml Prilocaine hydrochloride 30 mg per 1 ml Citanest 3% with Octapressin Dental 0.054units/1.8ml solution for injection self-aspiring cartridges | 100 cartridge (PSt) no price available
  - Citanest 3% with Octapressin Dental 0.0666units/2.2ml solution for injection self-aspiring cartridges | 100 cartridge (PSt) no price available

### Ropivacaine hydrochloride

**INDICATIONS AND DOSE**

**Acute pain, peripheral nerve block**
- **BY REGIONAL ADMINISTRATION**
- Adult: 10–20 mg/hour, dose administered as a continuous infusion or by intermittent injection using a 2 mg/mL (0.2%) solution

**Acute pain, field block**
- **BY REGIONAL ADMINISTRATION**
- Adult: 2–200 mg, dose administered using a 2 mg/mL (0.2%) solution

**Acute pain, lumbar epidural block**
- **BY LUMBAR EPIDURAL**
- Adult: 20–40 mg, followed by 20–30 mg at least every 30 minutes, dose administered using a 2 mg/mL (0.2%) solution

**Acute labour pain**
- **BY CONTINUOUS EPIDURAL INFUSION**
- Adult: 12–20 mg/hour, dose administered using a 2 mg/mL (0.2%) solution

**Acute postoperative pain**
- **BY CONTINUOUS EPIDURAL INFUSION**
- Adult: Up to 28 mg/hour, dose administered using a 2 mg/mL (0.2%) solution

**Postoperative pain, thoracic epidural block**
- **BY CONTINUOUS EPIDURAL INFUSION**
- Adult: 12–28 mg/hour, dose administered using a 2 mg/mL (0.2%) solution

**Surgical anaesthesia, field block**
- **BY REGIONAL ADMINISTRATION**
- Adult: 7.5–225 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, major nerve block (brachial plexus block)**
- **BY REGIONAL ADMINISTRATION**
- Adult: 225–300 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, thoracic epidural block (to establish block for postoperative pain)**
- **BY THORACIC EPIDURAL**
- Adult: 38–113 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, caesarean section**
- **BY LUMBAR EPIDURAL**
- Adult: 113–150 mg, to be administered in incremental doses using a 7.5 mg/mL (0.75%) solution

**DOSES AT EXTREMES OF BODY-WEIGHT**
To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal bodyweight.

**IMPORTANT SAFETY INFORMATION**
Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

**CONTRA-INDICATIONS** Application to the middle ear (can cause otoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) - should not be applied to damaged skin

**CONTRA-INDICATIONS, FURTHER INFORMATION**
Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

**CAUTIONS** Acute porphyrias p. 930 - cardiovascular disease - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - shock

**INTERACTIONS** → Appendix 1 (ropivacaine).

**SIDE-EFFECTS**
- **Common or very common** Hypertension - pyrexia
- **Uncommon** Hypothermia - syncope
- **Frequency not known** Arrhythmias - blurred vision - cardiac arrest - convulsions - dizziness - drowsiness - feeling of inebriation - headache - lightheadedness - muscle twitching - myocardial depression (resulting in hypotension and bradycardia) - nausea - numbness of the tongue and perioral region - paraesthesia (including sensations of hot and cold) - peripheral vasodilatation (resulting in hypotension and bradycardia) - restlessness - tinnitus - transient excitation (followed by depression with drowsiness, respiratory failure, un consciousness, and coma) - tremors - vomiting
SIDE-EFFECTS, FURTHER INFORMATION

- Toxic effects: Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection.

  Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection.

  The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- ALLERGY AND CROSS-SENSITIVITY
  - Hypersensitivity and cross-sensitivity: Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.
  - PREGNANCY: Not known to be harmful. Do not use for paracervical block in obstetrics.
  - BREAST FEEDING: Not known to be harmful.
  - HEPATIC IMPAIRMENT: Use with caution in severe impairment.
  - RENAL IMPAIRMENT: Caution in severe impairment. Increased risk of systemic toxicity in chronic renal failure.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  Solution for injection
  ELECTROLYTES: May contain Sodium
  - **Ropivacaine hydrochloride (Non-proprietary)**
    - Ropivacaine hydrochloride 2 mg per 1 ml \Ropivacaine 20mg/10ml solution for injection ampoules | 10 ampoule £16.50 (Hospital only)
    - Ropivacaine hydrochloride 7.5 mg per 1 ml \Ropivacaine 75mg/10ml solution for injection ampoules | 10 ampoule £25.00 (Hospital only)
    - Ropivacaine hydrochloride 10 mg per 1 ml \Ropivacaine 100mg/10ml solution for injection ampoules | 10 ampoule £30.00 (Hospital only)
  - **Naropin (AstraZeneca UK Ltd)**
    - Naropine hydrochloride 2 mg per 1 ml Naropin 20mg/10ml solution for injection ampoules | 5 ampoule £12.79
    - Naropine hydrochloride 7.5 mg per 1 ml Naropine 75mg/10ml solution for injection ampoules | 5 ampoule £15.90
    - Naropine hydrochloride 10 mg per 1 ml Naropine 100mg/10ml solution for injection ampoules | 5 ampoule £19.22

  Infusion
  ELECTROLYTES: May contain Sodium
  - **Ropivacaine hydrochloride (Non-proprietary)**
    - Ropivacaine hydrochloride 2 mg per 1 ml \Ropivacaine 400mg/200ml infusion bags | 5 bag £72.25 | 10 bag £137.00 (Hospital only)
  - **Naropin (AstraZeneca UK Ltd)**
    - Naropine hydrochloride 2 mg per 1 ml Naropine 400mg/200ml infusion Polybags | 5 bag £86.70

Tetracaine (Amethocaine)

- INDICATIONS AND DOSE
  - Anaesthesia before venepuncture or venous cannulation
    - TO THE SKIN
      - Child 1 month–4 years: Apply contents of up to 1 tube (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation
      - Child 5–17 years: Apply contents of up to 5 tubes (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation
    - Adult: Apply contents of up to 5 tubes (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

- CONTRA-INDICATIONS: Should not be applied to damaged skin

- SIDE-EFFECTS: Local skin reactions
  - The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems; systemic side effects unlikely as minimal absorption following topical application.

- ALLERGY AND CROSS-SENSITIVITY
  - Hypersensitivity and cross-sensitivity: Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- BREAST FEEDING: Not known to be harmful.

- PATIENT AND CARER ADVICE
  - Medicines for Children leaflet: Tetracaine gel for local anaesthesia www.medicinesforchildren.org.uk/tetracaine-gel-for-local-anaesthesia

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  Gel
  EXCIPIENTS: May contain Hydroxybenzoates (parabens)
  - **Ametop** (Smith & Nephew Healthcare Ltd)
    - Tetracaine 40 mg per 1 gram Ametop 4% gel | 1.5 gram £1.08 | 18 gram no price available
# Emergency treatment of poisoning

## Overview

These notes provide only an overview of the treatment of poisoning, and it is strongly recommended that either TOXBASE or the UK National Poisons Information Service be consulted when there is doubt about any aspect of suspected poisoning.

### Hospital admission

Patients who have features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed action should also be admitted, even if they appear well. Delayed-action poisons include aspirin p. 114, iron, paracetamol p. 414, tricyclic antidepressants, and codeine p. 62 (diphenoxylate with atropine, Lomotil®); the effects of modified-release preparations are also delayed. A note of all relevant information, including what treatment has been given, should accompany the patient to hospital.

### Further information

TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, is available on the internet to registered users at [www.toxbasebackup.org](http://www.toxbasebackup.org) (a backup site is available at [www.toxbasebackup.org](http://www.toxbasebackup.org) if the main site cannot be accessed). It provides information about routine diagnosis, treatment, and management of patients exposed to drugs, household products, and industrial and agricultural chemicals.

Specialist information and advice on the treatment of poisoning is available day and night from the UK National Poisons Information Service on the following number:

Tel: 0344 892 0111

Advice on laboratory analytical services can be obtained from TOXBASE or from the National Poisons Information Service. Help with identifying capsules or tablets may be obtained from TOXBASE or from the National Poisons Information Service (out of hours).

### General care

It is often impossible to establish with certainty the identity of the poison and the size of the dose. This is not usually important because even a few poisons (such as opioids, paracetamol, and iron) have specific antidotes; few patients require active removal of the poison. In most patients, treatment is directed at managing symptoms as they arise. Nevertheless, knowledge of the type and timing of poisoning can help in anticipating the course of events. All relevant information should be sought from the poisoned individual and from carers or parents. However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses and patients should be assessed carefully. Accidents may involve domestic and industrial products (the contents of which are not generally known). The National Poisons Information Service should be consulted when there is doubt about any aspect of suspected poisoning.

### Respiration

Respiration is often impaired in unconscious patients. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be useful in patients with reduced consciousness to prevent obstruction, provided ventilation is adequate. Intubation and ventilation should be considered in patients whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation; such patients should be monitored in a critical care area.

Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

### Blood pressure

Hypotension is common in severe poisoning with central nervous system depressants. A systolic blood pressure of less than 70 mmHg may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by raising the foot of the bed and administration of an infusion of either sodium chloride p. 914 or a colloid. Vasoconstrictor sympathomimetics are rarely required and their use may be discussed with the National Poisons Information Service.

Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnoea.

Hypertension, often transient, occurs less frequently than hypotension in poisoning; it may be associated with sympathomimetic drugs such as amphetamines, phenylcyclidine, and cocaine.

### Heart

Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias often respond to correction of underlying hypoxia, acidosis,
or other biochemical abnormalities, but ventricular arrhythmias that cause serious hypotension require treatment. If the QT interval is prolonged, specialist advice should be sought because the use of some anti-arrhythmic drugs may be inappropriate. Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld until the patient reaches hospital.

**Body temperature**

Hypothermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer or by some other means. Hypothermia should be managed by prevention of further heat loss and appropriate re-warming as clinically indicated.

Hyperthermia can develop in patients taking CNS stimulants; children and the elderly are also at risk when taking therapeutic doses of drugs with antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with tepid water will promote evaporation. Advice should be sought from the National Poisons Information Service on the management of severe hyperthermia resulting from conditions such as the serotonin syndrome.

Both hypothermia and hyperthermia require urgent hospitalisation for assessment and supportive treatment.

**Convulsions**

Single short-lived convulsions (lasting less than 5 minutes) do not require treatment. If convulsions are protracted or recur frequently, lorazepam p. 317 or diazepam p. 321 (preferably as emulsion) should be given by slow intravenous injection into a large vein. Benzodiazepines should not be given by the intramuscular route for convulsions. If the intravenous route is not readily available, midazolam oromucosal solution p. 318 [unlicensed use in adults and children under 3 months] can be given by the buccal route or diazepam can be administered as a rectal solution.

**Methaemoglobininaemia**

Drug- or chemical-induced methaemoglobinemia should be treated with methylthioninium chloride p. 1216 if the methaemoglobin concentration is 30% or higher, or if symptoms of tissue hypoxia are present despite oxygen therapy. Methylthioninium chloride reduces the ferric iron of methaemoglobin back to the ferrous iron of haemoglobin; in high doses, methylthioninium chloride can itself cause methaemoglobinemia.

**Removal and elimination**

**Prevention of absorption**

Given by mouth, charcoal, activated p. 1211 can bind many poisons in the gastro-intestinal system, thereby reducing their absorption. The sooner it is given the more effective it is, but it may still be effective up to 1 hour after ingestion of the poison—longer in the case of modified-release preparations or of drugs with antimuscarinic (anticholinergic) properties. It is particularly useful for the prevention of absorption of poisons that are toxic in small amounts, such as antidepressants.

**Active elimination techniques**

Repeated doses of charcoal, activated p. 1211 by mouth enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with:

- Carbamazepine
- Dapsone
- Phenobarbital
- Quinine
- Theophylline

If vomiting occurs after dosing it should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment. In cases of intolerance, the dose may be reduced and the frequency increased but this may compromise efficacy.

Charcoal, activated should not be used for poisoning with petroleum distillates, corrosive substances, alcohols, malathion, cyanides and metal salts including iron and lithium salts.

Other techniques intended to enhance the elimination of poisons after absorption are only practicable in hospital and are only suitable for a small number of severely poisoned patients. Moreover, they only apply to a limited number of poisons. Examples include:

- haemodialysis for ethylene glycol, lithium, methanol, phenobarbital, salicylates, and sodium valproate;
- alkalisation of the urine for salicylates.

**Removal from the gastro-intestinal tract**

Gastric lavage is rarely required; for substances that cannot be removed effectively by other means (e.g. iron), it should be considered only if a life-threatening amount has been ingested within the previous hour. It should be carried out only if the airway can be protected adequately. Gastric lavage is contra-indicated if a corrosive substance or a petroleum distillate has been ingested, but it may occasionally be considered in patients who have ingested drugs that are not adsorbed by charcoal, such as iron or lithium. Induction of enesis (e.g. with ipecacuanha) is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration.

**Whole bowel irrigation** (by means of a bowel cleansing preparation) has been used in poisoning with certain modified-release or enteric-coated formulations, in severe poisoning with iron and lithium salts, and if illicit drugs are involved. Whole bowel irrigation (enterally) has been used in poisoning with certain substances such as lithium and iron. Whole bowel irrigation is potentially hazardous and should be performed only by experienced staff.

**Poison management**

Mainly supportive treatment, with particular attention to maintaining a clear airway and measures to reduce the risk of aspiration of gastric contents. The blood glucose is measured and glucose given if indicated.

**Aspirin**

The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning. The associated acid-base disturbances are complex.

Treatment must be in hospital, where plasma salicylate, pH, and electrolytes can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement. Plasma-salicylate concentration may not correlate with clinical severity in the young and the elderly, and clinical and biochemical assessment is necessary. Generally, the clinical severity of poisoning is less below a plasma-salicylate concentration of 500 mg/litre (3.6 mmol/litre), unless there is evidence of metabolic acidosis. Activated charcoal can be given within 1 hour of ingesting more than 125 mg/kg of aspirin. Fluid losses should be replaced and intravenous sodium bicarbonate may be given (ensuring plasma-potassium concentration is within the reference range) to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5).
Plasma-potassium concentration should be corrected before giving sodium bicarbonate as hypokalaemia may complicate alkalinisation of the urine.

Haemodialysis is the treatment of choice for severe salicylate poisoning and should be considered when the plasma-salicylate concentration exceeds 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis.

Opioids

Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone hydrochloride p. 1214 is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to vital signs. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone.

Dextropropoxyphene and methadone have very long durations of action; patients may need to be monitored for long periods following large overdoses.

Naloxone reverses the opioid effects of dextropropoxyphene. The long duration of action of dextropropoxyphene calls for prolonged monitoring and further doses of naloxone may be required.

Norpropoxyphene, a metabolite of dextropropoxyphene, also has cardiotoxic effects which may require treatment with sodium bicarbonate p. 910 or magnesium sulfate p. 924, or both. Arrhythmias may occur for up to 12 hours.

**Paracetamol**

In cases of intravenous paracetamol poisoning contact the National Poisons Information Service for advice on risk assessment and management.

Toxic doses of paracetamol may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis. Liver damage is maximal 3–4 days after paracetamol overdose and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Therefore, despite a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently.

To avoid underestimating the potentially toxic paracetamol dose ingested by obese patients who weigh more than 110 kg, use a body-weight of 110 kg (rather than their actual body-weight) when calculating the total dose of paracetamol ingested (in mg/kg). Acetylcysteine p. 1215 protects the liver if infused up to, and possibly beyond, 24 hours of ingesting paracetamol. It is most effective if given within 8 hours of ingestion, after which effectiveness declines. Very rarely, giving acetylcysteine by mouth [unlicensed route] is an alternative if intravenous access is not possible—contact the National Poisons Information Service.
Poisons Information Service for advice.
Neonates less than 45 weeks corrected gestational age may be more susceptible to paracetamol-induced liver toxicity, therefore, treatment with acetylcysteine p. 1215 should be considered in all paracetamol overdoses, and advice should be sought from the National Poisons Information Service.

**Acute overdose**
Hepatotoxicity may occur after a single ingestion of more than 150 mg/kg paracetamol taken in less than 1 hour. Rarely, hepatotoxicity may develop with single ingestions as low as 75 mg/kg of paracetamol taken in less than 1 hour. Patients who have ingested 75 mg/kg or more of paracetamol in less than 1 hour should be referred to hospital. Administration of charcoal, activated p. 1211 should be considered if paracetamol in excess of 150 mg/kg is thought to have been ingested within the previous hour.

Patients at risk of liver damage and, therefore, requiring acetylcysteine, can be identified from a single measurement of the plasma-paracetamol concentration, related to the time from ingestion, provided this time interval is not less than 4 hours; earlier samples may be misleading. The concentration is plotted on a paracetamol treatment graph, with a reference line (‘treatment line’) joining plots of 100 mg/litre (0.66 mmol/litre) at 4 hours and 3.13 mg/litre (0.02 mmol/litre) at 24 hours. Acetylcysteine treatment should commence immediately in patients:
- whose plasma-paracetamol concentration falls on or above the treatment line on the paracetamol treatment graph;
- who present 8–24 hours after taking an acute overdose of more than 150 mg/kg of paracetamol, even if the plasma-paracetamol concentration is not yet available; acetylcysteine can be discontinued if the plasma-paracetamol concentration is later reported to be below the treatment line on the paracetamol treatment graph, provided that the patient is asymptomatic and liver function tests, serum creatinine and INR are normal.

The prognostic accuracy of a plasma-paracetamol concentration taken after 15 hours is uncertain, but a concentration on or above the treatment line on the paracetamol treatment graph should be regarded as carrying a serious risk of liver damage. If more than 15 hours have elapsed since ingestion, or there is doubt about appropriate management, advice should be sought from the National Poisons Information Service.

‘Staggered’ overdose, uncertain time of overdose, or therapeutic excess
A ‘staggered’ overdose involves ingestion of a potentially toxic dose of paracetamol over more than one hour, with the possible intention of causing self-harm. Therapeutic excess is the inadvertent ingestion of a potentially toxic dose of paracetamol during its clinical use. The paracetamol treatment graph is unreliable if a ‘staggered’ overdose is taken, if there is uncertainty about the time of the overdose, or if there is therapeutic excess. In these cases, patients who have taken more than 150 mg/kg of paracetamol in any 24-hour period are at risk of toxicity and should be commenced on acetylcysteine immediately, unless it is more than 24 hours since the last ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal.

Rarely, toxicity can occur with paracetamol doses between 75–150 mg/kg in any 24-hour period; clinical judgement of the individual case is necessary to determine whether to treat those who have ingested this amount of paracetamol. For small adults, this may be within the licensed dose, but ingestion of a licensed dose of paracetamol is not considered an overdose.

Although there is some evidence suggesting that factors such as the use of liver enzyme-inducing drugs (e.g. carbamazepine p. 291, efavirenz p. 593, nevirapine p. 594, phenobarbital p. 313, phenytoin p. 302, primidone p. 313, rifabutin p. 530, rifampicin p. 535, St John’s wort), chronic alcoholism, and starvation may increase the risk of hepatotoxicity, the CHM has advised that these should no longer be used in the assessment of paracetamol toxicity.

Significant toxicity is unlikely if, 24 hours or longer after the last paracetamol ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal. Patients with clinical features of hepatic injury such as jaundice or hepatic tenderness should be treated urgently with acetylcysteine. If there is uncertainty about a patient’s risk of toxicity after paracetamol overdose, treatment with acetylcysteine should be commenced. Advice should be sought from the National Poisons Information Service whenever necessary.

**Acetylcysteine dose and administration**
For paracetamol overdose, acetylcysteine is given in a total dose that is divided into 3 consecutive intravenous infusions over a total of 21 hours. The tables below include the dose of acetylcysteine, for adults and children of body-weight 40 kg and over, in terms of the volume of acetylcysteine Concentrate for Intravenous Infusion required for each of the 3 infusions. The requisite dose of acetylcysteine is added to glucose intravenous infusion 5% p. 915.

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous Infusion 200 mg/mL required to prepare first infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>34 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>42 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>49 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>57 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>64 mL</td>
</tr>
<tr>
<td>90–99 kg</td>
<td>72 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>79 mL</td>
</tr>
<tr>
<td>≥110 kg</td>
<td>83 mL (max. dose)</td>
</tr>
</tbody>
</table>

**First infusion** (based on an acetylcysteine dose of approx. 150 mg/kg)—add requisite volume of Acetylcysteine Concentrate for Intravenous Infusion to 200 mL Glucose Intravenous Infusion 5%; infuse over 1 hour.

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous Infusion 200 mg/mL required to prepare second infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>12 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>14 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>17 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>19 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>22 mL</td>
</tr>
<tr>
<td>90–99 kg</td>
<td>24 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>27 mL</td>
</tr>
<tr>
<td>≥110 kg</td>
<td>28 mL (max. dose)</td>
</tr>
</tbody>
</table>

**Second infusion** (based on an acetylcysteine dose of approx. 50 mg/kg; start immediately after completion of first infusion)—add requisite volume of Acetylcysteine Concentrate for Intravenous Infusion to 500 mL Glucose Intravenous Infusion 5%; infuse over 4 hours.
Service is essential. Life-threatening features include treat. Urgent advice from the National Poisons Information
hydroxychloroquine is extremely hazardous and dif
Antimalarials
hyperthermia, rhabdomyolysis, renal failure, and neuromuscular hyperactivity, and autonomic instability; syndrome, with marked neuropsychiatric effects,
inhibitors include nausea, vomiting, agitation, tremor, Selective serotonin re-uptake inhibitors (SSRIs)
of varying degree, hypotension, hypothermia, hyperre
Tricyclic and related antidepressants cause dry mouth, coma
Tricyclic and related antidepressants
100
Charcoal given within
form) may be required to treat convulsions. Activated
lorazepam or intravenous diazepam (preferably in emulsion
ventilation during transfer are mandatory. Intravenous
Supportive measures to ensure a clear airway and adequate
complicate severe poisoning; delirium with confusion,
cardiac conduction defects, and arrhythmias. Dilated pupils
Convulsions can be treated with
Diazepam given by mouth is usually adequate to sedate
prevent them in those with an extended QRS duration.
infusion of sodium bicarbonate can arrest arrhythmias or
absorption of the drug. Although arrhythmias are worrying,
since prolongation of the QT interval). Management is supportive.
Charcoal, activated p. 1211 can be given within 1 hour of
ingesting a significant quantity of a second-generation antipsychotic drug.

**Antidepressants**

**Tricyclic and related antidepressants**

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery.

Assessment in hospital is strongly advised in case of poisoning by tricyclic and related antidepressants but symptomatic treatment can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or intravenous diazepam (preferably in emulsion form) may be required to treat convulsions. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

**Selective serotonin re-uptake inhibitors (SSRIs)**

Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, dystonia, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathy may develop.

Management of SSRI poisoning is supportive. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Convulsions can be treated with lorazepam, diazepam, or midazolam oromucosal solution [unlicensed use in adults and children under 3 months] (see Convulsions). Contact the National Poisons Information Service for the management of hyperthermia or the serotonin syndrome.

**Antimalarials**

Overdosage with quinine, chloroquine, or hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

**Antipsychotics**

**Phenothiazines and related drugs**

Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with prochlorperazine and trifluoperazine), and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia, acidosis, and other biochemical abnormalities, but specialist advice should be sought if arrhythmias result from a prolonged QT interval; the use of some anti-arrhythmic drugs can worsen such arrhythmias. Dystonic reactions are rapidly abolished by injection of drugs such as procyclidine hydrochloride p. 384 or diazepam p. 321 (emulsion preferred).

**Second-generation antipsychotic drugs**

Features of poisoning by second-generation antipsychotic drugs include drowsiness, convulsions, extrapyramidal symptoms, hypotension, and ECG abnormalities (including prolongation of the QT interval). Management is supportive. Charcoal, activated p. 1211 can be given within 1 hour of ingesting a significant quantity of a second-generation antipsychotic drug.

**Benzodiazepines**

Benzodiazepines taken alone cause drowsiness, ataxia, dystarxia, dystagmus, and occasionally respiratory depression, and coma. Charcoal, activated can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected. Benzodiazepines potentiate the effects of other central nervous system depressants taken concomitantly. Use of the benzodiazepine antagonist flumazenil p. 1213 [unlicensed indication] can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; it should be used on expert advice only and not as a diagnostic test in patients with a reduced level of consciousness.

**Beta blockers**

Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in patients with conduction system disorders or impaired myocardial function. Bradycardia is the most common arrhythmia caused by beta-blockers, but sotalol may induce ventricular tachyarrhythmias (sometimes of the torsade de pointes type). The effects of massive overdosage can vary from one beta-blocker to another; propranolol overdose in particular may cause coma and convulsions. Acute massive overdose must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory. An intravenous injection of atropine sulfate p. 1179 is required to treat bradycardia. Cardiogenic shock unresponsive to atropine sulfate is probably best treated with an intravenous injection of glucagon p. 660 [unlicensed] in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an intravenous infusion. If glucagon is not available, intravenous isoprenaline (available from specialist-order manufacturers or specialist importing companies) is an alternative. A cardiac pacemaker can be used to increase the heart rate.

<table>
<thead>
<tr>
<th>Third infusion</th>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous Infusion 200 mg/mL required to prepare third infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>23 mL</td>
<td></td>
</tr>
<tr>
<td>50–59 kg</td>
<td>28 mL</td>
<td></td>
</tr>
<tr>
<td>60–69 kg</td>
<td>33 mL</td>
<td></td>
</tr>
<tr>
<td>70–79 kg</td>
<td>38 mL</td>
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</tr>
<tr>
<td>80–89 kg</td>
<td>43 mL</td>
<td></td>
</tr>
<tr>
<td>90–99 kg</td>
<td>48 mL</td>
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<tr>
<td>100–109 kg</td>
<td>53 mL</td>
<td></td>
</tr>
<tr>
<td>≥110 kg</td>
<td>55 mL (max. dose)</td>
<td></td>
</tr>
</tbody>
</table>
Calcium-channel blockers

Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. Verapamil and diltiazem have a profound calcium depressant effect causing hypotension and arrhythmias, including complete heart block and asystole. The dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

Charcoal, activated should be considered if the patient presents within 1 hour of overdosage with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved. In patients with significant features of poisoning, calcium chloride p. 919 or calcium gluconate p. 920 is given by injection; atropine is an effective measure of hypotension. In severe cases, an insulin and glucose infusion may be required in the management of hypotension and myocardial failure. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vasodilatation or to myocardial depression—advice should be sought from the National Poisons Information Service.

Iron salts

Iron poisoning in childhood is usually accidental. The symptoms are nausea, vomiting; abdominal pain; diarrhoea, haematemesis, and rectal bleeding. Hypotension and hepatocellular necrosis can occur later. Coma, shock, and metabolic acidosis indicate severe poisoning.

Advice should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour.

Mortality is reduced by intensive and specific therapy with desferrioxamine mesilate p. 902, which chelates iron. The serum–iron concentration is measured as an emergency and intravenous desferrioxamine mesilate given to chelate absorbed iron in excess of the expected iron binding capacity. In severe toxicity intravenous desferrioxamine mesilate should be given immediately without waiting for the result of the serum–iron measurement.

Lithium

Most cases of lithium intoxication occur as a complication of long-term therapy and are caused by reduced excretion of the drug because of a variety of factors including dehydration, deterioration of renal function, infections, and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) owing to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes arising from the patient’s depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic serum-lithium concentrations are within the range of 0.4–1 mmol/litre; concentrations in excess of 2 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis if neurological symptoms or renal failure are present. In acute overdosage much higher serum-lithium concentrations may be present without features of toxicity and all that is usually necessary is to take measures to increase urine output (e.g. by increasing fluid intake but avoiding diuretics). Otherwise, treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions. Gastric lavage may be considered if it can be performed within 1 hour of ingesting significant quantities of lithium. Wholebowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service.

Stimulants

Amphetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled by diazepam p. 321 or lorazepam p. 317; advice should be sought from the National Poisons Information Service on the management of hypertension. Later, tepid sponging, anticonvulsants, and artificial respiration may be needed.

Cocaine

Cocaine stimulates the central nervous system, causing agitation, delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Theophylline

Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Repetitive doses of theophylline can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion and especially if a modified-release preparation has been taken (see also under Active Elimination Techniques). Ondansetron p. 406 may be effective for severe vomiting that is resistant to other antiemetics [unlicensed indication]. Hypokalaemia is corrected by intravenous infusion of potassium chloride p. 929 and may be so severe as to require 60 mmol/hour (high doses require ECG monitoring). Convulsions should be controlled by intravenous administration of lorazepam or diazepam (see Convulsions). Sedation with diazepam may be necessary in agitated patients.

Provided the patient does not suffer from asthma, a short-acting beta-blocker can be administered intravenously to reverse severe tachycardia, hypokalaemia, and hyperglycaemia.
Emergency treatment of poisoning

Other poisons
Consult either the National Poisons Information Service day and night or TOXBASE, see under the National Poisons Information Service.

Cyanides
Oxygen should be administered to patients with cyanide poisoning. The choice of antidote depends on the severity of poisoning, certainty of diagnosis, and the cause. Dicobalt edetate p. 1212 is the antidote of choice when there is a strong clinical suspicion of severe cyanide poisoning, but it should not be used as a precautionary measure. Dicobalt edetate itself is toxic, associated with anaphylactoid reactions, and is potentially fatal if administered in the absence of cyanide poisoning. A regimen of sodium nitrite p. 1212 followed by sodium thiosulfate p. 1212 is an alternative if dicobalt edetate is not available.

Hydroxocobalamin p. 899 (Cyanokit®—no other preparation of hydroxocobalamin is suitable) can be considered for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

Ethylene glycol and methanol
Fomepizole (available from ‘special-order’ manufacturers or specialist importing companies) is the treatment of choice for ethylene glycol and methanol (methyl alcohol) poisoning. If necessary, ethanol (by mouth or by intravenous infusion) can be used, but with caution. Advice on the treatment of ethylene glycol and methanol poisoning should be obtained from the National Poisons Information Service. It is important to start antidote treatment promptly in cases of suspected poisoning with these agents.

Heavy metals
Heavy metal antidotes include succimer (DMSA) [unlicensed], unithiol (DMPS) [unlicensed], sodium calcium edetate [unlicensed], and dimercaprol. Dimercaprol in the management of heavy metal poisoning has been superseded by other chelating agents. In all cases of heavy metal poisoning, the advice of the National Poisons Information Service should be sought.

Noxious gases
Carbon monoxide
Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces. Immediate treatment of carbon monoxide poisoning is essential. The person should be moved to fresh air, the airway cleared, and high-flow oxygen administered through a tight-fitting mask with an inflated face seal. Artificial respiration should be given as necessary and continued until adequate spontaneous breathing starts, or stopped only after persistent and efficient treatment of cardiac arrest has failed. The patient should be admitted to hospital because complications may arise after a delay of hours or days. Cerebral oedema may occur in severe poisoning and is treated with an intravenous infusion of mannitol p. 217. Referral for hyperbaric oxygen treatment should be discussed with the National Poisons Information Service if the patient is pregnant or in cases of severe poisoning, such as if the patient is or has been unconscious, or has psychiatric or neurological features other than a headache, or has myocardial ischaemia or an arrhythmia, or has a blood carboxyhaemoglobin concentration of more than 20%.

Sulfur dioxide, chlorine, phosgene, ammonia
All of these gases can cause upper respiratory tract and conjunctival irritation. Pulmonary oedema, with severe breathlessness and cyanosis may develop suddenly up to 36 hours after exposure. Death may occur. Patients are kept under observation and those who develop pulmonary oedema are given oxygen. Assisted ventilation may be necessary in the most serious cases.

CS Spray
CS spray, which is used for riot control, irritates the eyes (hence ‘tear gas’) and the respiratory tract; symptoms normally settle spontaneously within 15 minutes. If symptoms persist, the patient should be removed to a well-ventilated area, and the exposed skin washed with soap and water after removal of contaminated clothing. Contact lenses should be removed and rigid ones washed (soft ones should be discarded). Eye symptoms should be treated by irrigating the eyes with physiological saline (or water if saline is not available) and advice sought from an ophthalmologist. Patients with features of severe poisoning, particularly respiratory complications, should be admitted to hospital for symptomatic treatment.

Nerve agents
Treatment of nerve agent poisoning is similar to organophosphorus insecticide poisoning, but advice must be sought from the National Poisons Information Service. The risk of cross-contamination is significant; adequate decontamination and protective clothing for healthcare personnel are essential. In emergencies involving the release of nerve agents, kits (‘NAAS pods’) containing pralidoxime chloride p. 1212 can be obtained through the Ambulance Service from the National Blood Service (or the Welsh Blood Service in South Wales or designated hospital pharmacies in Northern Ireland and Scotland—see TOXBASE for list of designated centres).

Pesticides
Organophosphorus insecticides
Organophosphorus insecticides are usually supplied as powders or dissolved in organic solvents. All are absorbed through the skin and intact skin as well as through the gut and inhibit cholinesterase activity, thereby prolonging and intensifying the effects of acetylcholine. Toxicity between different compounds varies considerably, and onset may be delayed after skin exposure.

Anxiety, restlessness, dizziness, headache, miosis, nausea, hypersalivation, vomiting, abdominal colic, diarrhoea, bradycardia, and sweating are common features of organophosphorus poisoning. Muscle weakness and fasciculation may develop and progress to generalised flaccid paralysis, including the ocular and respiratory muscles. Convulsions, coma, pulmonary oedema with copious bronchial secretions, hypoxia, and arrhythmias occur in severe cases. Hyperglycaemia and glycosuria without ketonuria may also be present.

Further absorption of the organophosphorus insecticide should be prevented by moving the patient to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear airway, frequent removal of bronchial secretions, and adequate ventilation and oxygenation; gastric lavage may be considered provided that the airway is protected. Atropine sulfate p. 1179 will reverse the muscarinic effects of acetylcholine and is given by intravenous injection until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished.

Pralidoxime chloride, a cholinesterase reactivator, is used as an adjunct to atropine sulfate in moderate or severe poisoning. It improves muscle tone within 30 minutes of administration. Pralidoxime chloride is continued until the patient has not required atropine sulfate for 12 hours. Pralidoxime chloride can be obtained from designated centres, the names of which are held by the National Poisons Information Service.
Snake bites and animal stings

Snake bites

Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (*Vipera berus*). The bite may cause local and systemic effects. Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Systemic effects include early anaphylactic symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhoea, and vomiting), with later persistent or recurrent syncope, angioedema, urticaria, abdominal colic, diarrhoea, anaphylactic symptoms (transient hypotension with regional lymph nodes. Systemic effects include early hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure.Fatal envenoming is rare but the potential for severe envenoming must not be underestimated.

Early anaphylactic symptoms should be treated with adrenaline/epinephrine p. 211. Indications for European viper snake venom antiserum p. 1216 treatment include systemic envenoming, especially hypotension, ECG abnormalities, vomiting, haemostatic abnormalities, and marked local envenoming such that after bites on the hand or foot, swelling extends beyond the wrist or ankle within 4 hours of the bite. For those patients who present with clinical features of severe envenoming (e.g. shock, ECG abnormalities, or local swelling that has advanced from the foot to above the knee or from the hand to above the elbow within 2 hours of the bite), a higher initial dose of the European viper snake venom antiserum is recommended; if symptoms of systemic envenoming persist contact the National Poisons Information Service. Adrenaline/epinephrine injection must be immediately to hand for treatment of anaphylactic reactions to the European viper snake venom antiserum.

European viper snake venom antiserum is available for bites by certain foreign snakes and spiders, stings by scorpions and fish. For information on identification, management, and for supply in an emergency, telephone the National Poisons Information Service. Whenever possible the TOXBASE entry should be read, and relevant information collected, before telephoning the National Poisons Information Service.

Insect stings

Stings from ants, wasps, hornets, and bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time. If the sting is in the mouth or on the tongue local swelling may threaten the upper airway. The stings from these insects are usually treated by cleaning the area with a topical antiseptic. Bee stings should be removed as quickly as possible. Anaphylactic reactions require immediate treatment with intramuscular adrenaline/epinephrine; self-administered intramuscular adrenaline/epinephrine (e.g. EpiPen®) is the best first-aid treatment for patients with severe hypersensitivity. An inhaled bronchodilator should be used for asthmatic reactions, see also the management of anaphylaxis. A short course of an oral antihistamine or a topical corticosteroid may help to reduce inflammation and relieve itching. A vaccine containing extracts of bee and wasp venom can be used to reduce the risk of anaphylaxis and systemic reactions in patients with systemic hypersensitivity to bee or wasp stings.

Marine stings

The severe pain of weeverfish (*Trachinus virena*) and Portuguese man-ō’-war stings can be relieved by immersing the sting area immediately in uncomfortably hot, but not scalding, water (not more than 45°C). People stung by jellyfish and Portuguese man-ō’-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater.

Alcoholic solutions, including suntan lotions, should not be applied because they can cause further discharge of stinging hairs. Ice packs can be used to reduce pain.

Other poisons

Consult either the National Poisons Information Service or TOXBASE.

1 Active elimination from the gastro-intestinal tract

ANTIDOTES AND CHELATORS > INTESTINAL ADSORBENTS

Charcoal, activated

- **INDICATIONS AND DOSE**
  
  Reduction of absorption of poisons in the gastro-intestinal system

  - BY MOUTH
    - Child 1 month–11 years: 1 g/kg (max. per dose 50 g)
    - Child 12–17 years: 50 g
    - Adult: 50 g

  Active elimination of poisons

  - BY MOUTH
    - Child 1 month–11 years: 1 g/kg every 4 hours (max. per dose 50 g), dose may be reduced and the frequency increased if not tolerated, reduced dose may compromise efficacy
    - Child 12–17 years: Initially 50 g, then 50 g every 4 hours, reduced if not tolerated to 25 g every 2 hours, alternatively 12.5 g every 1 hour, reduced dose may compromise efficacy
    - Adult: Initially 50 g, then 50 g every 4 hours, reduced if not tolerated to 25 g every 2 hours, alternatively 12.5 g every 1 hour, reduced dose may compromise efficacy

  Accelerated elimination of teriflunomide

  - BY MOUTH USING GRANULES
    - Adult: 50 g every 12 hours for 11 days

  Accelerated elimination of leflunomide (washout procedure)

  - BY MOUTH USING GRANULES
    - Adult: 50 g 4 times a day for 11 days

- **UNLICENSED USE** Activated charcoal doses in BNF may differ from those in product literature.

- **CAUTIONS** Comatose patient (risk of aspiration—ensure airway is protected) - drowsy patient (risk of aspiration—ensure airway protected · reduced gastrointestinal motility (risk of obstruction)

- **SIDE-EFFECTS** Black stools

- **DIRECTIONS FOR ADMINISTRATION** Suspension or reconstituted powder may be mixed with soft drinks (e.g. caffeine-free diet cola) or fruit juices to mask the taste.

- **MEDIcINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Granules**

  - Carbomix (Beacon Pharmaceuticals Ltd)
    - Activated charcoal 813 mg per 1 gram Carbomix 81.3% granules sugar-free | 50 gram £11.90

  **Oral suspension**

  - Actidose-Aqua Advance (Alliance Pharmaceuticals Ltd)
    - Activated charcoal 208 mg per 1 ml Actidose-Aqua Advance 1.04g/5ml oral suspension | 240 ml £12.89

  - Charcodote (Teva UK Ltd)
    - Activated charcoal 200 mg per 1 ml Charcodote 200mg/ml oral suspension sugar-free | 250 ml £11.88

Emergency treatment of poisoning
2 Chemical toxicity

2.1 Cyanide toxicity

ANTIDOTES AND CHELATORS

Dicobalt edetate

- **INDICATIONS AND DOSE**
  - Severe poisoning with cyanides
    - **BY INTRAVENOUS INJECTION**
    - Child: Consult the National Poisons Information Service
    - Adult: 300 mg, to be given over 1 minute (or 5 minutes if condition less serious), dose to be followed immediately by 50 mL of glucose intravenous infusion 50%; if response inadequate a second dose of both may be given, but risk of cobalt toxicity

- **CAUTIONS** Owing to toxicity to be used only for definite cyanide poisoning when patient tending to lose, or has lost, consciousness
- **SIDE-EFFECTS** Anaphylactoid reactions • cardiac abnormalities • facial oedema • hypotension • laryngeal oedema • tachycardia • vomiting
- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS**
  - Solution for injection
    - Dicobalt edetate (Non-proprietary)
      - Dicobalt edetate 15 mg per 1 ml
  - Other drugs used for Organophosphorus toxicity
    - Atropine sulfate, p. 1179

Sodium nitrite

- **INDICATIONS AND DOSE**
  - Poisoning with cyanides (used in conjunction with sodium thiosulfate)
    - **BY INTRAVENOUS INJECTION**
    - Child: 4–10 mg/kg (max. per dose 300 mg), to be given over 5–20 minutes followed by sodium thiosulphate injection
    - Adult: 300 mg, to be given over 5–20 minutes (as sodium nitrite injection 30 mg/mL)

- **DOSE EQUIVALENCE AND CONVERSION**
  - 4–10 mg/kg equates to 0.13–0.33 mL/kg of a 3% solution.
  - Dose max. of 300 mg equates to 10 mL of a 3% solution.

- **SIDE-EFFECTS** Flushing (due to vasodilatation) • headache (due to vasodilatation)

- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Sodium thiosulfate

- **INDICATIONS AND DOSE**
  - Poisoning with cyanides (used in conjunction with sodium nitrite)
    - **BY INTRAVENOUS INJECTION**
    - Child: 400 mg/kg (max. per dose 12.5 g), to be given over 10 minutes, dose may be repeated in severe cyanide poisoning if dicobalt edetate not available
    - Adult: 12.5 g, to be given over 10 minutes (as sodium thiosulfate injection 500 mg/mL), dose may be repeated in severe cyanide poisoning if dicobalt edetate not available

- **DOSE EQUIVALENCE AND CONVERSION**
  - 400 mg/kg equates to 0.8 mL/kg of a 50% solution.
  - 12.5 g equates to 25 mL of a 50% solution.

- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

2.2 Organophosphorus toxicity

ANTIDOTES AND CHELATORS

Pralidoxime chloride

- **INDICATIONS AND DOSE**
  - Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent
    - **BY INTRAVENOUS INFUSION**
    - Child: Initially 30 mg/kg, to be given over 20 minutes, followed by 8 mg/kg/hour; maximum 12 g per day
    - Adult: Initially 30 mg/kg, to be given over 20 minutes, followed by 8 mg/kg/hour; maximum 12 g per day

- **UNLICENSED USE** Pralidoxime chloride doses may differ from those in product literature. Licensed for use in children (age range not specified by manufacturer).
- **CONTRA-INDICATIONS** Poisoning with carbamates • poisoning with organophosphorus compounds without anticholinesterase activity
- **CAUTIONS** Myasthenia gravis
- **SIDE-EFFECTS** Disturbances of vision • dizziness • drowsiness • headache • hyperventilation • muscular weakness • nausea • tachycardia
- **RENAL IMPAIRMENT** Use with caution.
- **DIRECTIONS FOR ADMINISTRATION** The loading dose may be administered by intravenous injection (diluted to a concentration of 50 mg/mL with water for injections) over at least 5 minutes if pulmonary oedema is present or if it is not practical to administer an intravenous infusion.
  - With intravenous use in children For intravenous infusion, reconstitute each vial with 20 mL Water for Injections, then dilute to a concentration of 10–20 mg/mL with Sodium Chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION** Available from designated centres for organophosphorus insecticide poisoning or from the National Blood Service (or Welsh
Ambulance Services for Mid West and South East Wales)—see TOXBASE for list of designated centres).

- **EXCEPTIONS TO LEGAL CATEGORY**  Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for injection**
    - Pralidoxime chloride (Non-proprietary)
      - Pralidoxime chloride 1 gram Protopam Chloride 1g powder for solution for injection vials | 6 vial (PO) no price available

### 3 Drug toxicity

#### 3.1 Benzodiazepine toxicity

**ANTIDOTES AND CHELATORS > BENZODIAZEPINE ANTAGONISTS**

**Flumazenil**

- **INDICATIONS AND DOSE**  Reversal of sedative effects of benzodiazepines in anaesthesia and clinical procedures
  - BY INTRAVENOUS INJECTION
    - Adult: 200 micrograms, dose to be administered over 15 seconds, then 100 micrograms every 1 minute if required; usual dose 300–600 micrograms; maximum 1 mg per course

  Reversal of sedative effects of benzodiazepines in intensive care
  - BY INTRAVENOUS INJECTION
    - Adult: 300 micrograms, dose to be administered over 15 seconds, then 100 micrograms every 1 minute if required; maximum 2 mg per course

  Reversal of sedative effects of benzodiazepines in intensive care (if drowsiness recurs after injection)
  - INITIALLY BY INTRAVENOUS INFUSION
    - Adult: 100–400 micrograms/hour, adjusted according to response, alternatively (by intravenous injection) 300 micrograms, adjusted according to response

- **IMPORTANT SAFETY INFORMATION**  Flumazenil should only be administered by, or under the direct supervision of, personnel experienced in its use.

- **CONTRA-INDICATIONS**  Life-threatening condition (e.g. raised intracranial pressure, status epilepticus) controlled by benzodiazepines

- **CAUTIONS**  Avoid rapid injection following major surgery; avoid rapid injection in high-risk or anxious patients; benzodiazepine dependence (may precipitate withdrawal symptoms); elderly; ensure neuromuscular blockade cleared before giving; head injury (rapid reversal of benzodiazepine sedation may cause convulsions); history of panic disorders (risk of recurrence); prolonged benzodiazepine therapy for epilepsy (risk of convulsions); short-acting (repeat doses may be necessary—benzodiazepine effects may persist for at least 24 hours)

- **SIDE-EFFECTS**
  - Common or very common  Nausea · vomiting
  - Uncommon  Anxiety · fear · palpitation
  - Frequency not known  Agitation · chills · convulsions (particularly in those with epilepsy) · dizziness · flushing · sensory disturbance · sweating · tachycardia · transient hypertension

- **PREGNANCY**  Not known to be harmful.

- **BREAST FEEDING**  Avoid breast-feeding for 24 hours.

- **HEPATIC IMPAIRMENT**  Carefully titrate dose.

- **DIRECTIONS FOR ADMINISTRATION**  For continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%.

- **MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - Flumazenil (Non-proprietary)
    - Flumazenil 100 microgram per 1 ml Flumazenil 500micrograms/5ml solution for injection ampoules | 5 ampoule (PO) £65.50–£72.46

#### 3.2 Digoxin toxicity

**ANTIDOTES AND CHELATORS > ANTIBODIES**

**Digoxin-specific antibody**

- **INDICATIONS AND DOSE**  Treatment of known or strongly suspected life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine and when measures beyond the withdrawal of digoxin and correction of any electrolyte abnormalities are considered necessary
  - BY INTRAVENOUS INFUSION
    - Child:  Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service (consult product literature)
    - Adult:  Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service (consult product literature)

- **DIRECTIONS FOR ADMINISTRATION**
  - In adults  For intravenous infusion (DigiFab®), given intermittently in Sodium chloride 0.9%. Reconstitute with water for injections (4 mL/vial), then dilute with infusion fluid and give over 30 minutes.

- **MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for infusion**
  - DigiFab (BTG International Ltd)
    - Digoxin-specific antibody fragments 40 mg DigiFab 40mg powder for solution for infusion vials | 1 vial (PO) £750.00 (Hospital only)

#### 3.3 Heparin toxicity

**ANTIDOTES AND CHELATORS**

**Protamine sulfate**

- **INDICATIONS AND DOSE**  Overdosage with intravenous injection of unfractionated heparin
  - BY INTRAVENOUS INJECTION
    - Adult:  Dose to be administered at a rate not exceeding 5 mg/minute, 1 mg neutralises 80–100 units heparin when given within 15 minutes; if longer than 15 minute since heparin, less protamine required (consult product literature for details) as heparin rapidly excreted; maximum 50 mg continued →
Emergency treatment of poisoning

OPIOID RECEPTOR ANTAGONISTS

Opioid toxicity

3.4 Opioid toxicity

OPIOID RECEPTOR ANTAGONISTS

Naloxone hydrochloride

INDICATIONS AND DOSE

Overdosage with opioids

- BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

Child 1 month–11 years: Initially 100 micrograms/kg, if no response, repeat at intervals of 1 minute to a total max. 2 mg, then review diagnosis; further doses may be required if respiratory function deteriorates

Child 12–17 years: Initially 400 micrograms, then 800 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose, then increased to 2 mg for 1 dose if still no response (4 mg dose may be required in seriously poisoned patients), then review diagnosis; further doses may be required if respiratory function deteriorates

Child: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes

Adult: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes

Overdosage with opioids in a non-medical setting

- BY INTRAMUSCULAR INJECTION

Child: 400 micrograms every 2–3 minutes, each dose given in subsequent resuscitation cycles if patient not breathing normally, continue until consciousness regained, breathing normally, medical assistance available, or contents of syringe used up; to be injected into deltoid region or anterolateral thigh

Reversal of postoperative respiratory depression

- INITIALLY BY INTRAVENOUS INJECTION

Child 1 month–11 years: 1 microgram/kg, repeated every 2–3 minutes if required

Child 12–17 years: Initially 100–200 micrograms, alternatively (by intravenous injection) initially 1.5–3 micrograms/kg, if response inadequate, give subsequent doses, (by intravenous injection) 100 micrograms every 2 minutes, alternatively (by intramuscular injection) 100 micrograms every 1–2 hours

Adult: Initially 100–200 micrograms, alternatively (by intravenous injection) initially 1.5–3 micrograms/kg, if response inadequate, give subsequent doses, (by intravenous injection) 100 micrograms every 2 minutes, alternatively (by intramuscular injection) 100 micrograms every 1–2 hours

PHARMACOKINETICS

Naloxone has a short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.

Important: Only give by subcutaneous or intramuscular routes if intravenous route is not feasible; intravenous administration has more rapid onset of action.

UNLICENSED USE

Naloxone doses in BNF may differ from those in product literature.

IMPORTANT SAFETY INFORMATION

SAFE PRACTICE

Doses used in acute opioid overdose may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use.
3.5 Paracetamol toxicity

**ANTIDOTES AND CHELATORS**

**Acetylcysteine**

- **INDICATIONS AND DOSE**
  - **Paracetamol overdose**
    - **BY INTRAVENOUS INFUSION**
      - Child (body-weight up to 20 kg): Initially 150 mg/kg over 1 hour, dose to be administered in 3 mL/kg glucose 5%, followed by 50 mg/kg over 4 hours, dose to be administered in 7 mL/kg glucose 5%, then 100 mg/kg over 16 hours, dose to be administered in 14 mL/kg glucose 5%.
      - Child (body-weight 20–39 kg): Initially 150 mg/kg over 1 hour, dose to be administered in 100 mL glucose 5%, followed by 50 mg/kg over 4 hours, dose to be administered in 250 mL glucose 5%, then 100 mg/kg over 16 hours, dose to be administered in 500 mL glucose 5%.
      - Child (body-weight 40 kg and above): 150 mg/kg over 1 hour, dose to be administered in 200 mL glucose Intravenous Infusion 5%, then 50 mg/kg over 4 hours, to be started immediately after completion of first infusion, dose to be administered in 500 mL glucose Intravenous Infusion 5%, then 100 mg/kg over 16 hours, to be started immediately after completion of second infusion, dose to be administered in 1 litre glucose Intravenous Infusion 5%.
      - Adult (body-weight 40 kg and above): 150 mg/kg over 1 hour, dose to be administered in 200 mL glucose Intravenous Infusion 5%, then 50 mg/kg over 4 hours, to be started immediately after completion of first infusion, dose to be administered in 500 mL glucose Intravenous Infusion 5%, then 100 mg/kg over 16 hours, to be started immediately after completion of second infusion, dose to be administered in 1 litre glucose Intravenous Infusion 5%.

- **CAUTIONS** Asthma (see Side-effects for management of asthma but do not delay acetylcysteine treatment) • atopy • may slightly increase INR • may slightly increase prothrombin time

- **SIDE-EFFECTS** Hypersensitivity-like reactions • slight increase in INR and prothrombin time • rashes

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Hypersensitivity-like reactions: Hypersensitivity-like reactions are managed by reducing infusion rate or suspending until reaction settled (rash also managed by giving antihistamine; acute asthma managed by giving nebulised short-acting beta, agonist) — contact the National Poisons Information Service if reaction severe.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children: For continuous intravenous infusion, dilute to a concentration of up to 200 micrograms/mL with glucose 5% or Sodium Chloride 0.9%.
  - With intravenous use in adults: For intravenous infusion (Minijet®, Naloxone Hydrochloride), give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute to a concentration of up to 200 micrograms/mL and administer via an infusion pump.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Naloxone hydrochloride (Non-proprietary)**
  - Naloxone hydrochloride 1 mg per 1 ml Naloxone 2mg/2ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £16.80
  - Naloxone hydrochloride 20 microgram per 1 ml Naloxone 40micrograms/2ml solution for injection ampoules | 10 ampoule £55.00
  - Naloxone hydrochloride 400 microgram per 1 ml Naloxone 400micrograms/1ml solution for injection ampoules | 3 ampoule £17.70 | 10 ampoule £41.00–£53.70
  - Prenoxad (Martindale Pharmaceuticals Ltd)
  - Naloxone hydrochloride 1 mg per 1 ml Prenoxad 2mg/2ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £15.30

**Solution for infusion**

- Electolytes: May contain Sodium

**Acetylcysteine (Non-proprietary)**

- Acetylcysteine 200 mg per 1 ml Acetylcysteine 2g/10ml solution for infusion ampoules | 10 ampoule £21.26–£24.59
- Parvolex (Phoenix Labs Ltd)
  - Acetylcysteine 200 mg per 1 ml Parvolex 2g/10ml concentrate for solution for infusion ampoules | 10 ampoule £22.50

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
4 Methaemoglobinaemia

ANTIDOTES AND CHELATORS

Methylthioninium chloride
(Methylene blue)

- **INDICATIONS AND DOSE**
  - Drug- or chemical-induced methaemoglobinaemia
    - BY SLOW INTRAVENOUS INJECTION
      - Child 3 months–17 years: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course
      - Adult: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course

- **CAUTIONS**
  - Children under 3 months (more susceptible to methaemoglobinaemia from high doses of methylthioninium)
  - Chlorate poisoning (reduces efficacy of methylthioninium)
  - G6PD deficiency (seek advice from National Poisons Information Service)
  - Methaemoglobinaemia due to treatment of cyanide poisoning with sodium nitrite (seek advice from National Poisons Information Service)
  - Pulse oximetry may give false estimation of oxygen saturation

- **INTERACTIONS**
  - Appendix 1 (methylthioninium).

- **SIDE-EFFECTS**
  - Abdominal pain
  - Agitation
  - Anxiety
  - Arrhythmia
  - Blue-green discoloration of faeces
  - Blue-green discoloration of skin
  - Confusion
  - Dizziness
  - Dyspnoea
  - Fever
  - Haemolytic anaemia
  - Headache
  - Hyperbilirubinaemia (in infants)
  - Hypertension
  - Hypotension
  - Methaemoglobinaemia
  - Mydriasis
  - Nausea
  - Sweating
  - Tachypnoea
  - Tremor
  - Vomiting

- **PREGNANCY**
  - No information available, but risk to fetus of untreated methaemoglobinaemia likely to be significantly higher than risk of treatment.

- **BREAST FEEDING**
  - Manufacturer advises avoid breastfeeding for up to 6 days after administration—no information available.

- **RENAral IRRAIlMENT**
  - Use with caution in severe impairment; dose reduction may be required.

- **DIRECTIONS FOR ADMINISTRATION**
  - In children For intravenous injection, may be diluted with
    - Glucose 5% to minimise injection-site pain; not compatible with Sodium Chloride 0.9%

  - In adults
    - Initially 2 mg/kg
    - 15 minutes or by intravenous infusion over 30 minutes after diluting in sodium chloride 0.9%
    - Use 5 mL diluent/kg body-weight.

  - In severe cases
    - Initially 20 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

  - Adult: Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

- **MEDICATIONS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include:
    - Solution for injection
      - Methylthioninium chloride (Non-proprietary)
        - Methylthioninium chloride 5 mg per 1 mL
        - Methylthioninium chloride Proveblue 50mg/10mL solution for injection ampoules | 5 ampoule £167.36

5 Snake bites

**IMMUNE SERA AND IMMUNOGLOBULINS**

**ANTITOXINS**

European viper snake venom antiserum

- **INDICATIONS AND DOSE**
  - Systemic envenoming from snake bites
  - Marked local envenoming
    - BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
      - Child: Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service
      - Adult: Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

- **Severe systemic envenoming from snake bites in patients presenting with clinical features**
  - BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
    - Child: Initially 20 mL for 1 dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service
    - Adult: Initially 20 mL for 1 dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

- **DIRECTIONS FOR ADMINISTRATION**
  - By intravenous injection given over 10–15 minutes or by intravenous infusion over 30 minutes after diluting in sodium chloride 0.9% (use 5 mL diluent/kg body-weight).

- **PRESCRIBING AND DISPENSING INFORMATION**
  - To order, email immform@dh.gsi.gov.uk.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- European viper snake venom antiserum (Non-proprietary)
  - European viper snake venom antiserum 100 mg per 1 mL
  - Viper venom antiserum, European (equine) 1g/10mL solution for injection vials | 1 vial £18.34
  - no price available
Appendix 1
Interactions

Two or more drugs given at the same time may exert their effects independently or may interact. The interaction may be potentiation or antagonism of one drug by another, or occasionally some other effect. Adverse drug interactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA), through the Yellow Card Scheme (see Adverse Reactions to Drugs), as for other adverse drug reactions.

Drug interactions may be pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions
These are interactions between drugs which have similar or antagonistic pharmacological effects or side-effects. They may be due to competition at receptor sites, or occur between drugs acting on the same physiological system. They are usually predictable from a knowledge of the pharmacology of the interacting drugs; in general, those demonstrated with one drug are likely to occur with related drugs. They occur to a greater or lesser extent in most patients who receive the interacting drugs.

Pharmacokinetic interactions
These occur when one drug alters the absorption, distribution, metabolism, or excretion of another, thus increasing or reducing the amount of drug available to produce its pharmacological effects. They are not easily predicted and many of them affect only a small proportion of patients taking the combination of drugs. Pharmacokinetic interactions occurring with one drug cannot be assumed to occur with related drugs unless their pharmacokinetic properties are known to be similar.

Pharmacokinetic interactions are of several types:

Affecting absorption The rate of absorption or the total amount absorbed can both be altered by drug interactions. Delayed absorption is rarely of clinical importance unless high peak plasma concentrations are required (e.g. when giving an analgesic). Reduction in the total amount absorbed, however, may result in ineffective therapy.

Due to changes in protein binding To a variable extent most drugs are loosely bound to plasma proteins. Protein-binding sites are non-specific and one drug can displace another thereby increasing its proportion free to diffuse from plasma to its site of action. This only produces a detectable increase in effect if it is an extensively bound drug (more than 90%) that is not widely distributed throughout the body. Even so displacement rarely produces more than transient potentiation because this increased concentration of free drug results in an increased rate of elimination.

Displacement from protein binding plays a part in the potentiation of warfarin by sulfonamides and tolbutamide but the importance of these interactions is due mainly to the fact that warfarin metabolism is also inhibited.

Affecting metabolism Many drugs are metabolised in the liver. Induction of the hepatic microsomal enzyme system by one drug can gradually increase the rate of metabolism of another, resulting in lower plasma concentrations and a reduced effect. On withdrawal of the inducer plasma concentrations increase and toxicity may occur.

Barbiturates, griseofulvin, many antiepileptics, and rifampicin are the most important enzyme inducers. Drugs affected include warfarin and the oral contraceptives.

Conversely when one drug inhibits the metabolism of another higher plasma concentrations are produced, rapidly resulting in an increased effect with risk of toxicity. Some drugs which potentiate warfarin and phenytoin do so by this mechanism.

Isoenzymes of the hepatic cytochrome P450 system interact with a wide range of drugs. Drugs may be substrates, inducers or inhibitors of the different isoenzymes. A great deal of in-vitro information is available on the effect of drugs on the isoenzymes; however, since drugs are eliminated by a number of different metabolic routes as well as renal excretion, the clinical effects of interactions cannot be predicted accurately from laboratory data on the cytochrome P450 isoenzymes. Except where a combination of drugs is specifically contra-indicated, the BNF presents only interactions that have been reported in clinical practice.

In all cases the possibility of an interaction must be considered if toxic effects occur or if the activity of a drug diminishes.

Affecting renal excretion Drugs are eliminated through the kidney both by glomerular filtration and by active tubular secretion. Competition occurs between those which share active transport mechanisms in the proximal tubule. For example, salicylates and some other NSAIDs delay the excretion of methotrexate; serious methotrexate toxicity is possible.

Relative importance of interactions
Many drug interactions are harmless and many of those which are potentially harmful only occur in a small proportion of patients; moreover, the severity of an interaction varies from one patient to another. Drugs with a small therapeutic ratio (e.g. phenytoin) and those which require careful control of dosage (e.g. anticoagulants, antihypertensives, and antidiabetics) are most often involved.

Patients at increased risk from drug interactions include the elderly and those with impaired renal or liver function. Serious interactions The symbol • has been placed against interactions that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring).

Interactions that have no symbol do not usually have serious consequences.
List of drug interactions

The following is an alphabetical list of drugs and their interactions; to avoid excessive cross-referencing each drug or group is listed twice: in the alphabetical list and also against the drug or group with which it interacts.

**Abiraterone**
- Analgesics: abiraterone increases plasma concentration of METHADONE
- Antibacterials: plasma concentration of abiraterone possibly reduced by RIFAMPICIN
- Antiepileptics: plasma concentration of abiraterone possibly reduced by POSPHENOTYNOXOPHYN, PHENOBARBITAL, PHENOTYNOXOPHYN and PRIMIDONE
- Antivirals: abiraterone possibly reduces effects of RIBAVIRIN; plasma concentration of abiraterone reduced by TIPRANIVAR
- Orlistat: absorption of abiraterone possibly reduced by ORLISTAT

**Abiraterone** (continued)
- Calcium-channel Blockers: enhanced hypertensive effect when ACE inhibitors given with CALCIUM-CHANNEL BLOCKERS
- Cardiac Glycosides: captopril possibly increases plasma concentration of DIGOXIN
- Ciclosporin: increased risk of hyperkalaemia when ACE inhibitors given with CICLOSPORIN
- Clonidine: enhanced hypertensive effect when ACE inhibitors given with CLONIDINE; antihypertensive effect of captopril possibly delayed by previous treatment with CLONIDINE
- Corticosteroids: hypertensive effect of ACE inhibitors antagonised by CORTICOSTEROIDS
- Cytoxics: increased risk of angular conjunctivitis when ACE inhibitors given with EVEROLIMUS
- Diazoxide: enhanced hypertensive effect when ACE inhibitors given with DIAZOXIDE
- Diuretics: increased risk of severe hyperkalaemia when ACE inhibitors given with EPELENONE and SPIRONOLACTONE—avoid concurrent use or use lowest possible doses of both drugs; increased risk of severe hyperkalaemia when ACE inhibitors given with AMILORIDE, POTASSIUM CANRENATE or TRIAMTERENE; enhanced hypertensive effect when ACE inhibitors given with DIURETICS
- Dopaminergics: enhanced hypertensive effect when ACE inhibitors given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
- Lithium: ACE inhibitors reduce excretion of LITHIUM (increased plasma concentration)
- Methydopa: enhanced hypertensive effect when ACE inhibitors given with METHYLDOPA
- Moxisylyte: enhanced hypertensive effect when ACE inhibitors given with MOXISYLYTE
- Moxonidine: enhanced hypertensive effect when ACE inhibitors given with MOXONIDINE
- Muscle Relaxants: enhanced hypertensive effect when ACE inhibitors given with BACLOFEN or TIZANIDINE
- Nitrates: enhanced hypertensive effect when ACE inhibitors given with NITRATES
- Oestrogens: hypertensive effect of ACE inhibitors antagonised by OESTROGENS
- Potassium Salts: increased risk of severe hyperkalaemia when ACE inhibitors given with POTASSIUM SALTS
- Prostaglandins: enhanced hypertensive effect when ACE inhibitors given with ALPROSTADIL
- Sacubitril: manufacturer of sacubitril advises avoid ACE inhibitors for 36 hours before or after SACUBITRIL
- Sodium Aurothiomalate: flushing and hypotension reported when ACE inhibitors given with SODIUM AURITHIOMALATE
- Vasodilator Antihypertensives: enhanced hypertensive effect when ACE inhibitors given with HYDRALAZINE, MINOXIDIL or SODIUM NITRPRUSSIDE
- Wasp Venom Extracts: possible severe anaphylactoid reaction when ACE inhibitors given with WASP VENOM EXTRACTS

**Acetabulol** see Beta-blockers

**Acefocenac** see NSAIDs

**Acometacin** see NSAIDs

**ACA**
- Analgesics: abiraterone possibly reduces plasma concentration of METHADONE
- Antibacterials: plasma concentration of abiraterone possibly reduced by RIFAMPICIN
- Antiepileptics: plasma concentration of abiraterone possibly reduced by POSPHENOTYNOXOPHYN, PHENOBARBITAL, PHENOTYNOXOPHYN and PRIMIDONE
- Antivirals: abiraterone possibly reduces effects of RIBAVIRIN; plasma concentration of abiraterone reduced by TIPRANIVAR
- Orlistat: absorption of abiraterone possibly reduced by ORLISTAT

**ACA** (continued)
- Calcium-channel Blockers: enhanced hypertensive effect when ACE inhibitors given with CALCIUM-CHANNEL BLOCKERS
- Cardiac Glycosides: captopril possibly increases plasma concentration of DIGOXIN
- Ciclosporin: increased risk of hyperkalaemia when ACE inhibitors given with CICLOSPORIN
- Clonidine: enhanced hypertensive effect when ACE inhibitors given with CLONIDINE; antihypertensive effect of captopril possibly delayed by previous treatment with CLONIDINE
- Corticosteroids: hypertensive effect of ACE inhibitors antagonised by CORTICOSTEROIDS
- Cytoxics: increased risk of angular conjunctivitis when ACE inhibitors given with EVEROLIMUS
- Diazoxide: enhanced hypertensive effect when ACE inhibitors given with DIAZOXIDE
- Diuretics: increased risk of severe hyperkalaemia when ACE inhibitors given with EPELENONE and SPIRONOLACTONE—avoid concurrent use or use lowest possible doses of both drugs; increased risk of severe hyperkalaemia when ACE inhibitors given with AMILORIDE, POTASSIUM CANRENATE or TRIAMTERENE; enhanced hypertensive effect when ACE inhibitors given with DIURETICS
- Dopaminergics: enhanced hypertensive effect when ACE inhibitors given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
- Lithium: ACE inhibitors reduce excretion of LITHIUM (increased plasma concentration)
- Methydopa: enhanced hypertensive effect when ACE inhibitors given with METHYLDOPA
- Moxisylyte: enhanced hypertensive effect when ACE inhibitors given with MOXISYLYTE
- Moxonidine: enhanced hypertensive effect when ACE inhibitors given with MOXONIDINE
- Muscle Relaxants: enhanced hypertensive effect when ACE inhibitors given with BACLOFEN or TIZANIDINE
- Nitrates: enhanced hypertensive effect when ACE inhibitors given with NITRATES
- Oestrogens: hypertensive effect of ACE inhibitors antagonised by OESTROGENS
- Potassium Salts: increased risk of severe hyperkalaemia when ACE inhibitors given with POTASSIUM SALTS
- Prostaglandins: enhanced hypertensive effect when ACE inhibitors given with ALPROSTADIL
- Sacubitril: manufacturer of sacubitril advises avoid ACE inhibitors for 36 hours before or after SACUBITRIL
- Sodium Aurothiomalate: flushing and hypotension reported when ACE inhibitors given with SODIUM AURITHIOMALATE
- Vasodilator Antihypertensives: enhanced hypertensive effect when ACE inhibitors given with HYDRALAZINE, MINOXIDIL or SODIUM NITRPRUSSIDE
- Wasp Venom Extracts: possible severe anaphylactoid reaction when ACE inhibitors given with WASP VENOM EXTRACTS

**Acetabulol** see Beta-blockers

**Acefocenac** see NSAIDs

**Acometacin** see NSAIDs
Adefovir see Coumarins
Aciclovir see Aciclovir
Adalimumab

> NOTE Interactions do not apply to topical adalimumab preparations
  > Aminophylline: adalimumab possibly increases plasma concentration of AMINOPHYLLINE
  > Ciclosporin: increased risk of nephrotoxicity when adalimumab given with CICLOSPORIN
  > Mycophenolate: plasma concentration of adalimumab increased by MYCOPHENOLATE, also plasma concentration of inactive metabolite of mycophenolate increased
  > Tacrolimus: possible increased risk of nephrotoxicity when adalimumab given with TACROLIMUS
  > Theophylline: adalimumab possibly increases plasma concentration of THEOPHYLLINE

Acitretin see Retinoids
Aciclovir see Antivirals
Acetazolamide see Diuretics

Adrnergic Neurone Blockers (continued)
» Antidepressants: enhanced hypotensive effect when adrenergic neurone blockers given with MAOIS; hypotensive effect of adrenergic neurone blockers antagonised by TRICYCLICS
» Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by HALOPERIDOL; hypotensive effect of adrenergic neurone blockers antagonised by higher doses of CHLORPROMAZINE; enhanced hypotensive effect when adrenergic neurone blockers given with PHENOTHIAZINES
» Anxiolytics and Hypnotics: enhanced hypotensive effect when adrenergic neurone blockers given with ANXIOLYTICS AND HYPNOTICS
» Beta-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with BETA-BLOCKERS
» Calcium-channel Blockers: enhanced hypotensive effect when adrenergic neurone blockers given with CALCIUM-CHANNEL BLOCKERS
» Clonidine: enhanced hypotensive effect when adrenergic neurone blockers given with CLONIDINE
» Corticosteroids: hypotensive effect of adrenergic neurone blockers antagonised by CORTICOSTEROIDS
» Diazoxide: enhanced hypotensive effect when adrenergic neurone blockers given with DIAZoxide
» Diuretics: enhanced hypotensive effect when adrenergic neurone blockers given with DIURETICS
» Dopaminergics: enhanced hypotensive effect when adrenergic neurone blockers given with CO-ENZYME Q10, CO-CALCIUM or LEVODOPA
» Methyldopa: enhanced hypotensive effect when adrenergic neurone blockers given with METHYLDOPA
» Moxisylyte: enhanced hypotensive effect when adrenergic neurone blockers given with MOXISLYTE
» Moxonidine: enhanced hypotensive effect when adrenergic neurone blockers given with MOXONIDINE
» Muscle Relaxants: enhanced hypotensive effect when adrenergic neurone blockers given with BACLOFEN or TIZANIDINE
» Nitrites: enhanced hypotensive effect when adrenergic neurone blockers given with NITRATES
» Oestrogens: hypotensive effect of adrenergic neurone blockers antagonised by OESTROGENS
» Pizotifen: hypotensive effect of adrenergic neurone blockers antagonised by PIZOTifen
» Prostaglandins: enhanced hypotensive effect when adrenergic neurone blockers given with ALPROSTADIL
» Symptomatetics: increased risk of hypertension when guanethidine given with ADRENAline (EPINEPHRINE); hypotensive effect of guanethidine antagonised by DEXAMFETAMINE and Lisdexamfetamine; hypotensive effect of adrenergic neurone blockers antagonised by EPHEDRINE, ISOMETHETANE, METARAMINOL, METHYLPHENIDATE, NORADRENALINE (norepinephrine), OXYMETAZOLINE, PHENYLEPHRINE, Pseudoephedrine and XyloMetazine; avoidance of guanethidine advised by manufacturer of MIOdRINE
» Vasodilator Antihypertensives: enhanced hypotensive effect when adrenergic neurone blockers given with HYDRAZINE, MINOXIDIL or SODIUM NitROPRUSsE

Adsorbents see Kaolin
Afatinib

> Anti-arhythmics: plasma concentration of afatinib possibly increased by AMIODARONE — manufacturer of afatinib advises separating administration of amiodarone by 6 to 12 hours
» Anti-infectives: plasma concentration of afatinib possibly increased by ERYTHROMYCIN — manufacturer of afatinib advises separating administration of erythromycin by 6 to 12 hours; plasma concentration of afatinib reduced by RifAMPICIN
» Antifungals: plasma concentration of afatinib possibly increased by ITRACONAZOLE and KETOCONAZOLE — manufacturer of afatinib advises separating administration of itraconazole and ketoconazole by 6 to 12 hours
» Anti-psychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
» Antivirals: plasma concentration of afatinib increased by RITONAVIR — manufacturer of afatinib advises separating administration of ritonavir by 6 to 12 hours; plasma

Adrenocortical see Coumarins
Acetazolamide see Diuretics
Aciclovir

NOTE Interactions do not apply to topical aciclovir preparations
» Aminophylline: aciclovir possibly increases plasma concentration of AMINOPHYLLINE
» Ciclosporin: increased risk of nephrotoxicity when aciclovir given with CICLOSPORIN
» Mycophenolate: plasma concentration of aciclovir increased by MYCOPHENOLATE, also plasma concentration of inactive metabolite of mycophenolate increased
» Tacrolimus: possible increased risk of nephrotoxicity when aciclovir given with TACROLIMUS
» Theophylline: aciclovir possibly increases plasma concentration of THEOPHYLLINE

Aciclovir see Antivirals
Acetazolamide see Diuretics
Adrenaline (epinephrine)

> NOTE Antidepressants: enhanced hypotensive effect when adrenergic neurone blockers given with MAOIS; hypotensive effect of adrenergic neurone blockers antagonised by TRICYCLICS
> Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by HALOPERIDOL; hypotensive effect of adrenergic neurone blockers antagonised by higher doses of CHLORPROMAZINE; enhanced hypotensive effect when adrenergic neurone blockers given with PHENOTHIAZINES
> Anxiolytics and Hypnotics: enhanced hypotensive effect when adrenergic neurone blockers given with ANXIOLYTICS AND HYPNOTICS
> Beta-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with BETA-BLOCKERS
> Calcium-channel Blockers: enhanced hypotensive effect when adrenergic neurone blockers given with CALCIUM-CHANNEL BLOCKERS
> Clonidine: enhanced hypotensive effect when adrenergic neurone blockers given with CLONIDINE
> Corticosteroids: hypotensive effect of adrenergic neurone blockers antagonised by CORTICOSTEROIDS
> Diazoxide: enhanced hypotensive effect when adrenergic neurone blockers given with DIAZoxide
> Diuretics: enhanced hypotensive effect when adrenergic neurone blockers given with DIURETICS
> Dopaminergics: enhanced hypotensive effect when adrenergic neurone blockers given with CO-ENZYME Q10, CO-CARELDOPA or LEVODOPA
> Methyldopa: enhanced hypotensive effect when adrenergic neurone blockers given with METHYLDOPA
> Moxisylyte: enhanced hypotensive effect when adrenergic neurone blockers given with MOXISLYTE
> Moxonidine: enhanced hypotensive effect when adrenergic neurone blockers given with MOXONIDINE
> Muscle Relaxants: enhanced hypotensive effect when adrenergic neurone blockers given with BACLOFEN or TIZANIDINE
> Nitrites: enhanced hypotensive effect when adrenergic neurone blockers given with NITRATES
> Oestrogens: hypotensive effect of adrenergic neurone blockers antagonised by OESTROGENS
> Pizotifen: hypotensive effect of adrenergic neurone blockers antagonised by PIZOTifen
> Prostaglandins: enhanced hypotensive effect when adrenergic neurone blockers given with ALPROSTADIL
> Symptomatetics: increased risk of hypertension when guanethidine given with ADRENAline (EPINEPHRINE); hypotensive effect of guanethidine antagonised by DEXAMFETAMINE and Lisdexamfetamine; hypotensive effect of adrenergic neurone blockers antagonised by EPHEDRINE, ISOMETHETANE, METARAMINOL, METHYLPHENIDATE, NORADRENALINE (norepinephrine), OXYMETAZOLINE, PHENYLEPHRINE, Pseudoephedrine and XyloMetazine; avoidance of guanethidine advised by manufacturer of MIOdRINE
> Vasodilator Antihypertensives: enhanced hypotensive effect when adrenergic neurone blockers given with HYDRAZINE, MINOXIDIL or SODIUM NitROPRUSsE

Adsorbents see Kaolin
Afatinib

Anti-arhythmics: plasma concentration of afatinib possibly increased by AMIODARONE — manufacturer of afatinib advises separating administration of amiodarone by 6 to 12 hours
Anti-infectives: plasma concentration of afatinib possibly increased by ERYTHROMYCIN — manufacturer of afatinib advises separating administration of erythromycin by 6 to 12 hours; plasma concentration of afatinib reduced by RifAMPICIN
Antifungals: plasma concentration of afatinib possibly increased by ITRACONAZOLE and KETOCONAZOLE — manufacturer of afatinib advises separating administration of itraconazole and ketoconazole by 6 to 12 hours
Anti-psychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Antivirals: plasma concentration of afatinib increased by RITONAVIR — manufacturer of afatinib advises separating administration of ritonavir by 6 to 12 hours; plasma
Afatinib
Antivirals (continued)
concentration of afatinib possibly increased by SAQUINAVIR — manufacturer of afatinib advises separating administration of saquinavir by 6 to 12 hours
• Calcium-channel Blockers: plasma concentration of afatinib possibly increased by VERAPAMIL — manufacturer of afatinib advises separating administration of verapamil by 6 to 12 hours
• Ciclosporin: plasma concentration of afatinib possibly increased by CICLOSPORIN — manufacturer of afatinib advises separating administration of ciclosporin by 6 to 12 hours
• Tacrolimus: plasma concentration of afatinib possibly increased by TACROLIMUS — manufacturer of afatinib advises separating administration of tacrolimus by 6 to 12 hours

Agalsidase Alfa and Beta
• Anti-arrhythmics: effects of agalsidase alfa and beta possibly inhibited by AMIODARONE (manufacturers of agalsidase alfa and beta advise concomitant use)
• Antibacterials: effects of agalsidase alfa and beta possibly inhibited by CHLOROQUINE and HYDROXYCHLOROQUINE (manufacturers of agalsidase alfa and beta advise concomitant use concomitant use)

Agomelatine
• Antidepressants: manufacturer of agomelatine advises avoid concomitant use with CIPROFLOXACIN
• Antidepressants: metabolism of agomelatine inhibited by FLUOXETINEN (increased plasma concentration)
• Antimalarials: avoidance of antidepressants advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE and ARTEMIMOL WITH PIPERAQUINE
• Antihistamines: possible increased risk of convulsions when antidepressants given with ATOMOXETINE

Albendazole
• Anthelminitics: plasma concentration of both drugs possibly reduced when albendazole given with LEVAMISOLE
• Antiepileptics: plasma concentration of albendazole reduced by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE — consider increasing albendazole dose when given for systemic infections
• Antivirals: plasma concentration of active metabolite of albendazole reduced by RITONAVIR — consider increasing albendazole dose when given for systemic infections
• Corticosteroids: plasma concentration of active metabolite of albendazole increased by DEXMETHASONE
• Grapefruit Juice: plasma concentration of active metabolite of albendazole increased by GRAPEFRUIT JUICE
• Ulcer-healing Drugs: effects of albendazole possibly enhanced by CIMETIDINE

Albiglutide see Antidiabetics

Alcohol
• ACE Inhibitors: enhanced hypotensive effect when alcohol given with ACE INHIBITORS
• Adrenergic Neurone Blockers: enhanced hypotensive effect when alcohol given with ADRENERGIC NEURONE BLOCKERS
• Alpha-blockers: increased sedative effect when alcohol given with INDOMAMINE; enhanced hypotensive effect when alcohol given with ALPHA-BLOCKERS
• Analgesics: enhanced hypotensive and sedative effects when alcohol given with OPIOID ANALGESICS
• Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alcohol given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
• Anthelminitics: possibility of disulfiram-like reaction when alcohol given with LEVAMISOLE
• Antibacterials: disulfiram-like reaction when alcohol given with METRONIDAZOLE; possibility of disulfiram-like reaction when alcohol given with TINIDAZOLE; increased risk of convulsions when alcohol given with CYCLOSERINE
• Anticoagulants: major changes in consumption of alcohol may affect anticoagulant control with COUMARINS or PHENINDIONE
• Antidepressants: some beverages containing alcohol and some dealcoholised beverages contain tyramine which interacts with MAOIS (hypertensive crisis) — if no tyramine, enhanced hypotensive effect; sedative effects possibly increased when alcohol given with SCT; increased sedative effect when alcohol given with MIRTAZAPINE, TRICYCLIC-RELATED ANTIDEPRESSANTS or TRICYCLICS
• Antidiabetics: alcohol enhances hypoglycaemic effect of ANTIDIABETICS; increased risk of lactic acidosis when alcohol given with METFORMIN
• Antiepileptics: alcohol possibly increases CNS side-effects of CARBAMAZEPINE; chronic heavy consumption of alcohol possibly reduces plasma concentration of fosphenytoin and phenytoin; increased sedative effect when alcohol given with PHENOBARBITAL OR PRIMIDONE; increased risk of blurred vision when alcohol given with RETIGABINE
• Antifungals: possibility of disulfiram-like reaction when alcohol given with KETOCONAZOLE; effects of alcohol possibly enhanced by GRISOFULVIN
• Antihistamines: increased sedative effect when alcohol given with ANTIHISTAMINES (possibly less effect with non-sedating antihistamines)
• Antimuscarinics: increased sedative effect when alcohol given with HYOSCINE
• Antipsychotics: increased sedative effect when alcohol given with ANTISYPHYSCHTICS
• Anxiolytics and Hypnotics: increased sedative effect when alcohol given with ANXIOLYTICS AND HYPNOTICS
• Avanafil: possible enhanced hypotensive effect when alcohol given with AVANAFIL
• Beta-blockers: enhanced hypotensive effect when alcohol given with BETA-BLOCKERS
• Calcium-channel Blockers: enhanced hypotensive effect when alcohol given with CALCIUM-CHANNEL BLOCKERS; plasma concentration of alcohol possibly increased by VERAPAMIL
• Clonidine: enhanced hypotensive effect when alcohol given with CLONIDINE
• Cytotoxics: disulfiram-like reaction when alcohol given with PROCARBAZINE; avoidance of alcohol advised by manufacturer of TRABETEDIN
• Dapoxetine: increased sedative effect when alcohol given with DAPOXETINE
• Diazoxide: enhanced hypotensive effect when alcohol given with DIAZOXIDE
• Disulfiram: disulfiram reaction when alcohol given with DISULFIRAM
• Diuretics: enhanced hypotensive effect when alcohol given with DIURETICS
• Dopaminergics: alcohol reduces tolerance to BROMOCRIPINE
• Guanfacine: sedative effects possibly increased when alcohol given with GUANFACINE
• Lipid-regulating Drugs: avoidance of alcohol advised by manufacturer of LOMITAPIDE
• Lofexidine: increased sedative effect when alcohol given with LOFEXIDINE
• Methyl dopa: enhanced hypotensive effect when alcohol given with METHYLDOPA
• Metoclopramide: absorption of alcohol possibly increased by METOCLOPRAMIDE
• Moxonidine: enhanced hypotensive effect when alcohol given with MOXONIDINE
• Muscle Relaxants: increased sedative effect when alcohol given with BACLOFEN, METHOCELAMOL OR TIZANIDINE
• Nicorandil: alcohol possibly enhances hypotensive effect of NICORANDIL
• Nitrites: enhanced hypotensive effect when alcohol given with NITRATES
• Paraldehyde: increased sedative effect when alcohol given with PARALDEHYDE
• Retinoids: presence of alcohol causes etretinate to be formed from ACITRETIN (increased risk of teratogenicity in women of child-bearing potential)
• Sympathomimetics: alcohol possibly enhances effects of METHYLPHENIDATE
Interactions | Appendix 1

Alcohol — Alpha-blockers

### Alcohol

(continued)

- Vasodilator Antihypertensives: enhanced hypotensive effect when alcohol given with **Hydralazine, Minoxidil** or **Sodium Nitroprusside**

### Aldesleukin

- ACE Inhibitors: enhanced hypotensive effect when aldesleukin given with **ACE INHIBITORS**
- Alpha-blockers: enhanced hypotensive effect when aldesleukin given with **ALPHA-BLOCKERS**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when aldesleukin given with **ANGIOTENSIN-II RECEPTOR ANTAGONISTS**
- Antivirals: aldesleukin possibly increases plasma concentration of aliskiren given with **CLONIDINE**

#### ACE Inhibitors

- **Corticosteroids**: manufacturer of aldesleukin advises avoid concomitant use with **CORTICOSTEROIDS**
- **Cytoxics**: manufacturer of aldesleukin advises avoid concomitant use with **CISPLATIN, DACarbazine** and **VINBLASTINE**

#### Calcium-channel Blockers

- **Ciclosporin**: plasma concentration of aliskiren increased by **KETOCONAZOLE**, increased risk of hyperkalaemia when aliskiren given with **ALDOSTERONE ANTAGONISTS** or **POTASSIUM-SPARING DIURETICS**

#### Analgesics

- **Anticoagulants**: aldesleukin possibly increases plasma concentration of **AMINOPHYLLINE**
- **Beta-blockers**: enhanced hypotensive effect when alpha-blockers given with **ACE INHIBITORS**
- Calcium-channel Blockers: enhanced hypotensive effect when aldesleukin given with **CALCIUM-CHANNEL BLOCKERS**
- Clonidine: enhanced hypotensive effect when aldesleukin given with **CLONIDINE**

### Aliskiren

(continued)

- **Diuretics**: aliskiren reduces plasma concentration of **FUROSEMIDE**; increased risk of hyperkalaemia when aliskiren given with **ALDOSTERONE ANTAGONISTS** or **POTASSIUM-SPARING DIURETICS**
- **Grapefruit Juice**: plasma concentration of aliskiren reduced by **GRAPEFRUIT JUICE**—avoid concomitant use
- **Potassium Salts**: increased risk of hyperkalaemia when aliskiren given with **POTASSIUM SALTS**

### Alfentanil

(continued)

- **Antipsychotics**: allopurinol possibly enhances anticoagulant effect of **COUMARINS**
- **Antivirals**: allopurinol possibly increases plasma concentration of **AMOXYCILLIN, AMPICILLIN** or **CD-AMOXICLAV**
- **Anticoagulants**: allopurinol possibly enhances anticoagulant effect of **COUMARINS**

### Allopurinol

- **ACE Inhibitors**: manufacturers state possible increased risk of leucopenia and hypersensitivity reactions when allopurinol given with **ACE INHIBITORS** especially in renal impairment
- **Aminophylline**: allopurinol possibly increases plasma concentration of **AMINOPHYLLINE**
- **Antibacterials**: increased risk of rash when allopurinol given with **AMOXYCILLIN, AMPICILLIN** or **CD-AMOXICLAV**
- **Anticoagulants**: allopurinol possibly enhances anticoagulant effect of **COUMARINS**

### Aldosterone Antagonists

- **Corticosteroids**: manufacturer of aldesleukin advises avoid concomitant use with **CORTICOSTEROIDS**
- **Cytoxics**: manufacturer of aldesleukin advises avoid concomitant use with **CISPLATIN, DACarbazine** and **VINBLASTINE**

### Almotriptan

- **Diabetes**: aldesleukin possibly increases plasma concentration of **AMOXYCILLIN, AMPICILLIN** or **CD-AMOXICLAV**

### Alpha-blockers

(continued)

- **ACE Inhibitors**: enhanced hypotensive effect when alpha-blockers given with **ACE INHIBITORS**
- **Adrenergic Neurone Blockers**: enhanced hypotensive effect when alpha-blockers given with **ADRENERGIC NEURONE BLOCKERS**
- **Alcohol**: enhanced hypotensive effect when alpha-blockers given with **ALCOHOL**; increased sedative effect when indoramin given with **ALCOHOL**
- **Alpha-blockers**: enhanced hypotensive effect when alpha-blockers given with **ALDESLEUKIN**
- **Anaesthetics**: General: enhanced hypotensive effect when alpha-blockers given with **GENERAL ANAESTHETICS**
- **Alpha-blockers**: enhanced hypotensive effect of alpha-blockers antagonised by **NSAIDS**
- **Angiotensin-II Receptor Antagonists**: enhanced hypotensive effect when alpha-blockers given with **ANGIOTENSIN-II RECEPTOR ANTAGONISTS**
- **Antidepressants**: manufacturer of indoramin advises avoid concomitant use with **MAOIS**; enhanced hypotensive effect when alpha-blockers given with **MAOIS**
- **Antifungals**: plasma concentration of alfuzosin possibly increased by **KETOCONAZOLE**; plasma concentration of tamsulosin increased by **KETOCONAZOLE**
- **Antipsychotics**: enhanced hypotensive effect when alpha-blockers given with **ANTIPSYCHOTICS**
- **Antivirals**: plasma concentration of doxazosin and tamsulosin possibly increased by **BOCPEPREVIR**—manufacturer of boceprevir advises avoid concomitant use; plasma concentration of alfuzosin possibly increased by **RITONAVIR**—avoid concomitant use; avoidance of alfuzosin advised by manufacturer of **TELAPREVIR**
Alpha-blockers (continued)

- Axonalytics and Hypnotics: enhanced hypotensive and sedative effects when alpha-blockers given with ANXIOLYTICS AND HYPNOTICS
- Avasanil: enhanced hypotensive effect when alpha-blockers given with ▶ AVANAFIL—when patient is stable on the alpha blocker initiate avanafil at the lowest possible dose
- Beta-blockers: enhanced hypotensive effect when alpha-blockers given with ▶ BETA-BLOCKERS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Calcium-channel Blockers: enhanced hypotensive effect when alpha-blockers given with ▶ CALCIUM-CHANNEL BLOCKERS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Cardiac Glysidoses: prazosin increases plasma concentration of TAMSULOSIN increased by VERAPAMIL
- Dopaminergics: enhanced hypotensive effect when alpha-blockers given with ▶ DOPAMINERGICS
- Diuretics: enhanced hypotensive effect when alpha-blockers given with ▶ DIURETICS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Dopaminergics: enhanced hypotensive effect when alpha-blockers given with ▶ DIURETICS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Nitrates: increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Sympathomimetics: enhanced hypotensive effect when alpha-blockers given with ▶ SYMPATHOMIMETICS
- Prostaglandins:

Amantadine
- Antimalarial: plasma concentration of amantadine possibly increased by QUININE
- Antipsychotics: increased risk of extrapyramidal side-effects when amantadine given with ▶ ANTIPSYCHOTICS
- Propafenone: increased risk of side-effects when amantadine given with ▶ PROPAFENONE
- Memantine: increased risk of CNS toxicity when amantadine given with ▶ MEMANTINE (manufacturer of memantine advises avoid concomitant use); effects of dopaminergics possibly enhanced by ▶ MEMANTINE
- Methyldopa: increased risk of extrapyramidal side-effects when amantadine given with METHYLDOPA; antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA
- Tetroxanezine: increased risk of extrapyramidal side-effects when amantadine given with TETRAZEPINE

Ambrisentan
- Antibacterials: plasma concentration of ambrisentan possibly increased by ▶ RIFAMPICIN
- Ciclosporin: plasma concentration of ambrisentan increased by ▶ CICLOSPORIN (see under Ambrisentan, p. 174)

Amikacin
- See Aminoglycosides

Aminodrines
- See Diuretics

Aminoglycosides
- Agalsidase Alfa and Beta: gentamicin possibly inhibits effects of AGALSIDASE ALFA AND BETA (manufacturers of agalsidase alfa and beta advise avoid concomitant use)
- Analgesics: plasma concentration of amikacin and gentamicin in neonates possibly increased by INDOMETACIN
- Antibacterials: neomycin reduces absorption of PHENODIMETHYLPHENICILLIN; increased risk of nephrotoxicity when aminoglycosides given with CICLOSPORIN or POLYMYXINS; increased risk of nephrotoxicity and oto toxicity when aminoglycosides given with CAPREOMYCIN or VANCOMYCIN; possible increased risk of nephrotoxicity when aminoglycosides given with CEPHALOSPORINS
- Anticoagulants: experience in anticoagulant clinics suggests that INR possibly altered when neomycin (given for local action on gut) is given with ▶ COUMARINS or PHENINDIONE
- Antidiabetics: neomycin possibly enhances hypoglycaemic effect of ACARBOSE, also severity of gastro-intestinalal effects increased
- Antifungals: increased risk of nephrotoxicity when aminoglycosides given with ▶ AMPHOTERICIN
- Bisphosphonates: increased risk of hypocalcaemia when aminoglycosides given with ▶ BISPHOSPHONATES
- Cardiac Glysidoses: gentamicin possibly increases plasma concentration of DIGOXIN; neomycin reduces absorption of DIGOXIN
- Ciclosporin: increased risk of nephrotoxicity when aminoglycosides given with ▶ CICLOSPORIN
- Cytotoxics: neomycin possibly reduces absorption of MEOXYREDXATE; neomycin reduces bioavailability of SORAFLIB; increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides given with ▶ PLATINUM COMPOUNDS
- Diuretics: increased risk of otoxicity when aminoglycosides given with ▶ LOOP DIURETICS
- Mannitol: manufacturer of tobramycin advises avoid concomitant use with ▶ MANNITOL
- Muscle Relaxants: aminoglycosides enhance effects of ▶ NON-DEPOLARISING MUSCLE RELAXANTS and ▶ SUXAMETHONIUM
- Parasympathomimetics: aminoglycosides antagonise effects of ▶ NEOSTIGMINE and ▶ PYRIDOSTIGMINE
- Tacrolimus: increased risk of nephrotoxicity when aminoglycosides given with ▶ TACROLIMUS
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC
- Vitamins: neomycin possibly reduces absorption of ▶ VITAMIN A

Amphoterin
- Alopurinol: plasma concentration of aminophylline possibly increased by ▶ ALOPURINOL
- Anaesthetics, General: increased risk of convulsions when aminophylline given with ▶ KETAMINE
- Anti-arrrhythmics: aminophylline antagonises anti-arrrhythmic effect of ADENOSINE—manufacturer of adenosine advises
Aminophylline

Anti-arrhythmics (continued)

Avoid aminophylline for 24 hours before adenosine; plasma concentration of aminophylline increased by PROPafenone

- Antibacterials: plasma concentration of aminophylline possibly increased by CLARITHROMYCIN and ROPIVACAIN; plasma concentration of aminophylline increased by ERYTHROMYCIN (also aminophylline may reduce absorption of oral erythromycin); plasma concentration of aminophylline increased by CAPROFLOXACIN and NORFLOXACIN; metabolism of aminophylline accelerated by RIFAMPICIN (reduced plasma concentration); possible increased risk of convulsions when aminophylline given with QUINOLONES

- Antidepressants: plasma concentration of aminophylline possibly increased by FLUCONAZOLE and KETOCONAZOLE

- Antivirals: plasma concentration of aminophylline possibly increased by ACICLOVIR and VALACLOVIR; metabolism of aminophylline accelerated by RITONAVIR (reduced plasma concentration)

- Anti-epileptics: metabolism of aminophylline accelerated by CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE (reduced effect); plasma concentration of both drugs reduced when aminophylline given with FOSFENPYRON and PHENYTOIN

- Antifungals: plasma concentration of aminophylline possibly increased by FLUCONAZOLE and KETOCONAZOLE

- Anticoagulants: avoidance of aminophylline advised by manufacturer of ALENDRONATE, DISOPROPYRAMIDE or DRONERADONE—avoid concomitant use; aminophylline increases plasma concentration of FLECAIN IDE (halve dose of flecainide)

- Anti-arrhythmics: increased risk of ventricular arrhythmias when aminophylline given with PHENYTOIN, ERYTHROMYCIN—avoid concomitant use; increased risk of ventricular arrhythmias when aminophylline given with LEVOFLOXACIN

- Anticoagulants: aminophylline inhibits metabolism of COUMARINS and PHENIDIONE (enhanced anticoagulant effect); aminophylline increases plasma concentration of DABIGATRAN (see under Dabigatran Etxecllate, p. 128)

- Antidepressants: avoidance of aminophylline advised by manufacturer of CITOLOPRAM, ESCITALOPRAM and SULPIRIDE

- Antihistamines: increased risk of ventricular arrhythmias when aminophylline given with CITALOPRAM, MOXIFLOXACIN and PIMOZIDE

- Antimalarials: metabolism of aminophylline increased by PHENINDIONE (reduced plasma concentration); possible increased risk of ventricular arrhythmias when aminophylline given with ARTEMETHER AND LUMEFANTRINE (risk of ventricular arrhythmias); avoidance of aminophylline advised by manufacturer of ARTENIMOL WITH PIPAQUEIN (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when aminophylline given with CHLOROQUINE, HYDOXYCHLOROQUINE, MEfloQUINE or QUININE—avoid concomitant use

- Antimuscarnics: increased risk of ventricular arrhythmias when aminophylline given with TOLTERODINE

- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval; increased risk of ventricular arrhythmias when aminophylline given with BENPERIDOL—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when aminophylline given with AMISULPIDE, DROPERIDOL, HALOPERIDOL, PHENOTHIAZINES, PIMOZIDE or ZUCLOPENTHIXOL—avoid concomitant use; increased risk of ventricular arrhythmias when aminophylline given with SULPIRE

- Anticoagulants: aminophylline inhibits metabolism of PHENYTOIN and FOSFENPYRON (increased plasma concentration)

- Anti-H1 antihistamines: increased risk of ventricular arrhythmias when aminophylline given with PREDNISOLONE, LITHIUM—avoid concomitant use

- Anticoagulants: increased risk of ventricular arrhythmias when aminophylline given with ARIANTHROMycin and AZITHROMycin

- Anticoagulants: aminophylline increases excretion of LITHIUM (reduced plasma concentration)

- Anticoagulants: plasma concentration of aminophylline increased by LEUKOTRIENe RECEPTOR ANTAGONISTS; plasma concentration of aminophylline increased with ZAFIRUkAST, also plasma concentration of zafirlukast reduced

- Anticoagulants: increased risk of hypokalaemia when aminophylline given with ACETAMiDOPHEN, LOOP DIURETICS and THIAZIDES AND RELATED DIURETICS

- Anticoagulants: increased risk of hypokalaemia when aminophylline given with TELITROMYCIN

- Anticoagulants: aminophylline increases excretion of LITHIUM (reduced plasma concentration)

- Anticoagulants: increased risk of hypokalaemia when aminophylline given with LEUKOTRIENe RECEPTOR ANTAGONISTS

- Anticoagulants: increased risk of hypokalaemia when aminophylline given with EPmEREDINE in children

- Anticoagulants: increased risk of hypokalaemia when aminophylline given with high doses of BETA2 SYMPATHOMIMETICS

- Anticoagulants: ulcer-healing Drugs: metabolism of aminophylline inhibited by CIMETIDE (increased plasma concentration); absorption of aminophylline possibly reduced by SUCRALFAE (give at least 2 hours apart)
Amiodarone

- Antivirals (Continued)
  - INDINAVIR —avoid concomitant use; plasma concentration of amiodarone increased by RITONAVIR (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when amiodarone given with 
  - SACHINJUINAVIR —avoid concomitant use; possible increased risk of bradycardia when amiodarone given with 
  - SOFOSBUVIR —see under Amiodarone, p. 99; avoidance of amiodarone advised by manufacturer of TELAPREVI (risk of ventricular arrhythmias)
  - Atorvastatin: increased risk of ventricular arrhythmias when amiodarone given with ATRVOSTAT
  - Beta-blockers: increased risk of bradycardia, AV block and myocardial depression when amiodarone given with 
  - BETA-BLOCKERS; increased myocardial depression when anti-arrhythmics given with BETA-BLOCKERS; increased risk of ventricular arrhythmias when amiodarone given with 
  - SOTALOL —avoid concomitant use
  - Calcium-channel Blockers: increased risk of bradycardia, AV block and myocardial depression when amiodarone given with 
  - DILTAZEM OR VERAPAMIL
  - Cardiolipins: amiodarone increases plasma concentration of DIGOXIN (half life of digitoxin)
  - Ciclosporin: amiodarone possibly increases plasma concentration of CICLOSPORIN
  - Cobimetap: plasma concentration of amiodarone possibly increased by COBIMETAP —manufacturer of cobimetap advises avoid concomitant use
  - Colecine: amiodarone possibly increases risk of COLCHICINE toxicity
  - Cytotoxics: amiodarone possibly increases the plasma concentration of AFABININ —manufacturer of afabinin advises separating administration of amiodarone by 6 to 12 hours; possible increased risk of ventricular arrhythmias when amiodarone given with 
  - BUSUTINIB and 
  - CERITINIB; amiodarone possibly increases the plasma concentration of 
  - IBURITINIB —reduce dose of iburitinib (see under iburitinib, p. 867); avoidance of amiodarone advised by manufacturer of IDELALISIB; possible increased risk of ventricular arrhythmias when amiodarone given with 
  - VANDETINIB —avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with 
  - ARSENIC TRIOXIDE
  - Diuretics: amiodarone increases plasma concentration of 
  - EPLERONE (reduce dose of eplerenone); increased cardiac toxicity with amiodarone if hypokalaemia occurs with 
  - ACETAZOLAMIDE, LOOP DIURETICS OR THIAZIDES AND RELATED DIURETICS
  - Fingolimod: possible increased risk of bradycardia when amiodarone given with 
  - FINGOLIMOD
  - Grapefruit juice: plasma concentration of amiodarone increased by 
  - GRAPEFRUIT JUICE
  - Ibradadine: increased risk of ventricular arrhythmias when amiodarone given with 
  - IYABRADINE
  - Lipid-regulating Drugs: increased risk of myopathy when amiodarone given with 
  - SIMVASTATIN (see under Simvastatin, p. 194); separating administration from amiodarone by 12 hours advised by manufacturer of 
  - LOMITAPIDE
  - Lithium: manufacturer of amiodarone advises avoid concomitant use with 
  - LITHIUM (risk of ventricular arrhythmias)
  - Orlisat: plasma concentration of amiodarone possibly reduced by 
  - ORLISTAT
  - Panobinostat: possible increased risk of ventricular arrhythmias when amiodarone given with 
  - PANOBINOSTAT —avoid concomitant use
  - Pentamidine Isetionate: increased risk of ventricular arrhythmias when amiodarone given with 
  - PENTAMIDINE ISETIONATE —avoid concomitant use
  - Tacrolimus: amiodarone possibly increases plasma concentration of 
  - TACROLIMUS
  - Thyroid Hormones: amiodarone can affect serum concentrations of 
  - THYROID HORMONES —monitor thyroid function closely
  - Ulcer-healing Drugs: plasma concentration of amiodarone increased by 
  - CIMETIDINE

Amisolpride see Antipsychotics
Amiprivitryline see Antidepressants, Tricyclic
Amlodipine see Calcium-channel Blockers
Amodicillin see Penicillins

Amphotericin

NOTE Close monitoring required with concomitant administration of nephrotoxic drugs or cytotoxics
Antibacterials: increased risk of nephrotoxicity when amphotericin given with 
- AMINOLYSISIDES or POLYMIXINS; possible increased risk of nephrotoxicity when amphotericin given with 
- VANCOCYN
> Antiinflamms: amphotericin reduces renal excretion and increases cellular uptake of FLUCYTOSINE (toxicity possibly increased); effects of amphotericin possibly antagonised by 
- IMIDAZOLES and TRAIZOLES; plasma concentration of amphotericin possibly increased by 
- MICAFUNGIN
> Cardiac Glycosides: hypokalaemia caused by amphotericin increases cardiac toxicity with 
- CARDIAC GLYCOSIDES
> Ciclosporin: increased risk of nephrotoxicity when amphotericin given with 
- CICLOSPORIN
> Corticosteroids: increased risk of hypokalaemia when amphotericin given with 
- CORTICOSTEROIDS—avoid concomitant use unless corticosteroids needed to control reactions
> Cytoxics: increased risk of ventricular arrhythmias when amphotericin given with 
- ARSENIC TRIOXIDE
> Diuretics: increased risk of hypokalaemia when amphotericin given with 
- LOOP DIURETICS OR THIAZIDES AND RELATED DIURETICS
> Pentamidine Isetionate: possible increased risk of nephrotoxicity when amphotericin given with 
- PENTAMIDINE ISETIONATE
> Sodium Stibogluconate: possible increased risk of arrhythmias when amphotericin given after 
- SODIUM STIBOGLUCONATE —manufacturer of sodium stibogluconate advises giving 14 days apart
> Tacrolimus: increased risk of nephrotoxicity when amphotericin given with 
- TACROLIMUS

Ampicillin see Penicillins

Anabolic Steroids

- Antiocoagulants: anabolic steroids enhance anticoagulant effect of 
- COUMARINS AND 
- PHENINDINE
- Antidiabetics: anabolic steroids possibly enhance hypoglycaemic effect of 
- ANTIDIABETICS

Anasthetics, General

NOTE See also Surgery and Long-term Medication, under 
- General Anaesthesia in BNF
> ACE Inhibitors: enhanced hypotensive effect when general anaesthetics given with 
- ACE INHIBITORS
> Adrenergic Neuron Blockers: enhanced hypotensive effect when general anaesthetics given with 
- ADRENERGIC NEURONE BLOCKERS
> Alpha-blockers: enhanced hypotensive effect when general anaesthetics given with 
- ALPHA-BLOCKERS
> Aminophylline: increased risk of convulsions when ketamine given with 
- AMINOPHYLLINE
> Analgesics: metabolism of etomidate inhibited by 
- FENTANYL (consider reducing dose of etomidate); effects of thiopental possibly enhanced by 
- ASPARIN; effects of intravenous general anaesthetics and volatile liquid general anaesthetics possibly enhanced by 
- OPIOID ANALGESICS
> Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when general anaesthetics given with 
- ANGIOTENSIN-II RECEPTOR ANTAGONISTS
> Antibacterials: increased risk of hepatotoxicity when isoflurane given with 
- ISONIAZIDE; effects of thiopental enhanced by 
- SULFONAMIDES; hypersensitivity–like reactions can occur when 
- intraavenous VANCOCYN
> Antidepressants: increased risk of arrhythmias and hypotension when general anaesthetics given with 
- TRICYCLICS
> Antipsychotics: enhanced hypotensive effect when general anaesthetics given with 
- ANTIPSYCHOTICS; effects of thiopental enhanced by 
- DROPERIDOL
> Anxiolytics and Hypnotics: increased sedative effect when 
- general anaesthetics given with 
- ANXIOLYTICS AND HYPNOTICS
> Beta-blockers: enhanced hypotensive effect when general anaesthetics given with 
- BETA-BLOCKERS

Amitrazine see See Antiparasitics

Ampicillin see Penicillins

Amphotericin
Angiotensin-II Receptor Antagonists

ACE Inhibitors: increased risk of hyperkalaemia, hypotension, and impaired renal function when angiotensin-II receptor antagonists given with ACE INHIBITORS.

Adrenergic Neurone Blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with ADRENERGIC NEURONE BLOCKERS.

Alcohol: enhanced hypertensive effect when angiotensin-II receptor antagonists given with ALCOHOL.

Aldesleukin: enhanced hypertensive effect when angiotensin-II receptor antagonists given with ALDESLEUKIN.

Aliksiren: increased risk of hyperkalaemia, hypotension, and impaired renal function when angiotensin-II receptor antagonists given with ALIXISIREN.

Alpha-blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with ALPHA-BLOCKERS.

Anaesthetics, General: enhanced hypertensive effect when angiotensin-II receptor antagonists given with GENERAL ANAESTHETICS.

Antipsychotics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with ANTI PSYCHOTICS.

Antivirals: plasma concentration of candesartan, losartan and valsartan possibly increased by PARITAPREVIN—manufacturer of paritaprevin advises reduce dose of candesartan, losartan and valsartan.

Anxiolytics and Hypnotics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with ANXIOLYTICS AND HYPNOTICS.

Beta-blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with BETA-BLOCKERS.

Calcium-channel Blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with CALCIUM-CHANNEL BLOCKERS.

Ciclosporin: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with CICLOSPORIN.

Clonidine: enhanced hypertensive effect when angiotensin-II receptor antagonists given with CLONIDINE.

Corticosteroids: hypertensive effect of angiotensin-II receptor antagonists antagonised by CORTICOSTEROIDS.

Diazoxide: enhanced hypertensive effect when angiotensin-II receptor antagonists given with DIAZOXIDE.

Diuretics: increased risk of severe hyperkalaemia when angiotensin-II receptor antagonists given with EPIERENONE and SPIRONOLACTONE—avoid concurrent use or use lowest possible doses of both drugs; increased risk of severe hyperkalaemia when angiotensin-II receptor antagonists given with AMILORIDE, POTASSIUM CANRENOATE or TRIAMTERENE; enhanced hypertensive effect when angiotensin-II receptor antagonists given with DIURETICS; valsartan reduces plasma concentration of FUROSEMIDE.

Dopaminergics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with MOXISLYTE.

Etanercept: avoid concomitant use of anakinra with ETANERCEPT.

Epleronone and SPIRONOLACTONE—avoid concurrent use or use lowest possible doses of both drugs; increased risk of severe hyperkalaemia when angiotensin-II receptor antagonists given with AMILORIDE, POTASSIUM CANRENOATE or TRIAMTERENE; enhanced hypertensive effect when angiotensin-II receptor antagonists given with DIURETICS; valsartan reduces plasma concentration of FUROSEMIDE.

Furosemide: enhanced hypertensive effect when angiotensin-II receptor antagonists given with FUROSEMIDE.

Gemfibrozil: enhanced hypertensive effect when angiotensin-II receptor antagonists given with GEMFIBROZIL.

Lithium: improved plasma concentration when angiotensin-II receptor antagonists given with LITHIUM.

Methyldopa: enhanced hypertensive effect when angiotensin-II receptor antagonists given with METHYLDOPA.

Moxisylyte: enhanced hypertensive effect when angiotensin-II receptor antagonists given with MOXISLYTE.

Opioids: enhanced hypertensive effect when angiotensin-II receptor antagonists given with OPIOIDS.

Paracetamol: enhanced hypertensive effect when angiotensin-II receptor antagonists given with PARACETAMOL.

Peprotin: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with PEPROTIN.

Potassium Canrenone: enhanced hypertensive effect when angiotensin-II receptor antagonists given with POTASSIUM CANRENOATE.

Potassium Pulitzer: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with POTASSIUM PULVERISE.

Propafenone: enhanced hypertensive effect when angiotensin-II receptor antagonists given with PROPAFENONE.

Quinapril: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with QUINAPRIL.

Ritonavir: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with RITONAVIR.

Rifampicin: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with RIFAMPICIN.

Sodium Citrate: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with SODIUM CITRATE.

Spirinolactone: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with SPIRONOLACTONE.

Valproate: enhanced hypertensive effect when angiotensin-II receptor antagonists given with VALPROATE.

Verapamil: enhanced hypertensive effect when angiotensin-II receptor antagonists given with VERAPAMIL.
Angiotensin-II Receptor Antagonists (continued)

- Muscle Relaxants: enhanced hypotensive effect when angiotensin-II receptor antagonists given with Baclofen or Tizanidine.
- Nitrates: enhanced hypotensive effect when angiotensin-II receptor antagonists given with Nitrates.
- Oestrogens: hypotensive effect of angiotensin-II receptor antagonists antagonised by Oestrogens.
- Potassium Salts: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with Potassium Salts.
- Prostaglandins: enhanced hypotensive effect when angiotensin-II receptor antagonists given with Hydralazine, Minoxidil or Sodium Nitroprusside.

Antacids

Note: Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.

- ACE Inhibitors: antacids possibly reduce absorption of ACE Inhibitors; antacids reduce absorption of Captopril, Enalapril and Fosinopril.
- Analgesics: antacids possibly reduce absorption of Acemetacin; alkaline urine due to some antacids increases excretion of Aspirin.
- Antihelmintics: sodium bicarbonate reduces excretion of Diethylcarbamazine.
- Antibacterials: antacids reduce absorption of Ceftazidime, Ciprofloxacin, Levofloxacin and Rifampicin; antacids reduce absorption of Azithromycin (give at least 2 hours before or 1 hour after antacids); antacids reduce absorption of Ciprofloxacin and Levofloxacin (give at least 2 hours before or 4 hours after ciprofloxacin and levofloxacin); antacids reduce absorption of Moxifloxacin (give at least 6 hours apart); antacids reduce absorption of Olopatadine (give at least 2 hours apart); avoid concomitant use of antacids with Methenamine; oral magnesium salts (as magnesium trisilicate) reduce absorption of Nitrofurantoin; antacids possibly reduce absorption of Tetracyclines (give at least 2 to 3 hours apart).
- Antiepileptics: antacids reduce absorption of Fosphenytoin, Gabapentin and Phenytoin.
- Antifungals: antacids reduce absorption of Itraconazole and Ketoconazole.
- Antihistamines: antacids reduce absorption of Fexofenadine.
- Antimalarials: antacids reduce absorption of Chloroquine and Hydroxychloroquine; oral magnesium salts (as magnesium trisilicate) reduce absorption of Proguanil.
- Antipsychotics: antacids reduce absorption of Phenothiazines and Sulpiride.
- Antivirals: antacids reduce absorption of Atazanavir (give at least 2 hours before or 1 hour after antacids); oral magnesium salts reduce absorption of Dolasetodarin — manufacturer of dolasetodarin advises give at least 2 hours before or 6 hours after oral magnesium salts; aluminium hydroxide reduces absorption of Dolasetodarin — manufacturer of dolasetodarin advises give at least 2 hours before or 6 hours after aluminium hydroxide; oral magnesium salts reduce absorption of Elvitegravir (give at least 4 hours apart); aluminium hydroxide reduces absorption of Elvitegravir (give at least 4 hours apart); separating administration from antacids by 4 hours advised by manufacturer of Ledipasvir; aluminium hydroxide reduces plasma concentration of Raltegravir — manufacturer of raltegravir advises avoid concomitant use; oral magnesium salts reduce plasma concentration of Raltegravir — manufacturer of raltegravir advises avoid concomitant use; manufacturer of rilpivirine advises give antacids 2 hours before or 4 hours after Rilpivirine; antacids reduce absorption of Tipranavir (give at least 2 hours apart).
- Bile Acids: antacids possibly reduce absorption of Bile Acids; aluminium hydroxide probably reduces effects of Cholic Acid (manufacturer of cholic acid advises give at least 5 hours apart).

Antacids (continued)

- Bisphosphonates: antacids reduce absorption of Bisphosphonates.
- Cardiac Glycosides: antacids possibly reduce absorption of Digoxin.
- Corticosteroids: antacids reduce absorption of Deflazacort.
- Cytoxins: aluminium hydroxide and oral magnesium salts possibly reduce absorption of Estramustine — manufacturer of estramustine advises avoid concomitant administration; separating administration with antacids by about 12 hours advised by manufacturer of Bosutinib; antacids possibly reduce absorption of Dasatinib (give at least 2 hours apart); antacids possibly reduce plasma concentration of Erlotinib — give antacids at least 4 hours before or 2 hours after erlotinib.
- Deferasirox: antacids containing aluminium possibly reduce absorption of Deferasirox (manufacturer of deferasirox advises avoid concomitant use).
- Deferiprone: antacids containing aluminium possibly reduce absorption of Deferiprone (manufacturer of deferiprone advises avoid concomitant use).
- Dipyradomol: antacids possibly reduce absorption of Dipyradomol.
- Erlotinib: antacids reduce absorption of Erlotinib.
- Eltrombopag: antacids reduce absorption of Eltrombopag (give at least 4 hours apart).
- Folates: antacids possibly reduce absorption of Folic Acid (manufacturer of folic acid advises give at least 2 hours apart).
- Iron Salts: oral magnesium salts (as magnesium trisilicate) reduce absorption of Oral IRON SALTS.
- Lipid-regulating Drugs: antacids reduce absorption of Rosuvastatin.
- Lithium: sodium bicarbonate increases excretion of Lithium (reduced plasma concentration).
- Misoprostol: antacids possibly reduce absorption of Misoprostol.
- Mycophenolate: antacids reduce absorption of Mycophenolate.
- Penicillamine: antacids reduce absorption of Penicillamine.
- Polystyrene Sulfonate Resins: risk of intestinal obstruction when aluminium hydroxide given with Polystyrene Sulfonate Resins;
- Risk of metabolic alkalosis when oral magnesium salts given with Polystyrene Sulfonate Resins.
- Riociguat: antacids reduce absorption of Riociguat (give at least 2 hours before or 1 hour after riociguat).
- Symptomatics: aluminium hydroxide possibly increases absorption of Pseudoephedrine.
- Thyroid Hormones: antacids possibly reduce absorption of Levothyroxine.
- Ulcer-healing Drugs: antacids possibly reduce absorption of Lansoprazole.

Antazoline see Antihistamines

Antihelminitics see individual drugs

Anthrax Vaccine see Vaccines

Anti-D Immunoglobulins see Immunoglobulins

Anti-arrhythmics see Adenosine, Amiodarone, Disopyramide, Dronedaron, Flecaïnide, Lidocaine, and Propafenone

Antibacterials see individual drugs

Antibiotics (cytotoxic) see Bleomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, and Pixantrone

Anticoagulants see Apixaban, Argatroban, Bivalirudin, Coumarins, Dabigatran, Danaparoid, Edoxaban, Fondaparinux, Heparins, Phenindione, and Rivaroxaban

Antidepressants see Agomelatine; Antidepressants, SSRIs; Antidepressants, Tricyclic; Antidepressants, Tricyclic (related); MAOIs; Mirtazapine; Moclobemide; Reboxetine; St John’s Wort; Venlafaxine; Vortioxetine

Antidepressants, Noradrenaline Re-uptake Inhibitors see Reboxetine

Antidepressants, SSRIs

Note: see also Dapoxetine

- Alcohol: sedative effects possibly increased when SSRIs given with Alcohol.

- Amoxapine: fluvoxamine increases plasma concentration of Amoxapine (concomitant use should usually be avoided, but where not possible halve amoxapine dose and monitor plasma-amoxapine concentration)
Antidepressants, SSRI (continued)

Antifungals: fluvoxamine inhibits metabolism of *ROPIVACAINE*—avoid prolonged administration of ropivacaine

• Analgesics: Increased risk of bleeding when SSRIs given with *NSAIDS or ASPIRIN*: possible increased serotonergic effects when SSRIs given with *FENTANYL*; fluoxetine, fluvoxamine, paroxetine and sertraline possibly increase plasma concentration of *METHADONE*; increased risk of CNS toxicity when SSRIs given with *TRAMADOL*

• Anti-arrhythmics: manufacturer of citalopram and escitalopram advises avoid concomitant use with *AMIODARONE* (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with *DISOPYRAMIDE* (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with *DRONEDARONE* (risk of ventricular arrhythmias); fluoxetine increases plasma concentration of *FLECAINIDE*; fluoxetine and paroxetine possibly inhibit metabolism of *PROPafenONE*

• Antibacterials: manufacturer of citalopram and escitalopram advises avoid concomitant use with *intravenous ERYTHROMYCIN* (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with *MOXIFLOXACIN* (risk of ventricular arrhythmias); possible increased risk of ventricular arrhythmias when citalopram given with *TELITROMYCIN*

• Anticoagulants: SSRIs possibly enhance anticoagulant effect of *COUMARINS*; possible increased risk of bleeding when SSRIs given with *DABIGATRAN*

• Antidepressants: avoidance of fluvoxamine advised by manufacturer of *REboxetine*: possible increased serotonergic effects when SSRIs given with *DULOXETINE*; fluvoxamine inhibits metabolism of *DULOXETINE*—avoid concomitant use; citalopram, escitalopram, fluvoxamine, paroxetine or sertraline should not be started until 2 weeks after stopping *MAOIS*; also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine, paroxetine or sertraline; fluoxetine should not be started until 2 weeks after stopping *MAOIS*; also MAOIs should not be started until at least 5 weeks after stopping fluoxetine; CNS effects of SSRIs increased by *MAOIS* (risk of serious toxicity); increased risk of CNS toxicity when escitalopram given with *MOCLOBEMIDE*, preferably avoid concomitant use; after stopping citalopram, fluvoxamine, paroxetine or sertraline do not start *MOCLOBEMIDE* for at least 1 week; after stopping fluoxetine do not start *MOCLOBEMIDE* for 5 weeks; increased serotonergic effects when SSRIs given with *ST JOHN’S WORT*—avoid concomitant use; fluvoxamine inhibits metabolism of *AGOMELATINE* (increased plasma concentration); possible increased serotonergic effects when fluoxetine or fluvoxamine given with *MIrTAZAPINE*: SSRIs increase plasma concentration of some *TRICYCLICS*; manufacturer of citalopram and escitalopram advises avoid concomitant use with *TRICYCLICS* (risk of ventricular arrhythmias); possible increased risk of convulsions when SSRIs given with *VORtixETINE*; fluoxetine and paroxetine possibly increase plasma concentration of *VORtixETINE* (consider reducing dose of vortioxetine)

• Antiepileptics: SSRIs antagonise anti-epileptic effect of *ANTIEPILEPTICS* (convulsive threshold lowered); fluoxetine and fluvoxamine increase plasma concentration of *CARBARAZEPINE*; fluoxetine and fluvoxamine increase plasma concentration of *FosphENyTIN*; plasma concentration of sertraline possibly reduced by *FosphENyTIN and PHENyTOIN*, also plasma concentration of fosphenytoin and phenytoin possibly increased; plasma concentration of paroxetine reduced by *FosphENyTIN, PHENOBARBITAL, PHENyTOIN and ASPIRIN*; fluoxetine increases plasma concentration of *FosphENyTIN* and *PHENyTOIN*

• Antifungals: plasma concentration of paroxetine possibly increased by *TERBINAFINE*

• Antihistamines: manufacturer of citalopram and escitalopram advises avoid concomitant use with *MIZOLASTINE* (risk of ventricular arrhythmias); antidepressant effect of SSRIs possibly antagonised by *CYPROMEPATINE*

Antidepressants, SSRI (continued)

• Antimalarials: avoidance of antidepressants advised by manufacturer of *ARTEMETHER WITH LUMEFANTRINE* and *ARTENIMOL WITH PIPERAQUINE*: possible increased risk of ventricular arrhythmias when citalopram or escitalopram given with *ARTENIMOL WITH LUMEFANTRINE*: avoid concomitant use; possible increased risk of ventricular arrhythmias when citalopram or escitalopram given with *ARTENIMOL WITH PIPERAQUINE*: avoid concomitant use; possible increased risk of ventricular arrhythmias when citalopram or escitalopram given with *QUININE*: avoid concomitant use

• Antinociceptive: paroxetine increases plasma concentration of *DARIFENACIN* and *PROCYCLIDINE*

• Antipsychotics: avoidance of fluoxetine, fluvoxamine and sertraline advised by manufacturer of *DROPERIDOL* (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with *HALOPERIDOL* (risk of ventricular arrhythmias); fluoxetine increases plasma concentration of *CLOzapINE*, *HALOPERIDOL* and *RISPERIDONE*; fluvoxamine possibly increases plasma concentration of *ASENApINE* and *HALOPERIDOL*; paroxetine inhibits metabolism of *PERPHENAZINE* (reduce dose of perphenazine); fluoxetine and paroxetine possibly increase plasma concentration of *APRIPipRAZOLE* (reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of paroxetine possibly increased by *ASENApINE*; fluvoxamine, paroxetine and sertraline increase plasma concentration of *CLOzapINE*; citalopram possibly increases plasma concentration of *CLOzapINE* (increased risk of toxicity); fluvoxamine increases plasma concentration of *ASENApINE* and *HALOPERIDOL*; manufacturer of citalopram and escitalopram advises avoid concomitant use with *PHENOTHIAZINES* (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with *PIMOZIDE* (risk of ventricular arrhythmias); SSRIs possibly increase plasma concentration of *PIMOZIDE* (increased risk of ventricular arrhythmias—avoid concomitant use); paroxetine possibly increases plasma concentration of *RISPERIDONE* (increased risk of toxicity)

• Antivirals: plasma concentration of paroxetine and sertraline possibly reduced by *DARUNavIR*: plasma concentration of SSRIs possibly increased by *RITONAVIR*; plasma concentration of paroxetine possibly reduced by *RITONAVIR*

• Antiulcerotics and Hypnotics: fluoxetine increases plasma concentration of *ALPRAZOLAM*; fluvoxamine increases plasma concentration of some *BENZODIAZEPINES*; fluvoxamine increases plasma concentration of *MELATONIN*: avoid concomitant use; sedative effects possibly increased when sertraline given with *ZOLPIDEM*

• Atomoxetine: possible increased risk of convulsions when antidepressants given with *ATOMOXETINE*: fluoxetine and paroxetine possibly inhibit metabolism of *ATOMOXETINE*

• Beta-blockers: citalopram and escitalopram increase plasma concentration of *METOPROLOL*; paroxetine possibly increases the plasma concentration of *METOPROLOL*—increased risk of AV block (manufacturer of paroxetine advises avoid concomitant use in cardiac insufficiency); fluvoxamine increases plasma concentration of *PROPRANOLOL*; increased risk of ventricular arrhythmias when citalopram given with *SOTALOL*: avoid concomitant use; manufacturer of escitalopram advises avoid concomitant use with *SOTALOL* (risk of ventricular arrhythmias)

• Bupropion: plasma concentration of citalopram possibly increased by *BUPROPION*

• Calcium-channel Blockers: fluoxetine possibly inhibits metabolism of *NIFEDIPINE* (increased plasma concentration)

• Clidipogrel: fluoxetine and fluvoxamine possibly reduce antiplaetelet effect of *CLIDIPOGREL*

• Dapoxetine: possible increased risk of serotonergic effects when SSRIs given with *DAPOXETINE* (manufacturer of dapoxetine advises SSRIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SSRIs)
Antidepressants, SSRI (continued)

- Dopaminergics: increased risk of CNS toxicity when SSRIs given with **RASAGILINE**; fluvoxamine should not be started until 2 weeks after stopping **RASAGILINE**; fluoxetine should not be started until 2 weeks after stopping **RASAGILINE**, also rasagiline should not be started until at least 5 weeks after stopping fluoxetine; avoidance of citalopram and escitalopram advised by manufacturer of **SELEGILINE**; increased risk of hypertension and CNS excitation when fluvoxamine or sertraline given with **SELEGILINE** (selegiline should not be started until 1 week after stopping fluvoxamine or sertraline, avoid fluvoxamine or sertraline for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when paroxetine given with **SELEGILINE** (selegiline should not be started until 2 weeks after stopping paroxetine, avoid paroxetine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when fluoxetine given with **SELEGILINE** (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline)

- Grapefruit Juice: plasma concentration of sertraline possibly increased by **GRAPEFRUIT JUICE**

- Hormone Antagonists: fluoxetine and paroxetine possibly inhibit metabolism of **TAMOXIFEN** to active metabolite (avoid concomitant use)

- **SHTR-receptor Agonists**: increased risk of CNS toxicity when citalopram given with **SHTR-AGONISTS** (manufacturer of citalopram advises avoid concomitant use); fluvoxamine inhibits the metabolism of **FROYOVATRIPTAN**; possible increased serotonergic effects when SSRIs given with **NARATRIPTAN**; CNS toxicity reported when sertraline given with **SUMATRIPTAN**; increased risk of CNS toxicity when citalopram, escitalopram, fluoxetine, fluvoxamine or paroxetine given with **SUMATRIPTAN**; fluvoxamine possibly inhibits metabolism of **ZOLMITRIPTAN** (reduce dose of zolmitriptan)

- **SHTR-receptor Antagonists**: possible increased serotonergic effects when SSRIs given with **SHTR-ANTAGONISTS**

- Lipid-Regulating Drugs: separating administration from fluoxetine and fluvoxamine by 12 hours advised by manufacturer of **LOMIDIFIDE**

- Lithium: Increased risk of CNS effects when SSRIs given with **LITHIUM** (lithium toxicity reported)

- Methylthioninium: risk of CNS toxicity when SSRIs given with **METHYLTHIONIUM**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

- Metoclopramide: CNS toxicity reported when SSRIs given with **METOCLOPRAMIDE**

- Muscle Relaxants: fluvoxamine increases plasma concentration of **TIZANIDINE** (increased risk of toxicity)—avoid concomitant use

- Parasympathomimetics: paroxetine increases plasma concentration of **GALANTAMINE**

- Pentamidine Isetionate: manufacturer of citalopram and escitalopram advises avoid concomitant use with **PENTAMIDINE ISETONATE** (risk of ventricular arrhythmias)

- Pirenidone: fluvoxamine increases plasma concentration of **PIRFENIDONE**—manufacturer of pirenidone advises avoid concomitant use

- Pomalidomide: fluvoxamine increases plasma concentration of **POMALIDOMIDE**

- Ranolazine: paroxetine increases plasma concentration of **RANOLAZINE**

- Roflumilast: fluvoxamine inhibits the metabolism of **ROFLUMILAST**

- Sympathomimetics: metabolism of SSRIs possibly inhibited by **METHYLPHENIDATE**

- Theophylline: fluvoxamine increases plasma concentration of **THEOPHYLLINE** (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration)

- Ticagrelor: possible increased risk of bleeding when citalopram, paroxetine or sertraline given with **TICAGRELOR**

- Ulcer-healing Drugs: plasma concentration of citalopram, escitalopram and sertraline increased by **CIMETIDINE**; fluvoxamine possibly increases plasma concentration of **LANSOPRAZOLE**; plasma concentration of escitalopram increased by **OMEPRAZOLE**

Antidepressants, SSRI (related)

See Duloxetine and Venlafaxine

Antidepressants, Tricyclic

- Adrenergic Neurone Blockers: tricyclics antagonise hypotensive effect of **ADRENERGIC NEURONE BLOCKERS**

- Alcohol: increased sedative effect when tricyclics given with **ALCOHOL**

- Alpha₂-adrenergic Stimulants: avoidance of tricyclics advised by manufacturer of **APRACLONIDINE** and **BRIMONIDINE**

- Anaesthetics, General: increased risk of arrhythmias and hypotension when tricyclics given with **GENERAL ANAESTHETICS**

- Analgesics: increased risk of CNS toxicity when tricyclics given with **TRAMADOL**—side-effects possibly increased when tricyclics given with **NEFOPAM**; sedative effects possibly increased when tricyclics given with **OPIOID ANALGESICS**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when tricyclics given with **AMIODARONE**—avoid concomitant use; increased risk of ventricular arrhythmias when tricyclics given with **DISOPYRAMIDE** or **FLECAINIDE**; avoidance of tricyclics advised by manufacturer of **DRONEDARONE** (risk of ventricular arrhythmias); increased risk of arrhythmias when tricyclics given with **PROPafenONE**

- Antibacterials: increased risk of ventricular arrhythmias when tricyclics given with **MOXIFLOXACIN**—avoid concomitant use; possible increased risk of ventricular arrhythmias when tricyclics that prolong the QT interval given with **DELAMINOL**; possible increased risk of ventricular arrhythmias when tricyclics given with **TELITHROMYCIN**

- Anticoagulants: tricyclics may enhance or reduce anticoagulant effect of **COUMARINS**

- Antidepressants: avoidance of tricyclics advised by manufacturer of **CITALOPRAM** and **ESCITALOPRAM** (risk of ventricular arrhythmias); possible increased serotonergic effects when amitriptyline or clomipramine given with **DULOXETINE**; increased risk of hypertension and CNS excitation when tricyclics given with **MADOS**, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine); after stopping tricyclics do not start **MOCLOBEMIDE** for at least 1 week; plasma concentration of some tricyclics increased by **SSRIS**; plasma concentration of amitriptyline reduced by **ST JOHN’S WORT**; possible increased risk of convulsions when tricyclics given with **VORTIXETINE**

- Antiepileptics: tricyclics antagonise anticonvulsant effect of **ANTIEPILEPTICS** (convulsive threshold lowered); metabolism of tricyclics accelerated by **CARBAMAZEPINE** (reduced plasma concentration and reduced effect); plasma concentration of tricyclics possibly reduced by **FOSPHENYTIN** and **PHENOBARBITAL** and **PRIMIDONE** (reduced plasma concentration)

- Antifungals: plasma concentration of amitriptyline and nortriptyline possibly increased by **TUCONAZOLE**; plasma concentration of tricyclics possibly increased by **TERBINAFINE**

- Antihistamines: increased antimuscarinic and sedative effects when tricyclics given with **ANTIHISTAMINES**

- Antimalarials: avoidance of antidepressants advised by manufacturer of **ARTEMETHER WITH LUMEFAUNTRINE** and **ARTENIMOL WITH PIPERAQUINE**

- Antibacterials: risk of antimuscarinic side-effects when tricyclics given with **ANTIMUSCARINICS**

- Antipsychotics: avoidance of tricyclics advised by manufacturer of **DROPERIDOL**, **FLUPHENAZINE**, **HALOPERIDOL**, **SULPIRIDE** and **ZUCLOPENTHIXOL** (risk of ventricular arrhythmias); possible increased antimuscarinic side-effects when tricyclics given with **CLOZAPINE**; increased risk of antimuscarinic side-effects when tricyclics given with **PHENOTHIAZINES**; possible increased risk of ventricular arrhythmias when tricyclics given with **RISPERIDONE**

- Antivirals: plasma concentration of tricyclics possibly increased by **ZITONAVIR**; increased risk of ventricular...
Antidepressants, Tricyclic

- **Antivirals** (continued)
  - arrhythmias when tricyclics given with ● **SAQUINAVIR**—avoid concomitant use
  - Anxiety and Hypnotics: increased sedative effect when tricyclics given with ● **ANXIOLYTICS AND HYPNOTICS**
  - Atomoxetine: increased risk of ventricular arrhythmias when tricyclics given with ● **ATOMOXETINE**; possible increased risk of convulsions when antidepressants given with **ATOMOXETINE**
  - Beta-blockers: plasma concentration of imipramine increased by **LABETALOL** and **PROPRANOLOL**; increased risk of ventricular arrhythmias when tricyclics given with ● **SOTALOL**
  - Bupropion: plasma concentration of tricyclics possibly increased by **BUPROPION** (possible increased risk of convulsions)
  - Calcium-channel Blockers: plasma concentration of imipramine increased by **DILTIAZEM** and **VERAPAMIL**; plasma concentration of tricyclics possibly increased by **DILTIAZEM** and **VERAPAMIL**
  - Cannabis Extract: possible increased risk of hypertension and tachycardia when tricyclics given with **CANNABIS EXTRACT**
  - Clonidine: tricyclics antagonise hypotensive effect of ● **CLONIDINE**, also increased risk of hypertension on clonidine withdrawal
  - Cytotoxics: increased risk of ventricular arrhythmias when amitriptyline or clomipramine given with ● **ARSENIC TRIOXIDE**
  - Dapoxetine: possible increased risk of serotoninergic effects when tricyclics given with ● **DAPoxetine** (manufacturer of dapoxetine advises tricyclics should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tricyclics)
  - Disulfiram: metabolism of tricyclics inhibited by **DISULFIRAM** (increased plasma concentration); concomitant amitriptyline reported to increase **DISULFIRAM** reaction with alcohol
  - Diuretics: increased risk of postural hypotension when tricyclics given with **DIURETICS**
  - Dopaminergics: caution with tricyclics advised by manufacturer of **ENTACAPONE**; increased risk of CNS toxicity when tricyclics given with ● **RASAGILINE**; CNS toxicity reported when tricyclics given with ● **SELEGILINE**
  - Histamine: tricyclics theoretically antagonise effects of **HISTAMINE**—manufacturer of histamine advises avoid concomitant use
  - Lithium: risk of toxicity when tricyclics given with **LITHIUM**
  - Methylthionium: risk of CNS toxicity when clomipramine given with ● **METHYLTHIONIUM**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthionium and observe patient for up to 4 hours after administration)
  - Moxonidine: tricyclics possibly antagonise hypotensive effect of **MOXONIDINE** (manufacturer of moxonidine advises avoid concomitant use)
  - Muscle Relaxants: tricyclics enhance muscle relaxant effect of **BACLOFEN**
  - Nicorandil: tricyclics possibly enhance hypotensive effect of **NICORANDIL**
  - Nitrates: tricyclics reduce effects of sublingual tablets of **NITRATES** (failure to dissolve under tongue owing to dry mouth)
  - Oestrogens: antidepressant effect of tricyclics antagonised by **OESTROGENS** (but side-effects of tricyclics possibly increased due to increased plasma concentration)
  - Pentamidine isetionate: increased risk of ventricular arrhythmias when tricyclics given with ● **PENTAMIDINE ISETIONATE**
  - Sodium Oxybate: increased risk of side-effects when tricyclics given with **SODIUM OXYBATE**
  - Sympathomimetics: increased risk of hypertension and arrhythmias when tricyclics given with ● **ADRENALINE (EPINEPHRINE)** (but local anaesthetics with adrenaline appear to be safe); metabolism of tricyclics possibly inhibited by **METHYLPHENIDATE**; avoidance of tricyclics advised by manufacturer of **MIDDORF**; increased risk of hypertension and arrhythmias when tricyclics given with ● **NORADRENALINE (NOREPINEPHRINE) OR PHENYLEPHRINE**

Antidepressants, Tricyclic (continued)

- Thyroid Hormones: effects of tricyclics possibly enhanced by **THYROID HORMONES**; effects of amitriptyline and imipramine enhanced by **THYROID HORMONES**
- Tricyclic-related Antidepressants: plasma concentration of tricyclics possibly increased by **CIMETIDINE**; metabolism of amitriptyline, doxepin, imipramine and nortriptyline inhibited by **CIMETIDINE** (increased plasma concentration)

Antidepressants, Tricyclic (related)

- Alcohol: increased sedative effect when tricyclic-related antidepressants given with ● **ALCOHOL**
- Alpha-adrenoceptor Stimulants: avoidance of tricyclic-related antidepressants advised by manufacturer of **APRALONIDINE** and **BRIMONIDINE**
- Antibacterials: plasma concentration of trazodone possibly increased by **CLARITHROMYCIN**
- Anticoagulants: trazodone may enhance or reduce anticoagulant effect of **WARFARIN**
- Antidepressants: tricyclic-related antidepressants should not be started until 2 weeks after stopping ● **MAIDS**, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; after stopping tricyclic-related antidepressants do not start ● **MOLOBEMIDE** for at least 1 week
- Antiepileptics: tricyclic-related antidepressants possibly antagonise anticonvulsant effect of ● **ANTIEPILEPTICS** (convulsive threshold lowered); plasma concentration of mianserin and trazodone reduced by ● **CARBAMAZEPINE**; plasma concentration of mianserin reduced by ● **FOSSPHENYTOIN** and ● **PHENYTOIN**; metabolism of mianserin accelerated by ● **PHENOBARBITAL** and ● **PRIMIDONE** (reduced plasma concentration)
- Antihistamines: possible increased antimuscarinic and sedative effects when tricyclic-related antidepressants given with **ANTIHISTAMINES**
- Antiinflammatories: avoidance of antidepressants advised by manufacturer of ● **ARTEMETHER WITH LUMEFANTRINE** and ● **ARTENIOMIL WITH PIPERAQUINE**
- Antimuscarinics: possible increased antimuscarinic side-effects when tricyclic-related antidepressants given with **ANTIMUSCARINICS**
- Antivirals: plasma concentration of trazodone increased by ● **SAQUINAVIR** (increased risk of toxicity); increased risk of ventricular arrhythmias when trazodone given with ● **SAQUINAVIR**—avoid concomitant use; plasma concentration of trazodone possibly increased by **TELAPREVIR**
- Anxiety and Hypnotics: increased sedative effect when tricyclic-related antidepressants given with **ANXIOLYTICS AND HYPNOTICS**
- Atomoxetine: possible increased risk of convulsions when antidepressants given with ● **ATOMOXETINE**
- Diazoxide: enhanced hypotensive effect when tricyclic-related antidepressants given with ● **DIAZOXIDE**
- Nitrates: tricyclic-related antidepressants possibly reduce effects of sublingual tablets of **NITRATES** (failure to dissolve under tongue owing to dry mouth)
- Vasodilator Antihypertensives: enhanced hypotensive effect when tricyclic-related antidepressants given with **HYDRAZINE OR SODIUM NITROPRUSSIDE**

Antidiabetics

**NOTE** Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after lixisenatide injection, or taken with a meal when lixisenatide is not administered, to minimise possible interference with absorption

**NOTE** Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when exenatide is not administered, to minimise possible interference with absorption

- ACE Inhibitors: hypoglycaemic effect of insulin, metformin and sulfonylureas possibly enhanced by **ACE INHIBITORS**
- Alcohol: hypoglycaemic effect of antidiabetics enhanced by **ALCOHOL**; increased risk of lactic acidosis when metformin given with **ALCOHOL**
- Anabolic Steroids: hypoglycaemic effect of antidiabetics possibly enhanced by **ANABOLIC STEROIDS**
Antidiabetics (continued)

- Analgesics: effects of sulfonylureas possibly enhanced by
  - NSAIDS; lidocaine possibly reduces the absorption of paracetamol when given 1 to 4 hours before paracetamol.
- Anti-arrhythmics: hypoglycaemic effect of gliclazide, insulin, and metformin possibly enhanced by digoxin.
- Antibacterials: hypoglycaemic effect of acarbose possibly enhanced by neomycin; also severity of gastrointestinal effects increased; effects of repaglinide enhanced by clarithromycin; effects of glibenclamide possibly enhanced by norfloxacin; plasma concentration of canagliflozin and nateglinide reduced by rifampicin; effects of sulfonylureas enhanced by clarithromycin; metabolism of tolbutamide accelerated by rifampicin; hypoglycaemic effect of repaglinide possibly enhanced by clarithromycin; effects of sulfonylureas rarely enhanced by sulfonylamides and trimethoprim; hypoglycaemic effect of sulfonylureas possibly enhanced by tetracyclines; hypoglycaemic effect of repaglinide possibly enhanced by trimethoprim — manufacturer advises avoid concomitant use.
- Anticoagulants: exenatide possibly enhances anticoagulant effect of warfarin; hypoglycaemic effect of sulfonylureas possibly enhanced by coumarins, also possible changes to anticoagulant effect.
- Antidepressants: hypoglycaemic effect of insulin, metformin and sulfonylureas enhanced by MAOIs; hypoglycaemic effect of antidiabetics possibly enhanced by MAOIs.
- Antidiabetics: manufacturer of dapagliflozin advises avoid concomitant use with pioglitazone; plasma concentration of dulaglutide increased by sitagliptin.
- Antiepileptics: tolbutamide transiently increases plasma concentration of fosphenytoin and phenoxytoin (possibility of toxicity); plasma concentration of metformin possibly increased by topiramate; plasma concentration of glibenclamide possibly reduced by topiramate.
- Antifungals: plasma concentration of pioglitazone, saxagliptin and tolbutamide increased by sitagliptin; plasma concentration of sulfonylureas increased by flucloxacillin and miconazole; hypoglycaemic effect of gliclazide and glipizide enhanced by miconazole — avoid concomitant use; hypoglycaemic effect of nateglinide possibly enhanced by flucloxacillin and miconazole.
- Antihistamines: thrombocyte count depressed when metformin given with ketotifen (manufacturer of ketotifen advises avoid concomitant use).
- Antipsychotics: hypoglycaemic effect of sulfonylureas possibly antagonised by phenothiazines.
- Antivirals: plasma concentration of metformin increased by dolabetgravir — consider reducing dose of metformin; plasma concentration of tolbutamide possibly increased by ritonavir; plasma concentration of metformin increased by telaprevir (consider reducing dose of metformin).
- Aprepitant: plasma concentration of tolbutamide reduced by aprepitant.
- Beta-blockers: warning signs of hypoglycaemia (such as tremor) with antidiabetics may be masked when given with beta-blockers; hypoglycaemic effect of insulin enhanced by beta-blockers.
- Bosentan: increased risk of hepatotoxicity when glibenclamide given with bosentan — avoid concomitant use.
- Cardiac Glycosides: acarbose possibly reduces plasma concentration of digoxin; canagliflozin and sitagliptin increase plasma concentration of digoxin.
- Ciclosporin: hypoglycaemic effect of repaglinide possibly enhanced by ciclosporin.

Antidiabetics (continued)

- Corticosteroids: hypoglycaemic effect of antidiabetics antagonised by corticosteroids.
- Cytotoxics: avoidance of repaglinide advised by manufacturer of lapatinib; plasma concentration of metformin possibly increased by vandetanib (consider reducing dose of metformin).
- Deferasirox: plasma concentration of repaglinide increased by deferasirox.
- Diuretics: canagliflozin possibly enhances diuretic effect of diuretics; dapagliflozin possibly enhances diuretic effect of loop diuretics and thiazides and related diuretics; manufacturer of canagliflozin advises avoid concomitant use with loop diuretics; hypoglycaemic effect of antidiabetics antagonised by loop diuretics and thiazides and related diuretics.
- Fosaprepitant: plasma concentration of tolbutamide reduced by fosaprepitant.
- Hormone Antagonists: requirements for antidiabetics possibly reduced by lanreotide, octreotide and pasireotide.
- Leflunomide: hypoglycaemic effect of tolbutamide possibly enhanced by leflunomide.
- Lipid-regulating Drugs: absorption of glibenclamide and glipizide reduced by colesevelam; absorption of glimepiride reduced by colesevelam — manufacturer of glimepiride advises give at least 4 hours before colesevelam; hypoglycaemic effect of acarbose possibly enhanced by colestyramine; hypoglycaemic effect of nateglinide possibly enhanced by gemfibrozil; increased risk of severe hypoglycaemia when repaglinide given with gemfibrozil; avoid concomitant use; plasma concentration of glibenclamide possibly increased by fluvastatin; manufacturer of canagliflozin advises give at least 1 hour before or 4–6 hours after bile acid sequestrants; may be improved glucose tolerance and an additive effect when insulin or sulfonylureas given with fibrates; separating administration from linagliptin by 12 hours advised by manufacturer of lomitapide.
- Oestrogens: hypoglycaemic effect of antidiabetics antagonised by oestrogens.
- Orlistat: avoidance of acarbose advised by manufacturer of orlistat.
- Pancreatin: hypoglycaemic effect of acarbose antagonised by pancreatin.
- Progestogens: hypoglycaemic effect of antidiabetics antagonised by progestogens.
- Sulfinpyrazone: effects of sulfonylureas enhanced by sulfinpyrazone.
- Teriflunomide: plasma concentration of repaglinide increased by teriflunomide.
- Testosterone: hypoglycaemic effect of antidiabetics possibly enhanced by testosterone.
- Ulcer-healing Drugs: excretion of metformin reduced by cimetidine (increased plasma concentration); hypoglycaemic effect of sulfonylureas enhanced by cimetidine.

Anti-epileptics see Carbamazepine, Eslicarbazepine, ethosuximide, fosphenytoin, gabapentin, lactosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, Phenobarbital, phenytoin, pregabalin, primidone, retigabine, Rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, valproic acid, vigabatrin, and zonisamide.

Anti-fungals see Amphotericin; Anti-fungals; Imidazole; Anti-fungals; Triazole; caspofungin; flucytosine; griseofulvin; micafungin; itraconazole; lamotrigine, levetiracetam, oxcarbazepine, perampanel, ethosuximide, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, valproic acid, vigabatrin, and zonisamide.

Antifungals see Amphotericin; Anti-fungals; Imidazole; Anti-fungals; Triazoles; caspofungin; flucytosine; griseofulvin; micafungin; itraconazole.

Anti-fungals, imidazole

- Alcohol: possibility of disulfiram-like reaction when ketoconazole given with alcohol.
- Aliskiren: ketoconazole increases plasma concentration of aliskiren.
- Alpha-blockers: ketoconazole possibly increases plasma concentration of alfuzosin; ketoconazole increases plasma concentration of tamsulosin.
- Aminophylline: ketoconazole possibly increases plasma concentration of aminophylline.
Interactions

Antifungals, Imidazole

Antimuscarinics: ketoconazole increases metabolism of
- BUPRENORPHINE (reduce dose of buprenorphine); possible increased risk of ventricular arrhythmias when ketoconazole given with METHADONE — manufacturer of ketoconazole advises avoid concomitant use; ketoconazole increases plasma concentration of OXYCODONE; manufacturer of ketoconazole advises avoid concomitant use with PARACETAMOL

Antacids: absorption of ketoconazole reduced by ANTACIDS

Antihistamines: ketoconazole increases plasma concentration of PRAZIQUENTAL

Anti-arrhythmics: increased risk of ventricular arrhythmias when ketoconazole given with DISOPYRAMIDE — avoid concomitant use; ketoconazole increases plasma concentration of DRONEDARONE — avoid concomitant use

Antibacterials: manufacturer of ketoconazole advises avoid concomitant use
- CLARITHROMYCIN in severe renal impairment; metabolism of ketoconazole accelerated byrifampicin (reduced plasma concentration), also plasma concentration of rifampicin may be reduced by ketoconazole; ketoconazole increases plasma concentration of BEDAQUILINE — avoid concomitant use if ketoconazole given for more than 14 days; avoidance of ketoconazole advised by manufacturer of FIDAXOMICIN; plasma concentration of ketoconazole possibly reduced byisoniazid; ketoconazole increases the plasma concentration of telithromycin — avoid in severe renal and hepatic impairment

Anticoagulants: ketoconazole increases plasma concentration of
- APIXABAN — manufacturer of apixaban advises avoid concomitant use; ketoconazole enhances anticoagulant effect of coumarins; miconazole (including oral gel and possibly vaginal and topical formulations) greatly enhances the anticoagulant effect of coumarins — avoid concomitant use if possible; ketoconazole increases plasma concentration of dabigatran and rivaroxaban — avoid concomitant use; ketoconazole increases plasma concentration of edoxaban (reduce dose of edoxaban — see under Edoxaban, p. 118)

Antidepressants: avoidance of imidazoles advised by manufacturer of reboxetine; ketoconazole increases plasma concentration of mirtazapine

Antidiabetics: miconazole enhances hypoglycaemic effect of
- GLICLIZIDE and GLIPIZIDE — avoid concomitant use; ketoconazole increases plasma concentration of pioglitazone, saxagliptin and tolbutamide; miconazole increases plasma concentration of sulfonylureas

Antiepileptics: plasma concentration of ketoconazole possibly reduced by CARBAMAZEPINE, also plasma concentration of carbamazepine possibly increased; miconazole possibly increases plasma concentration of carbamazepine; miconazole enhances anticonvulsant effect of fosphenytoin and phenytoin (plasma concentration of fosphenytoin and phenytoin increased); plasma concentration of ketoconazole reduced by fosphenytoin and phenytoin; ketoconazole increases plasma concentration of perampanel

Antifungals: imidazoles possibly antagonise effects of
- GLICLIZIDE and GLIPIZIDE — avoid concomitant use; ketoconazole increases plasma concentration of pioglitazone, saxagliptin and tolbutamide; miconazole increases plasma concentration of sulfonylureas

Antihistamines: avoidance of imidazoles advised by manufacturer of arteether with lumefantrine; avoidance of imidazoles advised by manufacturer of arteminol with piperaquine (possible risk of ventricular arrhythmias); ketoconazole increases plasma concentration of mefloquine

Antimuscarinics: concentration of Darifenacin — avoid concomitant use; manufacturer of fesoterodine advises dose reduction when ketoconazole given with fesoterodine — consult fesoterodine product literature; ketoconazole increases plasma concentration of oxybutynin; ketoconazole increases plasma concentration of solifenacin — see under Solifenacin, p. 713; avoidance of ketoconazole advised by manufacturer of tolterodine

Antipsychotics: ketoconazole inhibits metabolism of
- ARIPIPRAZOLE (reduce dose of aripiprazole); ketoconazole increases plasma concentration of lurasidone — avoid concomitant use; increased risk of ventricular arrhythmias when imidazoles given with pimozide — avoid concomitant use; imidazoles possibly increase plasma concentration of quetiapine — manufacturer of quetiapine advises avoid concomitant use

Antivirals: ketoconazole increases plasma concentration of
- BOCEPREVIR; ketoconazole increases the plasma concentration of daclatasvir — reduce dose of daclatasvir (see under Daclatasvir, p. 577); plasma concentration of both drugs increased when ketoconazole given with sarunavir; plasma concentration of both drugs increased when ketoconazole given with dasabuvir and paritaprevir — avoid concomitant use; plasma concentration of ketoconazole reduced by efavirenz; plasma concentration of ketoconazole increases fosamprenavir (also plasma concentration of fosamprenavir possibly increased); ketoconazole increases plasma concentration of indinavir and maraviroc (consider reducing dose of indinavir and maraviroc); plasma concentration of ketoconazole reduced by riuvirapine — avoid concomitant use; avoidance of ketoconazole advised by manufacturer of omibitasvir and pimodutar; ketoconazole increases plasma concentration of saquinavir — manufacturer of ketoconazole advises avoid concomitant use; imidazoles possibly increase plasma concentration of saquinavir; plasma concentration of both drugs possibly increased when ketoconazole given with telaprevir (increased risk of ventricular arrhythmias) — reduce dose of ketoconazole

Anxiolytics and Hypnotics: ketoconazole increases plasma concentration of
- ALPRAZOLAM — manufacturer of ketoconazole advises avoid concomitant use; ketoconazole increases plasma concentration of midazolam (risk of prolonged sedation — avoid concomitant use of oral midazolam); ketoconazole increases plasma concentration of zolpidem

Aprepitant: ketoconazole increases plasma concentration of
- AVAPRALIL — avoid concomitant use

Beta-blockers: ketoconazole possibly increases plasma concentration of nadolol

Bosentan: ketoconazole increases plasma concentration of
- BOSENTAN

Calcium-channel Blockers: ketoconazole inhibits metabolism of
- FELODIPINE (increased plasma concentration) — manufacturer of ketoconazole advises avoid concomitant use; avoidance of ketoconazole advised by manufacturer of lercanidipine; ketoconazole possibly inhibits metabolism of dihydropyridines (increased plasma concentration)

Cannabis Extract: ketoconazole increases plasma concentration of
- CANNABIS EXTRACT

Ciclosporin: ketoconazole inhibits metabolism of
- CICLOSPORIN (increased plasma concentration); miconazole possibly inhibits metabolism of ciclosporin (increased plasma concentration)

Cilostazol: ketoconazole increases plasma concentration of
- CILOSTAZOL (see under Cilostazol, p. 221)

Cinacalcet: ketoconazole inhibits metabolism of cinacalcet (increased plasma concentration)

Crontaurogels: ketoconazole possibly reduces antiplatelet effect of clopidogrel

Cobicistat: plasma concentration of ketoconazole possibly increased by cobicistat — manufacturer of cobicistat advises reduce dose of ketoconazole

Colchicine: ketoconazole possibly increases risk of colchicine toxicity — suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)

Corticosteroids: ketoconazole possibly inhibits metabolism of corticosteroids; ketoconazole increases the plasma concentration of inhaled and oral (and possibly also intranasal...
Antifungals, Imidazole

- Corticosteroids (continued) and rectal: Budesonide; ketoconazole increases plasma concentration of active metabolite of Ciclesonide; ketoconazole possibly increases plasma concentration of inhaled fluticasone; ketoconazole inhibits the metabolism of methyprednisolone; ketoconazole increases plasma concentration of inhaled mometasone.
- Cytotoxic: ketoconazole inhibits the metabolism of ifosfamide; possible increased risk of neutropenia when ketoconazole given with Bremtuximab vedotin; ketoconazole possibly increases the plasma concentration of afatinib—manufacturer of afatinib advises separating administration of ketoconazole by 6 to 12 hours; ketoconazole increases plasma concentration of axitinib (reduce dose of axitinib—consult axitinib product literature); ketoconazole increases the plasma concentration of bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; ketoconazole increases plasma concentration of bortezomib, cabozantinib, dabrafenin, etoposide, idelalisib, imatinib, nintedanib and ponatinib; ketoconazole increases plasma concentration of certinib—avoid concomitant use or consider reducing the dose of certinib (see under Certinib, p. 861); ketoconazole increases plasma concentration of crizotinib, lapatinib, nilotinib and regorafenib—avoid concomitant use; ketoconazole possibly increases plasma concentration of dasatinib; ketoconazole inhibits metabolism of erlotinib and sunitinib (increased plasma concentration); ketoconazole increases plasma concentration of everolimus—manufacturer of ketoconazole advises avoid concomitant use; ketoconazole increases plasma concentration of ibrutinib—reduce dose of ibrutinib (see under Ibrutinib, p. 861); ketoconazole increases plasma concentration of pazopanib (reduce dose of pazopanib); manufacturer of ruxolitinib advises dose reduction when ketoconazole given with ruxolitinib—consult ruxolitinib product literature; ketoconazole increases plasma concentration of the active metabolite of temsirolimus—avoid concomitant use; avoidance of ketoconazole advised by manufacturer of cabazitaxel; in vitro studies suggest a possible interaction between ketoconazole and docetaxel (consult docetaxel product literature); ketoconazole reduces plasma concentration of irinotecan (but concentration of active metabolite of irinotecan increased)—avoid concomitant use; ketoconazole increases plasma concentration of vinflunine—manufacturer of vinflunine advises avoid concomitant use.
- Dapoxetine: ketoconazole increases plasma concentration of dapoxetine—manufacturer of dapoxetine advises avoid concomitant use.
- Diuretics: ketoconazole increases plasma concentration of eplerenone—avoid concomitant use; domperidone: manufacturer of ketoconazole advises avoid concomitant use with domperidone (risk of ventricular arrhythmias).
- Ergot Alkaloids: manufacturer of ketoconazole advises avoid concomitant use with ergot alkaloids; increased risk of ergotism when imidazoles given with ergotamine—avoid concomitant use.
- Fingolimod: ketoconazole increases plasma concentration of fingolimod.
- Fosaprepitant: ketoconazole increases plasma concentration of fosaprepitant.
- Guanfacine: ketoconazole increases plasma concentration of guanfacine (halve dose of guanfacine).
- Hormone Antagonists: manufacturer of ketoconazole advises avoid concomitant use with pasireotide.
- SHT2 receptor Agonists: ketoconazole increases plasma concentration of almotriptan (increased risk of toxicity); ketoconazole increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use.
- Ibrutinib: ketoconazole increases plasma concentration of ivabradine—avoid concomitant use.

Antifungals, Imidazole (continued)

Ivacaftor: ketoconazole increases plasma concentration of ivacaftor—reduce dose of ivacaftor (see under Ivacaftor in BNF or BNFC, and Lumacaftor with Ivacaftor in BNF or BNFC).
- Lanthanum: absorption of ketoconazole possibly reduced by lanthanum (give at least 2 hours apart).
- Lenalidomide: ketoconazole possibly increases plasma concentration of lenalidomide (increased risk of toxicity).
- Lipid-regulating Drugs: possible increased risk of myopathy when imidazoles given with atorvastatin; possible increased risk of myopathy when ketoconazole given with atorvastatin—manufacturer of ketoconazole advises avoid concomitant use; possible increased risk of myopathy when miconazole given with simvastatin; ketoconazole increases plasma concentration of lobitapide—avoid concomitant use.
- Lumacaftor: plasma concentration of ketoconazole possibly reduced by lumacaftor (see under Lumacaftor with Ivacaftor in BNF or BNFC).
- Macitentan: ketoconazole increases plasma concentration of macitentan.
- Mirabegron: when given with ketoconazole avoid or reduce dose of mirabegron in hepatic or renal impairment—see Mirabegron, p. 715.
- Naloxegol: ketoconazole increases plasma concentration of naloxegol—avoid concomitant use.
- Netupitant: ketoconazole possibly increases plasma concentration of netupitant.
- Oestrogens: anecdotal reports of contraceptive failure when imidazoles given with oestrogens; ketoconazole increases plasma concentration of ethinylestradiol.
- Panobinostat: ketoconazole increases plasma concentration of panobinostat (reduce dose of panobinostat—see under Panobinostat, p. 834).
- Parasympathomimetics: ketoconazole increases plasma concentration of galantamine.
- Progestogens: ketoconazole increases plasma concentration of drospirenone.
- Ranolazine: ketoconazole increases plasma concentration of ranolazine—avoid concomitant use.
- Retinoids: ketoconazole increases plasma concentration of altiretinoin; ketoconazole possibly increases risk of tretinoin toxicity.
- Riociguat: avoidance of ketoconazole advised by manufacturer of riociguat.
- Sildenafil: ketoconazole increases plasma concentration of sildenafil—reduce initial dose of sildenafil for erectile dysfunction and avoid concomitant use of sildenafil for pulmonary hypertension.
- Sirolimus: ketoconazole increases plasma concentration of sirolimus—avoid concomitant use; miconazole increases plasma concentration of sirolimus.
- Sympathomimetics, Beta: ketoconazole increases plasma concentration of olsalazine (increased plasma concentration).
- Tacrolimus: ketoconazole increases plasma concentration of tacrolimus (consider reducing dose of tacrolimus); miconazole oral gel possibly increases plasma concentration of tacrolimus.
- Tadalafil: ketoconazole increases plasma concentration of tadalafl—avoid concomitant use of tadalafl for pulmonary hypertension.
- Theophylline: ketoconazole possibly increases plasma concentration of theophylline.
- Ticagrelor: ketoconazole increases plasma concentration of ticagrelor—manufacturer of ticagrelor advises avoid concomitant use.
- Tolvaptan: ketoconazole increases plasma concentration of tolvaptan—manufacturer of ketoconazole advises avoid concomitant use.
- Ulcer-healing Drugs: absorption of ketoconazole reduced by histamine H2-antagonists, proton pump inhibitors and sucralfate.
Antifungals, Imidazole (continued)

- Ulipristal: ketoconazole increases plasma concentration of low-dose ULIPRISTAL—manufacturer of low-dose ulipristal advises avoid concomitant use
- Vardenafil: ketoconazole increases plasma concentration of VARDENAFIL—avoid concomitant use
- Vitamins: miconazole possibly reduces effects of ALFACALCIDIOL, CALCITRIOL, COLECALCIFEROL, DIHYDROXYCHOLESTEROL, ERGOCALCIFEROL, PARICALCITOL and VITAMIN D; ketoconazole possibly increases plasma concentration of PARICALCITOL

Antifungals, Polyene see Amphotericin

Antifungals, Triazole

NOTE In general, fluconazole interactions relate to multiple-drug treatment.

- Aliskiren: itraconazole increases plasma concentration of ALISKIREN—avoid concomitant use
- Aminophylline: fluconazole possibly increases plasma concentration of AMINOPHYLLINE
- Analgesics: fluconazole increases plasma concentration of CELECOXIB (halve dose of celecoxib); voriconazole increases plasma concentration of DICLOFENAC, IBUPROFEN and OXYCODONE; fluconazole increases plasma concentration of FLURBIPROFEN, IBUPROFEN and METHADONE; fluconazole increases plasma concentration of PARECOXIB (reduce dose of parecoxib); voriconazole increases plasma concentration of ALFENTANIL and METHADONE (consider reducing dose of alfentanil and methadone); fluconazole inhibits metabolism of ALFENTANIL (risk of prolonged or delayed respiratory depression); itraconazole possibly inhibits metabolism of ALFENTANIL; triazoles possibly increase plasma concentration of ▶ FENTANYL; itraconazole possibly increases plasma concentration of ▶ METHADONE (increased risk of ventricular arrhythmias); itraconazole increases plasma concentration of OXYCODONE

Antacids: absorption of itraconazole reduced by ANTACIDS
- Anti-arrhythmics: manufacturer of itraconazole advises avoid concomitant use with ▶ DISOPYRAMIDE; avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of ▶ DRONERADONE
- Antibacterials: plasma concentration of itraconazole increased by CLARITHROMYCIN; manufacturer of fluconazole advises avoid concomitant use with ERYTHROMYCIN; triazoles possibly increase plasma concentration of ▶ RIFABUTIN (increased risk of uveitis—reduce rifabutin dose); plasma concentration of isavucnozole possibly reduced by ▶ RIFABUTIN—avoid concomitant use; posaconazole increases plasma concentration of ▶ RIFABUTIN (also plasma concentration of posaconazole reduced); voriconazole increases plasma concentration of ▶ RIFABUTIN, also rifabutin reduces plasma concentration of voriconazole (increased risk of uveitis and also monitor for rifabutin toxicity); fluconazole increases plasma concentration of ▶ RIFABUTIN (increased risk of uveitis—reduce rifabutin dose); plasma concentration of itraconazole reduced by ▶ RIFABUTIN and ▶ RIFAMPICIN—manufacturer of itraconazole advises avoid concomitant use; plasma concentration of isavucnozole and voriconazole reduced by ▶ RIFAMPICIN—avoid concomitant use; plasma concentration of posaconazole reduced by ▶ RIFAMPICIN; metabolism of fluconazole accelerated by ▶ RIFAMPICIN (reduced plasma concentration); fluconazole possibly increases plasma concentration of BEDAQUILINE—avoid concomitant use if fluconazole given for more than 14 days
- Anticoagulants: avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of APIXABAN; fluconazole, itraconazole and voriconazole enhance anticoagulant effect of ▶ COUMARINS; avoidance of itraconazole advised by manufacturer of DABIGATRAN and RIVAROXABAN; avoidance of posaconazole and voriconazole advised by manufacturer of RIVAROXABAN
- Antidepressants: avoidance of triazoles advised by manufacturer of ▶ REBOXETINE; fluconazole possibly increases plasma concentration of AMITRIPYLILINE and NORTRIPTYLILINE; plasma concentration of voriconazole reduced by ▶ ST JOHN’S WORT—avoid concomitant use; plasma concentration of isavucnozole possibly reduced by ▶ ST JOHN’S WORT—avoid concomitant use

Antifungals, Triazole (continued)

- Anti-diabetics: isavucnozole increases plasma concentration of METFORMIN; posaconazole possibly enhances hypoglycaemic effect of GLIPIZIDE; fluconazole possibly enhances hypoglycaemic effect of NATEGILINIDE; itraconazole possibly enhances hypoglycaemic effect of NATEGILINIDE; Voriconazole increases plasma concentration of SULFONYLUREAS; voriconazole possibly increases plasma concentration of SULFONYLUREAS
- Antiepileptics: plasma concentration of itraconazole and posaconazole possibly reduced by ▶ CARBAMAZEPINE; plasma concentration of isavucnozole and voriconazole possibly reduced by ▶ CARBAMAZEPINE—avoid concomitant use; fluconazole possibly increases plasma concentration of CARBAMAZEPINE; plasma concentration of isavucnozole possibly reduced by ▶ FOSPHENYTOIN; PHENOBARBITAL; ▶ PHENYOIN and ▶ PRIMIDONE—avoid concomitant use; plasma concentration of itraconazole reduced by ▶ FOSPHENYTOIN and ▶ PHENYOIN (consider reducing dose of fosphenytoin and phenytoin); voriconazole increases plasma concentration of ▶ FOSPHENYTOIN and ▶ PHENYOIN; plasma concentration of itraconazole possibly reduced by ▶ PHENOBARBITAL and ▶ PRIMIDONE—avoid concomitant use; plasma concentration of itraconazole and posaconazole possibly reduced by ▶ PRIMIDONE
- Antifungals: plasma concentration of isavucnozole increased by ▶ KETOCONAZOLE—avoid concomitant use; triazoles possibly antagonise effects of AMPHOTERICIN; monitoring for increased voriconazole side effects advised by manufacturer of FLUCONAZOLE if voriconazole given after fluconazole; plasma concentration of itraconazole increased by MICAFUNGIN (consider reducing dose of itraconazole); plasma concentration of fluconazole increased by TERBINAFINE
- Antihistamines: itraconazole inhibits metabolism of ▶ MIZOLASTINE—avoid concomitant use
- Anti-malarials: avoidance of triazoles advised by manufacturer of ▶ ARTEMETHER WITH LUMEFANTRINE; avoidance of triazoles advised by manufacturer of ▶ ARTENIOL WITH PIPERAQUINE (possible risk of ventricular arrhythmias)
- Antimuscarnics: avoidance of itraconazole advised by manufacturer of ▶ DARIFENACIN and TOLERODINE; manufacturer of fesoterodine advises dose reduction of ▶ DARIFENACIN—avoid concomitant use; itraconazole given with ▶ FESOTERODINE—consult fesoterodine product literature; itraconazole possibly increases plasma concentration of ▶ SOLifenacin—see under Solifenacin, p. 715
- Antipsychotics: itraconazole possibly increases plasma concentration of ▶ HALOPERIDOL; itraconazole possibly increases plasma concentration of ▶ ARIPIPRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); itraconazole, posaconazole and voriconazole possibly increase plasma concentration of ▶ ARIPIPRAZOLE; ▶ IBUPROFEN and ▶ RIFAMICIN; metabolism of fluconazole accelerated by ▶ FOSPHENYTOIN; ▶ PHENOBARBITAL, ▶ PHENYOIN and ▶ PRIMIDONE—avoid concomitant use; plasma concentration of itraconazole and posaconazole possibly reduced by ▶ PRIMIDONE; itraconazole possibly increases plasma concentration of ▶ QUetiapine—manufacturer of quetiapine advises avoid concomitant use; itraconazole possibly increases side-effects of ▶ RISPERIDONE
- Antivirals: plasma concentration of voriconazole increased or decreased by ▶ ATAZANAVIR and plasma concentration of atazanavir also reduced; posaconazole increases plasma concentration of ▶ ATAZANAVIR; itraconazole, posaconazole and voriconazole possibly increase the plasma concentration of ▶ DAclatasvir—reduce dose of daclatasvir (see under Dacatasvir, p. 577); plasma concentration of voriconazole possibly affected by ▶ DARUNAVIR; plasma concentration of both drugs possibly increased when itraconazole and posaconazole
Interactions

**Antifungals, Triazole**

- **Antivirals (continued)**
  - given with **DASABUVIR**—avoid concomitant use; plasma concentration of itraconazole and posaconazole reduced by **EFAVIREN**; plasma concentration of voriconazole reduced by **EFAVIREN**; plasma concentration of efavirenz increased (increase voriconazole dose and reduce efavirenz dose); manufacturer of isavuconazole advises avoid concomitant use with **EFAVIREN** and **ETRAVIRINE**; plasma concentration of posaconazole possibly reduced by **FOSAMPREN**; plasma concentration of both drugs may increase when itraconazole given with **FOSAMPREN**; isavuconazole reduces plasma concentration of **INDINAVI**; itraconazole increases plasma concentration of **INDINAVI** (consider reducing dose of indinavir); plasma concentration of itraconazole increased by **LOPINAVI** (also plasma concentration of Lopinavir reduced); fluconazole increases plasma concentration of **NEVIRAPINE, RITONAVI** and **TIPRANA**; plasma concentration of itraconazole possibly reduced by **NEVIRAPINE**—consider increasing dose of itraconazole; plasma concentration of both drugs possibly increased when itraconazole and posaconazole given with **PARITAPRE**—avoid concomitant use; plasma concentration of isavuconazole increased by **RITONAVI** (also plasma concentration of ritonavir reduced) avoid concomitant use of high-dose ritonavir; combination of itraconazole with **RITONAVI** may increase plasma concentration of either drug (or both); plasma concentration of voriconazole reduced by **RITONAVI**—avoid concomitant use; triazoles possibly increase plasma concentration of **SAQUINAVI**; fluconazole, itraconazole, posaconazole and voriconazole possibly increase plasma concentration of **SIMPEPRE**—manufacturer of simprevir advises avoid concomitant use; plasma concentration of voriconazole possibly affected by **TELAPRE** (possible increased risk of ventricular arrhythmias); plasma concentration of posaconazole possibly increased by **TELAPRE** (increased risk of ventricular arrhythmias); plasma concentration of itraconazole possibly increased by **TELAPRE**; fluconazole increases plasma concentration of **ZIDOVUDI** (increased risk of toxicity)
  - Amiodolys and Hypnotics: itraconazole increases plasma concentration of **ALPAZOLAM**; fluconazole and voriconazole increase plasma concentration of **DIAZEPAM** (risk of prolonged sedation); isavuconazole increases plasma concentration of **MIDAZOLAM**; fluconazole, itraconazole, posaconazole and voriconazole increase plasma concentration of **MIDAZOLAM** (risk of prolonged sedation); itraconazole increases plasma concentration of **BUSPIRONE** (reduce dose of buspirone)
  - Avanafil: itraconazole and voriconazole possibly increase plasma concentration of **AVANAFIL**—manufacturer of avanafil advises avoid concomitant use; fluconazole possibly increases plasma concentration of **AVANAFIL**—see under Avanafil, p. 744
  - Bosentan: fluconazole possibly increases plasma concentration of **BOSENTAN**—avoid concomitant use; itraconazole possibly increases plasma concentration of **BOSENTAN**
  - Calcium-channel Blockers: negative inotropic effect possibly increased when itraconazole given with **CALCIUM-CHANNEL BLOCKERS**; itraconazole inhibits metabolism of **FELODIPINE** (increased plasma concentration); avoidance of itraconazole advised by manufacturer of **LERCANDIPIN**; itraconazole possibly inhibits metabolism of **HYDRODROPYRIDINES** (increased plasma concentration)
  - Cardiac Glicosides: isavuconazole and itraconazole increase plasma concentration of **DIGOXIN**
  - Cilostazol: isavuconazole increases plasma concentration of **CILOSTAZOL**; fluconazole, itraconazole, posaconazole and voriconazole inhibit metabolism of **CILOSTAZOL** (increased plasma concentration)
  - Docetaxel: itraconazole possibly increases plasma concentration of **EPLERENONE** (reduce dose of eplerenone); itraconazole increases plasma concentration of **EPLERENONE**—avoid
  - Eplerenone: manufacturer of eplerenone advises dose reduction when fluconazole given with **DAPOXETINE** (see under Dapoxetine, p. 751); avoidance of itraconazole advised by manufacturer of **DAPOXETINE** (increased risk of toxicity)
  - **Diuretics**: fluconazole increases plasma concentration of **FLUTICASONE** (inhaled) increases risk of **COLCHICINE** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
  - Corticosteroids: itraconazole possibly inhibits metabolism of **CORTICOSTEROIDS** and **METHYLPREDNISOLON**; itraconazole increases the plasma concentration of **CORTICOSTEROIDS** and **METHYLPREDNISOLON**; itraconazole increases plasma concentration of **HILOFLUCI**
  - Cytoxics: itraconazole inhibits metabolism of **BUSULFAN** (increased risk of toxicity); fluconazole possibly increase side-effects of **CYCLOPHOSPHAMIDE**; itraconazole possibly increases the plasma concentration of **CABOZANTIN**; itraconazole, posaconazole and voriconazole possibly increase plasma concentration of **CEBITIBI**—avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 861); itraconazole and voriconazole possibly increase plasma concentration of **CRZITIBI**—manufacturer of crizotinib advises avoid concomitant use; avoidance of itraconazole advised by manufacturer of **LAPATIBI**; avoidance of itraconazole and voriconazole advised by manufacturer of **NILOTIBI**; itraconazole and voriconazole possibly increase plasma concentration of **EVEROLI**—manufacturer of everolimus advises avoid concomitant use; itraconazole increases plasma concentration of **GESITIBI**—reduce dose of efavirenz (also plasma concentration of lopinavir reduced); itraconazole and voriconazole possibly increase plasma concentration of **IBRUTINIB**—reduce dose of ibrutinib (see under ibrutinib, p. 867); avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of **DAZATIBI** and **TEMSELIMUS** (plasma concentration of dasatinib and temsirolimus possibly increased); itraconazole, posaconazole and voriconazole possibly increase plasma concentration of **EVEROLI**—manufacturer of everolimus advises avoid concomitant use; itraconazole increases plasma concentration of **FOSAMP**—reduce dose of pazopanib; itraconazole and voriconazole possibly increase plasma concentration of **PONATIB**—consider reducing initial dose of ponatinib (see under Ponatinib, p. 873); manufacturer of ruxolitinib advises dose reduction when fluconazole, itraconazole, posaconazole and voriconazole given with **RUXOLITINIB**—consult ruxolitinib product literature; itraconazole and voriconazole possibly increase plasma concentration of **CABAZITAXEL**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; itraconazole and voriconazole possibly increase plasma concentration of **DOCETAXEL**—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose; increased risk of toxicity when itraconazole given with **IRINOTECAN**—avoid concomitant use; fluconazole possibly increases plasma concentration of **IRINOTECAN**; itraconazole and voriconazole possibly increase plasma concentration of **IRINOTECAN**—reduce dose of irinotecan; itraconazole and voriconazole possibly increase plasma concentration of **ITAL */**
Antifungals, Triazole
● Diuretics (continued) concomitant use; plasma concentration of fluconazole increased by HYDROCHLOROTHIAZIDE
● Dopemidine: possible increased risk of ventricular arrhythmias when itraconazole or voriconazole given with • DOPERIDONE—avoid concomitant use
● Ergot Alkaloids: increased risk of ergotism when voriconazole given with • ERGOMETRINE—avoid concomitant use; manufacturer of itraconazole advises avoid concomitant use with • ERGOTAMINE (increased risk of ergotism); increased risk of ergotism when triazoles given with • ERGOTAMINE—avoid concomitant use
● Guanafacine: fluconazole, itraconazole and posaconazole possibly increase the plasma concentration of • GUANAFACINE (halve dose of guanafacine)
● 5HT1-receptor Agonists: itraconazole increases plasma concentration of • ELERTRIPTAN (risk of toxicity)—avoid concomitant use
● Ivabradine: fluconazole increases plasma concentration of IVABRADINE—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of • IVABRADINE—avoid concomitant use
● Ivacaftor: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of • IVACAFTOR—reduce dose of ivacaftor (see under Ivacaftor in BNF or BNFC); fluconazole increases plasma concentration of • IVACAFTOR—reduce dose of ivacaftor (see under Ivacaftor, p. 275)
● Lenalidomide: itraconazole possibly increases plasma concentration of • LENALIDOMIDE (increased risk of toxicity)
● Leukotriene Receptor Antagonists: fluconazole increases plasma concentration of ZAFIRILUKAST
● Lipid-regulating Drugs: isavuconazole increases plasma concentration of ATORVASTATIN; increased risk of myopathy when itraconazole, posaconazole or voriconazole given with • ATORVASTATIN; possible increased risk of myopathy when fluconazole given with • ATORVASTATIN or • SIMVASTATIN; fluconazole increases plasma concentration of FLUVASTATIN—possible increased risk of myopathy; itraconazole increases plasma concentration of • ROSUVASTATIN—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when itraconazole or posaconazole given with • SIMVASTATIN (avoid concomitant use); increased risk of myopathy when voriconazole given with • SIMVASTATIN; avoidance of triazoles advised by manufacturer of • LOMITAPIDE (plasma concentration of lomitapide possibly increased).
● Lumacaftor: plasma concentration of posaconazole and voriconazole possibly reduced by • LUMACAFTOR—reduce dose of lumacaftor with ivacaftor (see under Lumacaftor with Ivacaftor in BNF or BNFC); plasma concentration of itraconazole reduced by • LUMACAFTOR—reduce dose of lumacaftor with ivacaftor (see under Lumacaftor with Ivacaftor in BNF or BNFC)
● Mirabegron: when given with itraconazole avoid or reduce dose of • MIRABEGRON in hepatic or renal impairment—see Mirabegron, p. 715
● Mycophenolate: isavuconazole increases plasma concentration of MYCOPHENOLATE
● Naloxegol: itraconazole possibly increases plasma concentration of • NALOXEGOL—avoid concomitant use
● Oestrogens: plasma concentration of voriconazole increased by OESTROGENS
● Panobinostat: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of • PANOBINOSTAT (reduce dose of panobinostat—see under Panobinostat, p. 834)
● Progestogens: plasma concentration of voriconazole possibly increased by • PROGESTOGENS
● Ranolazine: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of • RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
● Retinoids: fluconazole and voriconazole possibly increase risk of • TRETINOIN toxicity

Antifungals, Triazole (continued)
● Riociguat: avoidance of itraconazole and voriconazole advised by manufacturer of • RIOCIUGAT
● Sildenafil: itraconazole increases plasma concentration of SILDENAFIL—reduce initial dose of sildenafil
● Sirolimus: isavuconazole increases plasma concentration of SIROLIMUS; fluconazole and posaconazole possibly increase plasma concentration of SIROLIMUS; itraconazole and voriconazole increase plasma concentration of • SIROLIMUS—avoid concomitant use
● Tacrolimus: isavuconazole increases plasma concentration of TACROLIMUS; fluconazole, itraconazole, posaconazole and voriconazole increase plasma concentration of • TACROLIMUS (consider reducing dose of tacrolimus)
● Tadalafil: itraconazole possibly increases plasma concentration of TADALAFIL
● Theophylline: fluconazole possibly increases plasma concentration of • THEOPHYLLINE
● Ulcer-healing Drugs: plasma concentration of posaconazole reduced by • CIMETIDINE and • ESOMEPRAZOLE—manufacturer of posaconazole suspension advises avoid concomitant use; plasma concentration of posaconazole possibly reduced by • FAMOTIDINE, • LANSOPRAZOLE, • NIZATIDINE, • OMEPRAZOLE, • PANTOPRAZOLE, • RABEPRAZOLE and • RANITIDINE—manufacturer of posaconazole suspension advises avoid concomitant use; voriconazole possibly increases plasma concentration of ESOMEPRAZOLE; voriconazole increases plasma concentration of OMEPRAZOLE (consider reducing dose of omeprazole); absorption of itraconazole reduced by • HISTAMINE H 2-ANTAGONISTS and • PROTON PUMP INHIBITORS
● Ulipristal: avoidance of itraconazole advised by manufacturer of • ULRIPRISTAL
● Vardenafil: itraconazole possibly increases plasma concentration of • VARDENAFIL—avoid concomitant use

Antihistamines
NOTE Sedative interactions apply to a lesser extent to the non-sedating antihistamines. Interactions do not generally apply to antihistamines used for topical action (including nasal and ocular preparations).
● Alcohol: increased sedative effect when antihistamines given with • ALCOHOL (possibly less effect with non-sedating antihistamines)
● Analgesics: sedative effects possibly increased when sedating antihistamines given with • OPIOID ANALGESICS
● Antacids: absorption of fexofenadine reduced by • ANTACIDS
● Anti-arrhythmics: increased risk of ventricular arrhythmias when mizolastine given with • AMIODARONE, • DISOPYRAMIDE or • FLECAINIDE—avoid concomitant use; manufacturer of mizolastine advises avoid concomitant use with • PROPafenONE (possible risk of ventricular arrhythmias)
● Antibacterials: manufacturer of loratadine advises plasma concentration possibly increased by • ERYTHROMYCIN; metabolism of mizolastine inhibited by • ERYTHROMYCIN—avoid concomitant use; increased risk of ventricular arrhythmias when mizolastine given with • MOXIFLOXACIN—avoid concomitant use; effects of fexofenadine possibly reduced by • RIFAMPICIN; metabolism of mizolastine possibly inhibited by • MACROLIDES (avoid concomitant use)
● Antidepressants: avoidance of mizolastine advised by manufacturer of • CITOPRAM and • ESICITALOPRAM (risk of ventricular arrhythmias); increased antimuscarinic and sedative effects when antihistamines given with • MAOIS or • TRICYCLICS; manufacturer of promethazine advises avoid for 2 weeks after stopping • MAOIS; manufacturer of hydroxyzine advises avoid concomitant use with • MAOIS; cyproheptadine possibly antagonises antidepressant effect of • SSRIS; possible increased antimuscarinic and sedative effects when antihistamines given with • TRICYCLIC-RELATED ANTIDEPRESSANTS
● Antidiabetics: thrombocyte count depressed when ketotifen given with • METFORMIN (manufacturer of ketotifen advises avoid concomitant use)
● Antifungals: metabolism of mizolastine inhibited by • ITRAConazole—avoid concomitant use; metabolism of mizolastine possibly inhibited by • MIDAZOLES (avoid concomitant use)
Antihistamines — Antipsychotics

Antihistamines (continued)
- Antimalarial: avoidance of mizolastine advised by manufacturer of ARTENIL with PIPIRAQUAINE (possible risk of ventricular arrhythmias)
- Antimuscarinics: increased risk of antimuscarinic side-effects when antimuscarinics given with ANTUSARCINICS
- Antivirals: plasma concentration of chlorphenamine possibly increased by LOPINAVIR; plasma concentration of non-sedating antihistamines possibly increased by RITONAVIR; increased risk of ventricular arrhythmias when mizolastine given with SAQUINAVIR — avoid concomitant use
- Anxiolytics and Hypnotics: increased sedative effect when antimuscarinics given with ANXIOLYTICS AND HYPNOTICS
- Beta-blockers: increased risk of ventricular arrhythmias when mizolastine given with SOTALOL — avoid concomitant use
- Betahistine: antihistamines theoretically antagonise effect of BETAHISTINE
- Cytotoxic: possible increased risk of ventricular arrhythmias when mizolastine given with VANDETANIB — avoid concomitant use
- Grapefruit Juice: plasma concentration of bilastine reduced by GRAPEFRUIT JUICE
- Histamine: antihistamines theoretically antagonise effects of HISTAMINE — manufacturer of histamine advises avoid concomitant use
- Symptomimetics: avoidance of antihistamines advised by manufacturer of MIDODRINE
- Ulcer-healing Drugs: manufacturer of loratadine advises plasma concentration possibly increased by Cimetidine; plasma concentration of hydroxyzine increased by Cimetidine
- Ulipristal: manufacturer of ulipristal advises give fexofenadine at least 1.5 hours before or after ULIPRISTAL

Antihistamines, Non-sedating see Antihistamines

Antihistamines, Sedating see Antihistamines

Antimalarials see Artemether with Lumefantrine, Artennirol with Piperaquine, Chloroquine, Hydroxychloroquine, Mefloquine, Primaquine, Proguanil, Pyrimethamine, and Quinine

Antimetabolites see Capecitabine, Cladribine, Cytarabine, Decitabine, Fludarabine, Fluorouracil, Gemcitabine, Mercaptopurine, Methotrexate, Pemetrexed, Raltitrexed, Tegafur, and Tioguanine

Antimuscarinics
NOTE Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation; concomitant use can also lead to confusion in the elderly. Interactions do not generally apply to antimuscarinics used by inhalation.
- Alcohol: increased sedative effect when hyoscine given with ALCOHOL
- Analgesics: possible increased risk of antimuscarinic side-effects when antimuscarinics given with CODEINE; increased risk of antimuscarinic side-effects when antimuscarinics given with NEFOPAM
- Anti-arhythmics: increased risk of ventricular arrhythmias when tolterodine given with AMIODARONE, DISOPYRAMIDE or FLECAINIDE; increased risk of antimuscarinic side-effects when antimuscarinics given with DISOPYRAMIDE
- Antibacterials: manufacturer of fesoterodine advises dose reduction when fesoterodine given with CLARITHROMYCIN and TELITHROMYCIN — consult fesoterodine product literature; manufacturer of tolterodine advises avoid concomitant use with CLARITHROMYCIN and ERYTHROMYCIN; plasma concentration of active metabolite of fesoterodine reduced by RIFAMPICIN — avoid concomitant use

Antidepressants: plasma concentration of darifenacin and procyclidine increased by PAROXETINE; increased risk of antimuscarinic side-effects when antimuscarinics given with MAOIS or TRICYCLICS; plasma concentration of active metabolite of fesoterodine possibly reduced by ST JOHN’S WORT — manufacturer of fesoterodine advises avoid concomitant use; possible increased antimuscarinic side-effects when antimuscarinics given with TRICYCLIC-RELATED ANTIDEPRESSANTS

Antimuscarinics (continued)
- Antiepileptics: plasma concentration of active metabolite of fesoterodine possibly reduced by CARBAMAZEPINE, PHENOBARBITAL and PHENYTOIN — manufacturer of fesoterodine advises avoid concomitant use
- Antifungals: antimuscarinics reduce absorption of KETOCONAZOLE; manufacturer of fesoterodine advises dose reduction when fesoterodine given with IRACONAZOLE and KETOCONAZOLE — consult fesoterodine product literature; plasma concentration of darifenacin increased by KETOCONAZOLE — avoid concomitant use; plasma concentration of solifenacin increased by KETOCONAZOLE — see under Solifenacin, p. 715; plasma concentration of oxybutynin increased by KETOCONAZOLE; manufacturer of tolterodine advises avoid concomitant use with IRACONAZOLE and KETOCONAZOLE; manufacturer of darifenacin advises avoid concomitant use with IRACONAZOLE; plasma concentration of solifenacin possibly increased by IRACONAZOLE — see under Solifenacin, p. 713
- Antihistamines: increased risk of antimuscarinic side-effects when antimuscarinics given with ANTIHISTAMINES
- Antipsychotics: antimuscarinics possibly reduce effects of HALOPERIDOL; increased risk of antimuscarinic side-effects when antimuscarinics given with CLOZAPINE; antimuscarinics reduce plasma concentration of PHENOTHIAZINES, but risk of antimuscarinic side-effects increased
- Antivirals: manufacturer of darifenacin advises avoid concomitant use with ATAZANAVIR, FOSAMPRENAVIR, INDINAVIR, LOPINAVIR, RITONAVIR, SAQUINAVIR and TIPRANAVIR; manufacturer of fesoterodine advises dose reduction when fesoterodine given with ATAZANAVIR, INDINAVIR, RITONAVIR and SAQUINAVIR; plasma concentration of solifenacin possibly increased by RITONAVIR — see under Solifenacin, p. 713
- Beta-blockers: increased risk of ventricular arrhythmias when tolterodine given with SOTALOL
- Calcium-channel Blockers: plasma concentration of solifenacin increased by VERA PATIL; manufacturer of darifenacin advises avoid concomitant use with VEPAMIL
- Cardiac Glycosides: darifenacin possibly increases plasma concentration of DIGOXIN
- Ciclosporin: manufacturer of darifenacin advises avoid concomitant use with CICLOSPORIN
- Dopaminergics: antimuscarinics possibly reduce absorption of DOBUTAMINE and LEVODOPA; increased risk of antimuscarinic side-effects when antimuscarinics given with CLOZAPINE; antimuscarinics reduce plasma concentration of PHENOTHIAZINES, but risk of antimuscarinic side-effects increased
- Memantine: effects of antimuscarinics possibly enhanced by MEMANTINE
- Metoclopramide: antimuscarinics antagonise effects of METOCLOPRAMIDE on gastro-intestinal activity
- Nitrites: antimuscarinics possibly reduce effects of sublingual tablets of NITRATES (failure to dissolve under tongue owing to dry mouth)
- Parasympathomimetics: antimuscarinics antagonise effects of PARASYMPATHOMIMETICS

Antipsychotics
NOTE Increased risk of toxicity with myelosuppressive drugs
NOTE Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis
- ACE Inhibitors: enhanced hypertensive effect when antipsychotics given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypertensive effect when phenothiazines given with ADRENERGIC NEURONE BLOCKERS; higher doses of chlorpromazine antagonise hypertensive effect of ADRENERGIC NEURONE BLOCKERS; haloperidol antagonises hypertensive effect of ADRENERGIC NEURONE BLOCKERS
- Adsorbents: absorption of phenothiazines possibly reduced by KAOLIN
- Alcohol: increased sedative effect when antipsychotics given with ALCOHOL
Antipsychotics (continued)

- Alpha-blockers: enhanced hypotensive effect when antipsychotics given with ALPHA-BLOCKERS
  - Anaesthetics, General: droperidol enhances effects of THIOPENTAL; enhanced hypotensive effect when antipsychotics given with GENERAL ANAESTHETICS
  - Analgesics: possible severe drowsiness when haloperidol given with ACETAMIN or INDOMETACIN; increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with METHADONE; increased risk of ventricular arrhythmias when amisulpride given with METHADONE—avoid concomitant use; increased risk of convulsions when antipsychotics given with TRAMADOL; enhanced hypotensive and sedative effects when antipsychotics given with OPIOID ANALGESICS
  - Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when antipsychotics given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
  - Antacids: absorption of phenothiazines and sulpiride reduced by ANTACIDS
  - Anti-arrhythmics: increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with ANTI-ARRHYTHMICS that prolong the QT interval; increased risk of ventricular arrhythmias when amisulpride, droperidol, haloperidol, phenothiazines, pimozide or zuclopenthixol given with AMIODARONE—avoid concomitant use; increased risk of ventricular arrhythmias when amisulpride, droperidol, haloperidol, phenothiazines, pimozide or zuclopenthixol given with AMIODARONE or DISOPYRAMIDE; increased risk of ventricular arrhythmias when benperidol given with AMIODARONE—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with DISOPYRAMIDE; increased risk of ventricular arrhythmias when amisulpride, droperidol, pimozide or zuclopenthixol given with DISOPYRAMIDE—avoid concomitant use; possible increased risk of ventricular arrhythmias when haloperidol given with DISOPYRAMIDE—avoid concomitant use; avoidance of phenothiazines advised by manufacturer of DRONEDARONE (risk of ventricular arrhythmias); increased risk of arrhythmias when amisulpride given with FLECAINIDE; possible increased risk of ventricular arrhythmias when pimozide given with FLECAINIDE; plasma concentration of lurasidone possibly increased by CLARITHROMYCIN and TELITHROMYCIN—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with CLARITHROMYCIN, MOXIFLOXACIN or TELITHROMYCIN—avoid concomitant use; plasma concentration of quetiapine possibly increased by CLARITHROMYCIN—manufacturer of quetiapine advises avoid concomitant use; plasma concentration of lurasidone possibly increased by CLARITHROMYCIN and TELITHROMYCIN—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with CLARITHROMYCIN, MOXIFLOXACIN or TELITHROMYCIN—avoid concomitant use; plasma concentration of quetiapine possibly increased by CLARITHROMYCIN—manufacturer of quetiapine advises avoid concomitant use; plasma concentration of lurasidone possibly increased by CLARITHROMYCIN—manufacturer of quetiapine advises avoid concomitant use; plasma concentration of lurasidone possibly increased by ERYTHROMYCIN—avoid concomitant use; plasma concentration of quetiapine possibly increased by ERYTHROMYCIN—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias with sulpiride given with parenteral ERYTHROMYCIN; increased risk of ventricular arrhythmias when zuclopenthixol given with parenteral ERYTHROMYCIN—avoid concomitant use; plasma concentration of clozapine increased by CIPROFLOXACIN; plasma concentration of olanzapine possibly increased by CIPROFLOXACIN; increased risk of ventricular arrhythmias when droperidol, haloperidol, phenothiazines or zuclopenthixol given with MOXIFLOXACIN—avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with MOXIFLOXACIN—manufacturer of benperidol advises avoid concomitant use; plasma concentration of aripiprazole possibly reduced by RIFAMPICIN and RIFABUTIN—avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of lurasidone reduced by RIFAMPICIN—avoid concomitant use; plasma concentration of clozapine possibly reduced by RIFAMPICIN; metabolism of haloperidol accelerated by

Antipsychotics

- Antibacterials (continued)
  - RIFAMPICIN (reduced plasma concentration); avoid concomitant use of clozapine with RIFAMPICIN; CHLORAMPHENICOL or SULFONAMIDES (increased risk of agranulocytosis); increased risk of ventricular arrhythmias when droperidol, haloperidol or pimozide given with DELAMANID; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with DELAMANID; manufacturer of droperidol advises avoid concomitant use with MACROLIDES (risk of ventricular arrhythmias); possible increased risk of ventricular arrhythmias when chlorpromazine given with TELITHROMYCIN; plasma concentration of quetiapine possibly increased by TELITHROMYCIN

- Antidepressants: plasma concentration of clozapine possibly increased by CITALOPRAM (increased risk of toxicity); avoidance of haloperidol, phenothiazines and pimozide advised by manufacturer of CITALOPRAM (risk of ventricular arrhythmias); avoidance of haloperidol, phenothiazines and pimozide advised by manufacturer of ESCITALOPRAM (risk of ventricular arrhythmias); plasma concentration of aripiprazole possibly increased by FLUOXETINE and PAROXETINE (reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of clozapine, haloperidol and risperidone increased by FLUOXETINE; manufacturer of droperidol advises avoid concomitant use with FLUOXETINE, FLUOXAMINE, SERTRALINE and TRICYCLICS (risk of ventricular arrhythmias); plasma concentration of asenapine and haloperidol possibly increased by FLUOXAMINE; plasma concentration of clozapine and olanzapine increased by FLUOXAMINE; asenapine possibly increases plasma concentration of PAROXETINE; plasma concentration of clozapine increased by PAROXETINE and SERTRALINE; plasma concentration of risperidone possibly increased by PAROXETINE (increased risk of toxicity); metabolism of perphenazine inhibited by PAROXETINE (reduce dose of perphenazine); plasma concentration of haloperidol increased by VENLAFAXINE; clozapine possibly increases CNS effects of MAOI; plasma concentration of pimozide possibly increased by SSRIS (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of lurasidone possibly reduced by ST JOHN’S WORT—avoid concomitant use; plasma concentration of aripiprazole possibly reduced by ST JOHN’S WORT (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); possible increased risk of ventricular arrhythmias when risperidone given with TRICYCLICS; possible increased antimuscarinic side-effects when clozapine given with TRICYCLICS; manufacturer of fluphenazine, haloperidol, sulpiride and zuclopenthixol advises avoid concomitant use with TRICYCLICS (risk of ventricular arrhythmias); increased risk of antimuscarinic side-effects when phenothiazines given with TRICYCLICS; possible increased risk of convulsions when butyrophenones, phenothiazines or thioxanthenes given with VORTOXETINE

- Antidiabetics: phenothiazines possibly antagonise hypoglycaemic effect of SULFONLUREAS

- Antiepileptics: antipsychotics antagonise anticonvulsant effect of ANTIPELICUTICS (convulsive threshold lowered); plasma concentration of lurasidone possibly reduced by CARBAMAZEPINE, PEPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE—avoid concomitant use; metabolism of haloperidol, olanzapine, quetiapine and risperidone accelerated by CARBAMAZEPINE (reduced plasma concentration); metabolism of clozapine accelerated by CARBAMAZEPINE (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; plasma concentration of aripiprazole reduced by CARBAMAZEPINE (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of paliperidone reduced by CARBAMAZEPINE; plasma concentration of haloperidol reduced by CARBAMAZEPINE, PEPHENYTOIN and PHENYTOIN; chlorpromazine possibly increases or decreases
Antipsychotics

Antiepileptics (continued)

plasma concentration of *FOSPHENYTOIN* and *PHENYTOIN*; metabolism of clozapine and quetiapine accelerated by *FOSPHENYTOIN* (reduced plasma concentration); plasma concentration of aripiprazole possibly reduced by *FOSPHENYTOIN*; *PHENOBARBITAL*, *PHENYTOIN* and *PRIMIDONE* (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of clozapine possibly reduced by *PHENOBARBITAL* and *PRIMIDONE*; metabolism of haloperidol accelerated by *PHENOBARBITAL* and *PRIMIDONE* (reduced plasma concentration); plasma concentration of both drugs reduced when chlorpromazine given with *PHENOBARBITAL* and *PRIMIDONE*; metabolism of clozapine and quetiapine inhibited by *PHENYTOIN*; possible increased plasma concentration; increased risk of side-effects including neutropenia when olanzapine given with *SODIUM VALPROATE* and *VALPROIC ACID*; plasma concentration of clozapine possibly increased or decreased by *SODIUM VALPROATE* and *VALPROIC ACID*.

Antifungals: plasma concentration of lurasidone increased by *KETOCONAZOLE*—avoid concomitant use; metabolism of aripiprazole possibly increased by *KETOCONAZOLE* (reduce dose of aripiprazole); plasma concentration of lurasidone possibly increased by *FLUCONAZOLE* (see under Lurasidone, p. 373); plasma concentration of lurasidone possibly increased by *ITRACONAZOLE*, *POSaconazole* and *VORICONAZOLE*—avoid concomitant use; plasma concentration of aripiprazole possibly increased by *ITRACONAZOLE* (reduce dose of aripiprazole—consult aripiprazole product literature); side-effects of risperidone possibly increased by *ITRACONAZOLE*; plasma concentration of haloperidol possibly increased by *ITRACONAZOLE*; increased risk of ventricular arrhythmias when pimozide given with *IMIDAZOLEs* or *TRIAZOLEs*—avoid concomitant use; plasma concentration of quetiapine possibly increased by *IMIDAZOLEs* and *TRIAZOLEs*—manufacturer of quetiapine advises avoid concomitant use.

Antimalarials: avoidance of antipsychotics advised by manufacturer of *ARTEMETHER WITH LUMEFANTRINE*; avoidance of droperidol, haloperidol, phenothiazines and pimozide advised by manufacturer of *ARTENIMOL WITH PIPERAQUINE* (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when droperidol given with *CHLOROQUINE*, *HYDROXYCHLOROQUINE* or *QUININE*—avoid concomitant use; possible increased risk of ventricular arrhythmias when haloperidol given with *MEFLOQUINE* or *QUININE*—avoid concomitant use; manufacturer of risperidone advises possible risk of ventricular arrhythmias when risperidone given with *MEFLOQUINE*; increased risk of ventricular arrhythmias when pimozide given with *MEFLOQUINE*; possible increased risk of ventricular arrhythmias when risperidone given with *QUININE*.

Antimuscarnics: increased risk of antimuscarnic side-effects when clozapine given with *ANTIMUSCARNICS*; plasma concentration of phenothiazines reduced by *ANTIMUSCARNICS*, but risk of antimuscarnic side-effects increased; effects of haloperidol possibly reduced by *ANTIMUSCARNICS*.

Antipsychotics: increased risk of ventricular arrhythmias when phenothiazine or sulphuride given with *DROPERIDOL*—avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazine that prolong the QT interval given with *DROPERIDOL*—avoid concomitant use; avoid concomitant use of clozapine with depot formulation of *FLUPENTIXOL*, *FLUPHENAZINE*, *HALOPERIDOL*, *RISPERIDONE* or *ZUCLOPENTHIXOL* as cannot be withdrawn quickly if neutropenia occurs; increased risk of ventricular arrhythmias when sulphuride given with *HALOPERIDOL*; chlorpromazine possibly increases plasma concentration of *HALOPERIDOL*; increased risk of ventricular arrhythmias when droperidol given with *HALOPERIDOL*—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with *PHENOTHIAZINES*—avoid concomitant use; lurasidone possibly increases plasma concentration of *HALOPERIDOL*; increased risk of ventricular arrhythmias when droperidol given with *HALOPERIDOL*—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with *PHENOTHIAZINES*—avoid concomitant use; lurasidone possibly increases plasma concentration of...
Antipsychotics

- COBICISTAT (continued)
  - COBICISTAT — manufacturer of cobicistat advises avoid concomitant use

- Cytotoxics: avoid concomitant use of clozapine with
  - CYTOTOXICS (increased risk of agranulocytosis); possible increased risk of ventricular arrhythmias when haloperidol given with • BOSUTINIB and • CERITINIB; avoidance of pimozide advised by manufacturer of CERITINIB, IDELALISIB and • LAPATINIB; possible increased risk of ventricular arrhythmias when droperidol given with • BOSUTINIB and • CERITINIB; caution with pimozide advised by manufacturer of • CRIZOTINIB; avoidance of quetiapine advised by manufacturer of IDELALISIB; possible increased risk of ventricular arrhythmias when amisulpride, chlorpromazine, haloperidol, pimozide, sulpiride or zuclopenthixol given with • VANDETANIB — avoid concomitant use; increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with • ARSENIC TRIXIOIDE; increased risk of ventricular arrhythmias when haloperidol given with • ARSENIC TRIXIOIDE

- Deferasirox: avoidance of clozapine advised by manufacturer of DEFERASIROX

- Desferrioxamine: manufacturer of levomepromazine advises avoid concomitant use with DESFERRIOXAMINE; avoidance of prochloperazine advised by manufacturer of DESFERRIOXAMINE

- Diazoxide: enhanced hypotensive effect when phenothiazines given with • DIAZOXIDE

- Diuretics: risk of ventricular arrhythmias with amisulpride increased by hypokalaemia caused by • DIURETICS; risk of ventricular arrhythmias with pimozide increased by hypokalaemia caused by • DIURETICS (avoid concomitant use); enhanced hypotensive effect when phenothiazines given with • DIURETICS

- Dopaminergics: increased risk of extrapyramidal side-effects when antipsychotics given with • AMANTADINE; antipsychotics antagonise effects of • APOMORPHINE, • CO-BENELDOPA, • CO-CARELDOPA, • LEVODOPA and • PERGOLIDE; antipsychotics antagonise hypoprolactinaemic and antiparkinsonian effects of • BROMOCRIPTINE and • CABERGOLINE; manufacturer of amisulpride advises avoid concomitant use of • CO-BENELDOPA, • CO-CARELDOPA and • LEVODOPA (antagonism of effect); avoidance of antipsychotics advised by manufacturer of • PRAMIPEXOLE, • ROPINIROLE and • ROTIGOTINE (antagonism of effect)

- Ergot Alkaloids: lurasidone possibly increases plasma concentration of • ERGOT ALKALOIDS (increased risk of toxicity)

- Fosaprepitant: avoidance of pimozide advised by manufacturer of • FOSAPREPTANT

- Grapefruit Juice: manufacturer of lurasidone and pimozide advises avoid concomitant use with • GRAPEFRUIT JUICE; plasma concentration of quetiapine possibly increased by • GRAPEFRUIT JUICE — manufacturer of quetiapine advises avoid concomitant use

- Guanfacine: sedative effects possibly increased when antipsychotics given with • GUANFACINE

- Histamine: antipsychotics theoretically antagonise effects of • HISTAMINE — manufacturer of histamine advises avoid concomitant use

- Hormone Antagonists: manufacturer of droperidol advises avoid concomitant use with • TAMOXIFEN (risk of ventricular arrhythmias)

- Ivabradine: increased risk of ventricular arrhythmias when pimozide given with • IVABRADINE

- Lithium: increased risk of extrapyramidal side-effects and possibly neurotoxicity when clozapine, flupentixol, haloperidol, phenothiazines, risperidone or zuclopenthixol given with • LITHIUM; possible risk of toxicity when olanzapine given with • LITHIUM; extrapyramidal side-effects of quetiapine possibly increased by • LITHIUM; increased risk of extrapyramidal side-effects when sulpiride given with • LITHIUM

- Memantine: effects of antipsychotics possibly reduced by • MEMANTINE

- Methyldopa: enhanced hypotensive effect when antipsychotics given with • METHYLDOPA (also increased risk of extrapyramidal effects)

Antipsychotics (continued)

- Metoclopramide: increased risk of extrapyramidal side-effects when antipsychotics given with • METOCLOPRAMIDE

- Moxonidine: enhanced hypotensive effect when phenothiazines given with • MOXONIDINE

- Muscle Relaxants: promazine possibly enhances effects of • SUXAMETHONIUM

- Nitrates: enhanced hypotensive effect when phenothiazines given with • NITRATES

- Panobinostat: possible increased risk of ventricular arrhythmias when pimozide given with • PANOBINOSTAT — avoid concomitant use

- Penicillamine: increased risk of haematological toxicity when clozapine given with • PENICILLAMINE — manufacturer of penicillamine advises avoid concomitant use

- Pentamidine isetionate: increased risk of ventricular arrhythmias when amisulpride or droperidol given with • PENTAMIDINE ISETIONATE — avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with • PENTAMIDINE ISETIONATE

- Sodium Benzoate: haloperidol possibly reduces effects of • SODIUM BENZOATE

- Sodium Oxybate: antipsychotics possibly enhance effects of • SODIUM OXYBATE

- Sodium Phenylbutyrate: haloperidol possibly reduces effects of • SODIUM PHENYL BUTYRATE

- Sympathomimetics: antipsychotics antagonise hypertensive effect of • SYMPATHOMIMETICS; antipsychotic effects of chlorpromazine possibly antagonised by • DEXAMFETAMINE; chlorpromazine possibly reduces effects of • Lisdexamfetamine; side-effects of risperidone possibly increased by • METHYLPHENIDATE

- Tacrolimus: manufacturer of droperidol advises avoid concomitant use with • TACROLIMUS (risk of ventricular arrhythmias)

- Tetrabenazine: increased risk of extrapyramidal side-effects when antipsychotics given with • TETRABENAZINE

- Uterus-Healing Drugs: effects of antipsychotics, chlorpromazine and clozapine possibly enhanced by • CIMETIDINE; plasma concentration of clozapine possibly reduced by • OMEPRAZOLE; absorption of sulpiride reduced by • SUCRALFATE

- Vasodilator Antihypertensives: enhanced hypotensive effect when phenothiazines given with HYDRAZALINE, MINOXIDIL or • SODIUM NITROPRUSSIDE

Antivirals see individual drugs

Anxiolytics and Hypnotics

- ACE Inhibitors: enhanced hypotensive effect when anxiolytics and hypnotics given with • ACE INHIBITORS

- Adrenergic Neurone Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with • ADRENERGIC NEURONE BLOCKERS

- Alcohol: increased sedative effect when anxiolytics and hypnotics given with • ALCOHOL

- Alpha-blockers: enhanced hypotensive and sedative effects when anxiolytics and hypnotics given with • ALPHA-BLOCKERS

- Aminophylline: effects of benzodiazepines possibly reduced by • AMINOPHYLLINE

- Anaesthetics, General: increased sedative effect when anxiolytics and hypnotics given with • GENERAL ANAESTHETICS

- Analgesics: metabolism of midazolam possibly inhibited by • FENTANYL; increased sedative effect when anxiolytics and hypnotics given with • OPIOID ANALGESICS

- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when anxiolytics and hypnotics given with • ANGIOTENSIN-II RECEPTOR ANTAGONISTS

- Antibacterials: metabolism of midazolam inhibited by • CLARITHROMYCIN, • ERYTHROMYCIN and • TELITROMYCIN (increased plasma concentration with increased sedation); plasma concentration of buspirone increased by • ERYTHROMYCIN (reduce dose of buspirone); metabolism of zopiclone inhibited by • ERYTHROMYCIN; manufacturer of zolpidem advises avoid concomitant use with • CIPROFLOXACIN; metabolism of benzodiazepines possibly accelerated by • RIFAMPICIN (reduced plasma concentration); metabolism of diazepam and zaleplon accelerated by • RIFAMPICIN (reduced plasma concentration); metabolism of buspirone possibly
Antivirals: plasma concentration of alprazolam increased by
FLUOXETINE; plasma concentration of metronidazole possibly increased by
SODIUM VALPROATE; plasma concentration of midazolam possibly increased by
fOSAPREPITANT (risk of prolonged sedation); plasma concentration of buspirone increased by
RITONAVIR and
FELAPREVIR (risk of prolonged sedation—avoid concomitant use of oral midazolam); increased risk of

Antihistamines: plasma concentration of midazolam increased by
FLOXICETINE; plasma concentration of lorazepam possibly increased by
SODIUM VALPROATE; plasma concentration of buspirone increased by
RITONAVIR (risk of prolonged sedation and respiratory depression—avoid concomitant use); plasma concentration of antivirals and hypnotics possibly increased by
RITONAVIR; plasma concentration of buspirone increased by
RITONAVIR (increased risk of toxicity); plasma concentration of midazolam increased by
SAQUINAVIR (risk of prolonged sedation—avoid concomitant use of oral midazolam); plasma concentration of oral midazolam increased by
SIMEPREVIR

Anxiolytics and Hypnotics — Anxiolytics and Hypnotics
Anxiolytics and Hypnotics (continued)

- Moxonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with moxonidine; sedative effects possibly increased when benzodiazepines given with moxonidine
- Muscle Relaxants: increased sedative effect when anxiolytics and hypnotics given with baclofen or tizanidine
- Netupitant: plasma concentration of midazolam increased by
- Nitrates: enhanced hypotensive effect when anxiolytics and hypnotics given with nitrates
- Oestrogens: plasma concentration of melatonin increased by oestrogens; plasma concentration of chlordiazepoxide, diazepam and nitrazepam possibly increased by oestrogens; plasma concentration of lorazepam, oxazepam and temazepam possibly reduced by oestrogens
- Progestogens: plasma concentration of chlordiazepoxide, diazepam and nitrazepam possibly increased by progestogens; plasma concentration of lorazepam, oxazepam and temazepam possibly reduced by progestogens
- Sodium Oxybate: benzodiazepines enhance effects of sodium oxybate (avoid concomitant use)
- Theophylline: effects of benzodiazepines possibly reduced by theophylline
- Uler-healing Drugs: plasma concentration of melatonin increased by cimetidine; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by cimetidine (increased plasma concentration); metabolism of diazepam possibly inhibited by esomeprazole and omeprazole (increased plasma concentration)
- Vasodilator Antihypertensives: enhanced hypotensive effect when anxiolytics and hypnotics given with hydralazine, minoxidil or sodium nitroprusside

Apixaban

- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous diclofenac (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant use, including low-dose heparins)
- Antibacterials: manufacturer of apixaban advises avoid concomitant use with clarithromycin and telithromycin; plasma concentration of apixaban possibly reduced by rifampicin — manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism
- Anticoagulants: increased risk of haemorrhage when apixaban given with other anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with dabigatran, edoxaban and rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antidepressants: plasma concentration of apixaban possibly reduced by st john’s Wort — manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism
- Antiepileptics: plasma concentration of apixaban possibly reduced by carbamazepine — manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism; plasma concentration of apixaban possibly reduced by fosphenytoin, phenobarbital, phenytoin and primidone
- Antifungals: plasma concentration of apixaban increased by daptomycin (alternative contraception recommended)
- Antihypertensives: enhanced hypotensive effect when anxiolytics and hypnotics given with hydralazine, minoxidil or sodium nitroprusside
- Antipsychotics: manufacturer of apixaban advises avoid concomitant use with maid, tricyclic-related antidepressants and tricyclics
- Sympathomimetics: manufacturer of apixaban advises avoid concomitant use with sympathomimetics

Apopemiphene

- Antipsychotics: effects of apomorphine antagonised by antipsychotics
- Domperidone: possible increased risk of ventricular arrhythmias when apomorphine given with domperidone
- Dopaminergics: effects of apomorphine possibly enhanced by entacapone
- SHT-receptor Antagonists: possible increased hypotensive effect when apomorphine given with ondansetron — avoid concomitant use
- Memantine: effects of dopaminergics possibly enhanced by memantine
- Methylpoda: antiparkinsonian effect of dopaminergics antagonised by methylpoda

Apreamiplatin

- Antibacterials: plasma concentration of apremilast reduced by rifampicin
- Anticoagulants: apremilast possibly reduces anticoagulant effect of warfarin
- Antidepressants: manufacturer of apremilast advises avoid concomitant use with st john’s Wort
- Antidiabetics: apremilast reduces plasma concentration of tolbutamide
- Antiepileptics: plasma concentration of apremilast possibly reduced by carbamazepine, fosphenytoin, phenobarbital and phenytoin
- Antifungals: plasma concentration of apremilast increased by ketoconazole
- Antipsychotics: manufacturer of apremilast advises avoid concomitant use with pimozide
- Antivirals: plasma concentration of apremilast possibly increased by ritonavir
- Anxiolytics and Hypnotics: apremilast increases plasma concentration of midazolam (risk of prolonged sedation)
- Apanafil: apremilast possibly increases plasma concentration of apanafil — see under Apanafil, p. 744
- Calcium-channel Blockers: plasma concentration of both drugs may increase when apanafil given with diltiazem
- Corticosteroids: apremilast inhibits metabolism of dexamethasone and methylprednisolone (reduce dose of dexamethasone and methylprednisolone)
- Cytotoxics: apremilast possibly increases plasma concentration of bosutinib — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; apremilast possibly increases the plasma concentration of ibritinib — reduce dose of ibritinib (see under Ibrutinib, p. 867)
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when apanafil given with dapoxetine (see under Dapoxetine, p. 751)
- Guanfacine: apremilast possibly increases plasma concentration of guanfacine (halve dose of guanfacine)
- Oestrogens: apremilast possibly causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended)
- Progestogens: apremilast possibly causes contraceptive failure of hormonal contraceptives containing progestogens (alternative contraception recommended)

Argatroban

- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous diclofenac (avoid...
Argatroban

- Analgesics (continued)
  - concomitant use, including low-dose heparins; increased risk of haemorrhage when anticoagulants given with RETOROLAC (avoid concomitant use, including low-dose heparins)
  - Anticoagulants: increased risk of haemorrhage when other anticoagulants given with APIXABAN, DABIGATRAN, EDOXABAN and RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Aripiprazole see Antipsychotics

Arsenic Trioxide

- Anti-arrhythmics: increased risk of ventricular arrhythmias when arsenic trioxide given with AMIODARONE or DISOPYRAMIDE
- Antibacterials: increased risk of ventricular arrhythmias when arsenic trioxide given with ANTIPSYCHOTICS that prolong the QT interval; increased risk of ventricular arrhythmias when arsenic trioxide given with HALOPERIDOL; avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
- Beta-blockers: increased risk of ventricular arrhythmias when arsenic trioxide given with AMITRIPTYLINE or CLOMIPRAMINE
- Antifungals: increased risk of ventricular arrhythmias when arsenic trioxide given with PENTAMIDINE ISETIONATE
- Antipsychotics: increased risk of ventricular arrhythmias when arsenic trioxide given with ANALGESICS
- Antidepressants: increased risk of ventricular arrhythmias when arsenic trioxide given with SOTALOL
- Antivirals: increased risk of ventricular arrhythmias when arsenic trioxide given with AZT, ATTIVILOX, CERVICALIX, ERTIVAX, GLOBEX, INHERION, IVACATIN, LOPINAVIR, Ritonavir, SANCIVAX and TIPRANAVIR; avoidance of antimalarials given with ATAZANAVIR, FOSAMPRENACIV, INIDINAVIR, LOPINAVIR, Ritonavir, SANCIVAX and TIPRANAVIR; avoidance of antimalarials given with BOCREPRAVIR; plasma concentration of lumefantrine increased when artemether with lumefantrine given with DARUNAVIR; plasma concentration of arteether with lumefantrine reduced by EFAVIRENZ and ETARVIRINE
- Antipsychotics: manufacturer of antiprescribed with lumefantrine avoids concomitant use with BENZODIAZEPINES
- Antivirals: manufacturer of antiprescribed with lumefantrine advises caution with ATAZANAVIR, FOSAMPRENACIV, INIDINAVIR, LOPINAVIR, Ritonavir, SANCIVAX and TIPRANAVIR; avoidance of antimalarials given with ATAZANAVIR, FOSAMPRENACIV, INIDINAVIR, LOPINAVIR, Ritonavir, SANCIVAX and TIPRANAVIR; avoidance of antimalarials given with BOCREPRAVIR; plasma concentration of lumefantrine increased when artemether with lumefantrine given with DARUNAVIR; plasma concentration of arteether with lumefantrine reduced by EFAVIRENZ and ETARVIRINE
- Beta-blockers: manufacturer of antiprescribed with lumefantrine advises avoid concomitant use with METOPROLOL and SOTALOL

Artemether with Lumefantrine (continued)

- Cytotoxics: possible increased risk of ventricular arrhythmias when arteether with lumefantrine given with VANDENABR—avoid concomitant use
- Grapefruit Juice: plasma concentration of arteether with lumefantrine possibly increased by GRAPEFRUIT JUICE
- Histamine: avoidance of antimalarials advised by manufacturer of HISTAMINE
- Penicillamine: increased risk of haematological toxicity when antimalarials given with PENICILLAMINE—manufacturer of penicillamine advises avoid concomitant use
- Ulcer-healing Drugs: manufacturer of arteether with lumefantrine advises avoid concomitant use with CIMETIDINE—Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Artemisinin with Piperaquine

NOTE Piperaquine has a long half-life; there is a potential for drug interactions to occur for up to 5 months after treatment has been stopped

- Analgesics: manufacturer of arteether with piperaquine advises avoid concomitant use with METHADONE (possible risk of ventricular arrhythmias)
- Antiprescribed with arteether with piperaquine advises avoid concomitant use with AMIODARONE and DISOPYRAMIDE (possible risk of ventricular arrhythmias)
- Antibacterials: manufacturer of arteether with piperaquine advises avoid concomitant use with MACROLIDES and MOXIFLOXACIN (possible risk of ventricular arrhythmias)
- Antifungals: manufacturer of arteether with piperaquine advises avoid concomitant use with PENTAMIDINE ISETIONATE (possible risk of ventricular arrhythmias)
- Antipsychotics: manufacturer of arteether with piperaquine advises avoid concomitant use with ANTIPSYCHOTICS
- Antidepressants: manufacturer of arteether with piperaquine advises avoid concomitant use with ANTIPSYCHOTICS
- Antidiabetics: manufacturer of arteether with piperaquine advises avoid concomitant use with ANTIPSYCHOTICS (possible risk of ventricular arrhythmias)
- Antivirals: manufacturer of arteether with piperaquine advises avoid concomitant use with ANTIHISTAMINES
- Antihistamines: manufacturer of arteether with piperaquine advises avoid concomitant use with ANTIHISTAMINES (possible risk of ventricular arrhythmias)
- Antimalarials: avoidance of antimalarials advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE
- Antipsychotics: manufacturer of arteether with piperaquine advises avoid concomitant use with PROPRIDIO
- Beta-blockers: manufacturer of arteether with piperaquine advises avoid concomitant use with SAQUINAVIR (possible risk of ventricular arrhythmias)
- Antitussives: manufacturer of arteether with piperaquine advises avoid concomitant use with SOTALOL (possible risk of ventricular arrhythmias)
- Cytotoxics: manufacturer of arteether with piperaquine advises avoid concomitant use with VASCULAR DILATORS and ARTERIO-SOLVING (possible risk of ventricular arrhythmias)
- Cimetidine: manufacturer of arteether with piperaquine advises avoid concomitant use with VASCULAR DILATORS and ARTERIO-SOLVING (possible risk of ventricular arrhythmias)
- Grapefruit Juice: manufacturer of arteether with piperaquine advises avoid concomitant use with GRAPEFRUIT JUICE
- Histamine: avoidance of antimalarials advised by manufacturer of HISTAMINE
- Penicillamine: increased risk of haematological toxicity when antimalarials given with PENICILLAMINE—manufacturer of penicillamine advises avoid concomitant use
- Pentamidine isetionate: manufacturer of arteether with piperaquine advises avoid concomitant use with PENTAMIDINE ISETIONATE (possible risk of ventricular arrhythmias)
Arteminol with Piperaquine — Atazanavir

**Arteminol with Piperaquine** (continued)

- Vaccines: antimalarials inactivate oral Typhoid Vaccine — see under Typhoid Vaccine in BNF or BNFC.

**Ascorbic acid** see Vitamins

**Asenapine** see Antipsychotics

**Aspirin**

- Adsorpts: absorption of aspirin possibly reduced by kaolin
- Analgesics: generic: aspirin possibly enhances effects of thiopental

- Analgesics: avoid concomitant use of aspirin with:
  - **NSAIDS** (increased side-effects); antiplatelet effect of aspirin possibly reduced by ibuprofen
  - Antacids: excretion of aspirin increased by alkaline urine due to similar 

- Anticoagulants: increased risk of bleeding when aspirin given with:
  - comarin or phenindione (due to antiplatelet effect); increased risk of bleeding when high-dose aspirin given with:
  - edoxaban (avoid concomitant use); aspirin enhances anticoagulant effect of:
  - heparins

- Antidepressants: increased risk of bleeding when aspirin given with:
  - **SSRIs** or venlafaxine

- Antiepileptics: aspirin enhances effects of fosphenytoin, phenytoin, sodium valproate and valproic acid

- Clopidogrel: increased risk of bleeding when aspirin given with clopidogrel

- Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when aspirin given with corticosteroids, also corticosteroids reduce plasma concentration of salicylate

- Cytotoxics: aspirin reduces excretion of:
  - methotrexate (increased risk of toxicity); aspirin possibly reduces renal excretion of pemetrexed — consult product literature

- Diuretics: aspirin antagonises diuretic effect of:
  - spiranolactone; increased risk of toxicity when high-dose aspirin given with:
  - acetazolamide; possible increased risk of toxicity when high-dose aspirin given with:
  - loop diuretics (also possible reduced effect of loop diuretics)

- Ilprost: increased risk of bleeding when aspirin given with iloprost

- Leukotriene Receptor Antagonists: aspirin increases plasma concentration of:
  - zafirlukast

- Metoclopramide: rate of absorption of aspirin increased by:
  - metoclopramide (enhanced effect)

- Nicorandil: increased risk of gastro-intestinal bleeding and ulceration when aspirin given with:
  - nicorandil

- Sulfipyrazone: aspirin antagonises effects of:
  - sulfipyrazone

**Atazanavir**

- Analgesics: atazanavir increases plasma concentration of:
  - buprenorphine

- Antacids: absorption of atazanavir reduced by:
  - antacids (give at least 2 hours before or 1 hour after antacids)

- Anti-arrhythmics: atazanavir possibly increases plasma concentration of:
  - amiodarone and lidocaine

- Antibacterials: plasma concentration of both drugs increased when atazanavir given with:
  - clarithromycin; atazanavir increases plasma concentration of:
  - rifabutin (reduce dose of rifabutin); plasma concentration of atazanavir reduced by:
  - rifampicin — avoid concomitant use; avoidance of concomitant atazanavir in severe renal and hepatic impairment advised by manufacturer of:
  - telithromycin

- Anticoagulants: atazanavir may enhance or reduce anticoagulant effect of:
  - warfarin; avoidance of atazanavir advised by manufacturer of:
  - apixaban and rivaroxaban

- Antidepressants: plasma concentration of atazanavir reduced by:
  - St John's wort — avoid concomitant use

- Antifungals: plasma concentration of atazanavir increased by:
  - posaconazole; atazanavir increases or decreases the plasma concentration of:
  - voriconazole and plasma concentration of atazanavir also reduced

- Antimalarials: caution with atazanavir advised by manufacturer of:
  - arteether with lumefantrine; atazanavir possibly increases plasma concentration of:
  - quinine (increased risk of toxicity)

- Antimuscarinics: avoidance of atazanavir advised by manufacturer of:
  - darifenacin; manufacturer of fosoterodine advises dose reduction when atazanavir given with:
  - fosoterodine — consult fosoterodine product literature

**Atazanavir** (continued)

- Antipsychotics: atazanavir possibly increases plasma concentration of:
  - aripiprazole (reduce dose of aripiprazole — consult aripiprazole product literature)
  - atazanavir possibly increases plasma concentration of:
  - pimozide — avoid concomitant use; atazanavir possibly increases plasma concentration of:
  - quetiapine — manufacturer of quetiapine advises avoid concomitant use

- Antivirals: plasma concentration of atazanavir reduced by:
  - boceprevir; atazanavir increases the plasma concentration of:
  - daclatasvir — reduce dose of daclatasvir (see under Daclatasvir, p. 577); absorption of atazanavir reduced by:
  - didanosine tablets (give at least 2 hours before or 1 hour after didanosine tablets); manufacturer of atazanavir advises avoid concomitant use with:
  - efavirenz (plasma concentration of atazanavir reduced); atazanavir boosted with ritonavir increases plasma concentration of:
  - elvitegravir (reduce dose of elvitegravir); avoid concomitant use of atazanavir with:
  - indinavir; atazanavir increases plasma concentration of:
  - maraviroc (consider reducing dose of maraviroc); plasma concentration of atazanavir possibly reduced by:
  - nevirapine — avoid concomitant use; atazanavir increases plasma concentration of:
  - paritaprevir; increased risk of venricular arrhythmias when atazanavir given with:
  - saquinavir — avoid concomitant use; atazanavir possibly reduces plasma concentration of:
  - telaprevir, also plasma concentration of atazanavir possibly increased; plasma concentration of atazanavir reduced by:
  - tenofovir; also plasma concentration of tenofovir possibly increased; atazanavir increases plasma concentration of:
  - tipranavir (also plasma concentration of atazanavir reduced)

- Anxiolytics and Hypnotics: atazanavir possibly increases plasma concentration of:
  - midazolam — avoid concomitant use of oral midazolam

- Calcium-channel Blockers: atazanavir increases plasma concentration of:
  - diltiazem (reduce dose of diltiazem); atazanavir possibly increases plasma concentration of:
  - verapamil

- Ciclosporin: atazanavir possibly increases plasma concentration of:
  - ciclosporin

- Colchicine: atazanavir possibly increases risk of:
  - colchicine toxicity — suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)

- Cytotoxics: atazanavir possibly increases plasma concentration of:
  - axitinib (reduce dose of axitinib — consult axitinib product literature); atazanavir possibly increases the plasma concentration of:
  - bosutinib — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; atazanavir possibly increases plasma concentration of:
  - crizotinib and everolimus — manufacturer of crizotinib and everolimus advises avoid concomitant use; atazanavir possibly increases the plasma concentration of:
  - ibritinib — reduce dose of ibritinib (see under ibritinib, p. 867); atazanavir possibly increases plasma concentration of:
  - pazopanib (reduce dose of pazopanib); avoidance of atazanavir advised by manufacturer of:
  - cabazitaxel; atazanavir possibly inhibits metabolism of:
  - irinotecan (increased risk of toxicity)

- Dapoxetine: avoidance of atazanavir advised by manufacturer of:
  - dapoxetine (increased risk of toxicity)

- Ergot Alkaloids: atazanavir possibly increases plasma concentration of:
  - ergot alkaloids — avoid concomitant use

- Guanfacine: atazanavir possibly increases plasma concentration of:
  - guanfacine (halve dose of guanfacine)

- Lipid-regulating Drugs: possible increased risk of myopathy when atazanavir given with:
  - atorvastatin or pravastatin; atazanavir increases plasma concentration of:
  - rosuvastatin — adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when atazanavir given with:
  - simvastatin (avoid concomitant use)

- Oestrogens: atazanavir increases plasma concentration of:
  - ethinylestradiol

- Orlistat: absorption of atazanavir possibly reduced by:
  - orlistat

- Progestogens: atazanavir increases plasma concentration of:
  - norethisterone
Atazanavir (continued)
- Ranolazine: atazanavir possibly increases plasma concentration of ranolazine — manufacturer of ranolazine advises avoid concomitant use
- Simvastatin: atazanavir possibly increases plasma concentration of simvastatin — manufacturer of simvastatin advises avoid concomitant use
- Atorvastatin: atazanavir possibly increases plasma concentration of atorvastatin — manufacturer of atorvastatin advises avoid concomitant use
- Atomoxetine: plasma concentration of atomoxetine possibly reduced by atazanavir; increased risk of ventricular arrhythmias when atomoxetine given with atazanavir — when patient is stable on the alpha blocker initiate atazanavir at the lowest possible dose
- Rifampicin: plasma concentration of rifampicin possibly increased by atazanavir — avoid concomitant use; plasma concentration of atazanavir possibly reduced by rifampicin — manufacturer of atazanavir advises adjust concomitant use; plasma concentration of atazanavir reduced by disopyramide and antipyschotics — see under atazanavir product literature; plasma concentration of atazanavir reduced by propoxyphene and proton pump inhibitors — avoid or adjust dose of both drugs (consult product literature)

Atezolozole
- See Beta-blockers

Atomoxetine
- Analgesics: increased risk of ventricular arrhythmias when atomoxetine given with methadone — possible increased risk of convulsions when atomoxetine given with tramadol
- Anti-arrhythmics: increased risk of ventricular arrhythmias when atomoxetine given with amiadaron or disopyramide
- Antidepressants: increased risk of ventricular arrhythmias when atomoxetine given with paroxetine — erythromycin; increased risk of ventricular arrhythmias when atomoxetine given with moxifloxacin
- Antidiabetics: metabolism of atomoxetine possibly inhibited by fluoxetine and paroxetine — possible increased risk of convulsions when atomoxetine given with antidepressants; atomoxetine should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; increased risk of ventricular arrhythmias when atomoxetine given with tricyclics
- Antimalarials: increased risk of ventricular arrhythmias when atomoxetine given with melfloquine
- Antipsychotics: increased risk of ventricular arrhythmias when atomoxetine given with antipsychotics that prolong the QT interval
- Beta-blockers: increased risk of ventricular arrhythmias when atomoxetine given with sotalol
- Bupropion: possible increased risk of convulsions when atomoxetine given with bupropion
- Diuretics: risk of ventricular arrhythmias with atomoxetine increased by hypokalaemia caused by diuretics
- Sympathomimetics, beta-2: increased risk of cardiovascular side-effects when atomoxetine given with paroxetine sulbutamol

Atorvastatin
- See Statins

Atovaquone
- Antioxidants: manufacturer of atovaquone avoids anti oxidant use with rifabutin (plasma concentration of both drugs reduced); plasma concentration of atovaquone reduced by rifampicin (and concentration of rifampicin increased) — avoid concomitant use; plasma concentration of atovaquone reduced by tetrycycline
- Antivirals: plasma concentration of atovaquone reduced by efavirenz — avoid concomitant use; atovaquone possibly reduces plasma concentration of indinavir; plasma concentration of atovaquone possibly reduced by ritonavir — manufacturer of atovaquone advises avoid concomitant use; atovaquone increases plasma concentration of zidovudine (increased risk of toxicity)
- Cytotoxics: atovaquone possibly increases plasma concentration of etoposide
- Histamine: avoidance of atovaquone advised by manufacturer of histamine
- Metoclopramide: plasma concentration of atovaquone reduced by metoclopramide — avoid concomitant use

Atracurium see Muscle Relaxants

Atropine see Antimuscarinics

Avanafil
- ACE inhibitors: avanafil possibly enhances hypotensive effect of enalapril
- Alcohol: possible enhanced hypotensive effect when avanafil given with alcohol
- Alpha-blockers: increased hypotensive effect when avanafil given with alpha-blockers — when patient is stable on the alpha blocker initiate avanafil at the lowest possible dose
- Antibacterials: plasma concentration of avanafil possibly increased by clarithromycin and telithromycin — manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil increased by erythromycin — see under avanafil, p. 744; plasma concentration of avanafil possibly increased by rifampicin — manufacturer of avanafil advises avoid concomitant use
- Antiepileptics: plasma concentration of avanafil possibly reduced by carbamazepine, phenobarbital and primidone — manufacturer of avanafil advises avoid concomitant use
- Antifungals: plasma concentration of avanafil increased by ketoconazole — avoid concomitant use; plasma concentration of avanafil possibly increased by fluconazole — see under avanafil, p. 744; plasma concentration of avanafil possibly increased by itraconazole and voriconazole — manufacturer of avanafil advises avoid concomitant use
- Antivirals: plasma concentration of avanafil possibly reduced by efavirenz — manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil increased by fosamprenavir — see under avanafil, p. 744; plasma concentration of avanafil possibly increased by indinavir and saquinavir — manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil significantly increased by ritonavir — avoid concomitant use
- Aprepitant: plasma concentration of avanafil possibly increased by aprepitant — see under avanafil, p. 744
- Bosentan: plasma concentration of avanafil possibly reduced by bosentan — manufacturer of avanafil advises avoid concomitant use
- Calcium-channel blockers: plasma concentration of avanafil possibly increased by diltaizem and verapamil — see under avanafil, p. 744
- Cobicistat: plasma concentration of avanafil possibly increased by cobicistat — avoid concomitant use
- Fosaprepitant: plasma concentration of avanafil possibly increased by fosaprepitant
- Grapefruit juice: plasma concentration of avanafil possibly increased by grapefruit juice — manufacturer of avanafil advises avoid grapefruit juice for 24 hours before avanafil
- Nicorandil: avanafil significantly enhances hypotensive effect of nicorandil — avoid concomitant use
- Nitrates: avanafil significantly enhances hypotensive effect of nitrates (avoid concomitant use)
- Riociguat: possible enhanced hypotensive effect when avanafil given with riociguat — avoid concomitant use

Axitinib
- Antibacterials: plasma concentration of axitinib possibly increased by clarithromycin, erythromycin and telithromycin (reduce dose of axitinib — consult axitinib product literature); plasma concentration of axitinib decreased by rifabutin (increase dose of axitinib — consult axitinib product literature); plasma concentration of axitinib decreased by rifampicin (increase dose of axitinib — consult axitinib product literature)
- Antiepileptics: plasma concentration of axitinib possibly reduced by st john’s wort — consider increasing dose of axitinib
- Antifungals: plasma concentration of axitinib possibly decreased by carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone (increase dose of axitinib — consult axitinib product literature)
- Antifungals: plasma concentration of axitinib increased by ketoconazole (reduce dose of axitinib — consult axitinib product literature); plasma concentration of axitinib possibly
Axitinib

Antifungals (continued)
increased by ITRACONAZOLE (reduce dose of axitinib—consult axitinib product literature)

Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)

Antivirals: plasma concentration of axitinib possibly increased by AZATANAVIR, INDINAVIR, RITONAVIR and SAQUINAVIR (reduce dose of axitinib—consult axitinib product literature)

Corticosteroids: plasma concentration of axitinib possibly decreased by DEXAMETHASONE (increase dose of axitinib—consult axitinib product literature)

Grapefruit Juice: plasma concentration of axitinib possibly increased by GRAPEFRUIT JUICE

Azathioprine

ACE Inhibitors: increased risk of anaemia or leucopenia when azathioprine given with CAPTOPRIL especially in renal impairment; increased risk of anaemia when azathioprine given with ENALAPRIL especially in renal impairment

Allopurinol: enhanced effects and increased toxicity of azathioprine when given with ALLOPURINOL (reduce dose of azathioprine to one quarter of usual dose)

Anaesthetics: manufacturer of azathioprine advises possible increased risk of myelosuppression when azathioprine given with INDOMETACIN

Antibacterials: increased risk of haematological toxicity when azathioprine given with SULFAMETHOXAZOLE (as co-trimoxazole); increased risk of haematological toxicity when azathioprine given with TRIMETHOPRIM (also with co-trimoxazole)

Anticoagulants: azathioprine possibly reduces anticoagulant effect of ACENOCOUMAROL; azathioprine reduces anticoagulant effect of WARFARIN

Antivirals: myelosuppressive effects of azathioprine possibly enhanced by RIBAVIRIN

Febuxostat: avoidance of azathioprine advised by manufacturer of FEBOXOSTAT

Ulcer-healing Drugs: manufacturer of azathioprine advises possible increased risk of myelosuppression when azathioprine given with CIMETIDINE

Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

Azelastine see Antihistamines

Azilsartan see Angiotensin II Receptor Antagonists

Azithromycin see Macrolides

Aztrenam

Anticoagulants: aztrenam possibly enhances anticoagulant effect of CLOMANS

Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Baclofen see Muscle Relaxants

Bambuterol see Sympathomimetics, Beta2

Basiliximab

Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)

Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

BCG Vaccine see Vaccines

Beclometasone see Corticosteroids

Bedaquiline

Antibacterials: plasma concentration of bedaquiline possibly increased by CIPROFLOXACIN, CLARITHROMYCIN and ERTHROMYCIN—avoid concomitant use if ciprofloxacin, clarithromycin and erythromycin given for more than 14 days; manufacturer of bedaquiline advises avoid concomitant use with MOXIFLOXACIN; plasma concentration of bedaquiline possibly reduced by RIFABUTIN—manufacturer of bedaquiline advises avoid concomitant use; plasma concentration of bedaquiline reduced by Rifampicin—manufacturer of bedaquiline advises avoid concomitant use; possible increased risk of ventricular arrhythmias when bedaquiline given with CLOFAZILINE

Antidepressants: plasma concentration of bedaquiline possibly reduced by ST JOHN’S WORT—manufacturer of bedaquiline advises avoid concomitant use

Bedaquiline (continued)

Antiepileptics: plasma concentration of bedaquiline possibly reduced by CARBAMAZEPINE, FOSPHENYTIOIN and PHENYTOIN—manufacturer of bedaquiline advises avoid concomitant use

Antifungals: plasma concentration of bedaquiline increased by KETOCONAZOLE—avoid concomitant use if ketoconazole given for more than 14 days; plasma concentration of bedaquiline possibly increased by FLUCONAZOLE—avoid concomitant use if fluconazole given for more than 14 days

Antivirals: plasma concentration of bedaquiline possibly reduced by EFAVIRENZ and ETRAVIRINE—manufacturer of bedaquiline advises avoid concomitant use; plasma concentration of bedaquiline possibly increased by RITONAVIR—manufacturer of ritonavir advises avoid concomitant use

Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Bee Venom Extracts

ACE Inhibitors: possible severe anaphylactoid reaction when bee venom extracts given with ACE INHIBITORS

Belimumab

Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)

Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

Bendamustine

Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)

Bendroflumethiazide see Diuretics

Benperidol see Antipsychotics

Benzodiazepines see Anxiolytics and Hypnotics

Benztropine see Penicillins

Beta-blockers

NOTE Since systemic absorption may follow topical application of beta-blockers to the eye the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind

ACE Inhibitors: enhanced hypotensive effect when beta-blockers given with ACE INHIBITORS

Adrenergic Neurone Blockers: enhanced hypotensive effect when beta-blockers given with ADRENERGIC NEURONE BLOCKERS

Alcohol: enhanced hypotensive effect when beta-blockers given with ALCOHOL

Aldesleukin: enhanced hypotensive effect when beta-blockers given with ALDESLEUKIN

Alpha-blockers: enhanced hypotensive effect when beta-blockers given with ALPHABLOCKERS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin

Anaesthetics, General: enhanced hypotensive effect when beta-blockers given with GENERAL ANAESTHETICS

Anaesthetics, Local: propranolol increases risk of BUPIVACAINE toxicity

Analgesics: hypotensive effect of beta-blockers antagonised by NSAIDS; plasma concentration of esmolol possibly increased by MORPHINE

Angiotensin II Receptor Antagonists: enhanced hypotensive effect when beta-blockers given with ANGIOΤENSIN-II RECEPTOR ANTAGONISTS

Anti-arrhythmics: increased myocardial depression when beta-blockers given with ANTI-ARRHYTHMICS; increased risk of ventricular arrhythmias when sotalol given with AMIODARONE, DISOPYRAMIDE or DRONERADONE—avoid concomitant use; increased risk of bradycardia, AV block and myocardial depression when beta-blockers given with AMIODARONE; plasma concentration of metoprolol and propranolol possibly increased by DRONERADONE; increased risk of LIDOCAINE toxicity; propranolol increases risk of LIDOCAINE toxicity; plasma concentration of metoprolol and propranolol increased by PROPafenone

Antibacterials: increased risk of ventricular arrhythmias when sotalol given with MOXIFLOXACIN—avoid concomitant use;
Beta-blockers
- Antibacterial: possible increased risk of ventricular arrhythmias when sotalol given with • BOSUTINIB and • CEDIRINIB; possible increased risk of bradycardia when beta-blockers given with • CRIZOTINIB; possible increased risk of ventricular arrhythmias when sotalol given with • VANDETANIB—avoid concomitant use; increased risk of ventricular arrhythmias when sotalol given with • ARSENIC TRIOXIDE
- Diazoxide: enhanced hypotensive effect when beta-blockers given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when beta-blockers given with • DIURETICS; risk of ventricular arrhythmias with sotalol increased by hypokalaemia caused by • LOOP DIURETICS or • THIAZIDES AND RELATED DIURETICS
- Dopamine: enhanced hypotensive effect when beta-blockers given with • CO-BENEDOLPA, • CO-CARELDPRA and • LEVODOPRA
- Ergot Alkaloids: increased peripheral vasconstriction when beta-blockers given with ERGOT ALKALOIDS
- Fingolimod: possible increased risk of bradycardia when beta-blockers given with • FINGOLIMOD
- Hormone Antagonists: possible increased risk of bradycardia when corticosteroids or metoprolol, propranolol or sotalol given with • PASIREOTIDE
- 5HT1-receptor Agonists: propranolol increases plasma concentration of • RIZATRIPTAN (manufacturer of rizatRIPTAN advises halve dose and avoid within 2 hours of propranolol)
- Ibradine: increased risk of ventricular arrhythmias when sotalol given with • IVAABRIDE 
- Methylp: enhanced hypotensive effect when beta-blockers given with • METHYLDOPA
- Mirabegron: plasma concentration of metoprolol increased by • MIRABEGRON
- Moxylyte: possible severe postural hypotension when betablockers given with • MOXYLYTE
- Moxonidine: enhanced hypotensive effect when beta-blockers given with • MOKONIDINA
- Muscle Relaxants: propranolol enhances effects of • MUSCLE RELAXANTS; enhanced hypotensive effect when beta-blockers given with • BACLOFEN; possible enhanced hypotensive effect and bradycardia when beta-blockers given with • TIZANIDINA
- Nitrates: enhanced hypotensive effect when beta-blockers given with • NITRATES
- Oestrogens: hypotensive effect of beta-blockers antagonised by • OESTROGENS
- Panobinostat: possible increased risk of ventricular arrhythmias when sotalol given with • PANOBINOSTAT—avoid concomitant use
- Parasympathomimetics: propranolol antagonises effects of • NEOSTIGMIN and • PYRIDOSTIGNMIN; increased risk of arrhythmias when beta-blockers given with • PILOCARPINA
- Prostaglandins: enhanced hypotensive effect when beta-blockers given with • ALPROSTADIL
- Ranolazine: avoidance of sotalol advised by manufacturer of • RANOLAZINA
- Sympathomimetics: increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with • ADRENALINA (EPINEFIRINA), also response to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with • DOBUTAMINA; possible increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with • NORDRENALINA (NOREPINEFIRINA)
- Thyroid Hormone: metabolism of propranolol accelerated by • LEVOTHYROXINA
- Ulcer-healing Drug: plasma concentration of labetalol, metoprolol and propranolol increased by • CETIDINA; plasma concentration of oral timolol possibly increased by • CETIDINA
- Vasodilator Antihypertensives: enhanced hypotensive effect when beta-blockers given with • HYDRAZIN, • MINOXIDOL or • SODIUM NITROPRUSSIDE
Betahistine
- Antihistamines: effect of betahistine theoretically antagonised by • ANTIHISTAMINES
Betamethasone see Corticosteroids
Betaxolol see Beta-blockers
Bleomycin

- Antipsychotics: avoid concomitant use of cytotoxics with
  - CLOzapine (increased risk of agranulocytosis)
- Cytotoxics: avoidance of bevacizumab advised by manufacturer of Panitumumab
- Vaccines: risk of generalised infections when monoclonal antibodies given with live Vaccines—avoid concomitant use

Bevacizumab

- Antipsychotics: avoid concomitant use of cytotoxics with
  - CLOzapine (increased risk of agranulocytosis)
- Lipid-regulating Drugs: plasma concentration of bevacizumab increased by
  - GEMFIBrozil—avoid concomitant use

Bezafibrate see Fibrates

Bicalutamide

- Anticoagulants: bicalutamide possibly enhances anticoagulant effect of COUMARINS
- Lipid-regulating Drugs: separating administration from bicalutamide by 12 hours advised by manufacturer of LOMITAPIDE

Biguanides see Antidiabetics

Bilastine see Antihistamines

Bile Acid Sequestrants see Colesevelam, Colestipol, and Colestymamine

Bile Acids

- Antacids: absorption of bile acids possibly reduced by
  - ANTACIDS; effects of cholic acid probably reduced by ALUMINIUM HYDROXIDE (manufacturer of cholic acid advises give at least 5 hours apart)
- Antiepileptics: manufacturer of cholic acid advises avoid concomitant use with
  - PHENOBARBITAL
- Ciclosporin: manufacturer of cholic acid advises avoid concomitant use with
  - CICLOSPORIN; ursodeoxycholic acid increases absorption of
  - CICLOSPORIN
- Lipid-regulating Drugs: effects of cholic acid probably reduced by
  - COLESEVELAM, COLESTIPOL and COLESTYRAMINE (manufacturer of cholic acid advises give at least 5 hours apart); absorption of bile acids possibly reduced by
  - COLESTIPOL and COLESTYRAMINE

Bisoprolol see Beta-blockers

Bisphosphonates

- Antacids: absorption of bisphosphonates reduced by
  - ANTACIDS
- Antibacterials: increased risk of hypocalcaemia when bisphosphonates given with
  - AMINOGLYCOSIDES
- Calcium Salts: absorption of bisphosphonates reduced by
  - CALCIUM SALTS
- Cytotoxics: sodium clodronate increases plasma concentration of
  - ESTRAMUSTINE
- Iron Salts: absorption of bisphosphonates reduced by oral IRON SALTS

Bivalirudin

- Analgesics: increased risk of haemorrhage when anticoagulants given with
  - intravenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with a KETOROLAC (avoid concomitant use, including low-dose heparins)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with
  - APIXaban, DABIGATран, EDoxaban and RIVARoxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Bleomycin

- Antipsychotics: avoid concomitant use of cytotoxics with
  - CLOzapine (increased risk of agranulocytosis)
- Cardiac Glicosides: bleomycin possibly reduces absorption of
  - DIGOxin tablets
- Cytotoxics: increased risk of pulmonary toxicity when bleomycin given with
  - BRENTUXIMAB VEDOTIN—avoid concomitant use; increased pulmonary toxicity when bleomycin given with
  - CISPlatin
- Vaccines: risk of generalised infections when cytotoxic antibiotics given with live Vaccines—avoid concomitant use

Boceprevir

- Alpha-blockers; boceprevir possibly increases plasma concentration of
  - DOXAZOSIN and TAMsulosIN—manufacturer of boceprevir advises avoid concomitant use

Boceprevir (continued)

- Analgesics: possible increased risk of prolonged sedation and respiratory depression when boceprevir given with
  - BUPRENORPHINE; boceprevir possibly affects plasma concentration of METHADONE
- Antibacterials: manufacturer of boceprevir advises avoid concomitant use with
  - RifAMPICIN (plasma concentration of boceprevir possibly reduced)
- Anticoagulants: avoidance of boceprevir advised by manufacturer of APiXaban
- Antiepileptics: manufacturer of boceprevir advises avoid concomitant use with
  - CARBAMAZEPINE, FOsPHENytoIN, PHENOBARBITAL, PHENytoIN and PRIMIDONE (plasma concentration of boceprevir possibly reduced)
- Antifungals: plasma concentration of boceprevir increased by
  - KETOCONAZOLE
- Antimalarials: manufacturer of boceprevir advises avoid concomitant use with
  - ARTEMether with LUMEFanTriNE
- Antipsychotics: boceprevir possibly increases plasma concentration of
  - LURASIDONE—avoid concomitant use; manufacturer of boceprevir advises avoid concomitant use with
  - PIMOZIDE; boceprevir possibly increases plasma concentration of
  - QUETiapINE—manufacturer ofquetiapine advises avoid concomitant use
- Antivirals: boceprevir reduces plasma concentration of
  - ATRAzANAVIR; boceprevir possibly increases the plasma concentration of
  - DAclATARISVIR—reduce dose of daclatasvir (see under Daclatasvir, p. 577); avoid concomitant use of boceprevir with
  - DARUNAVIR; effects of both drugs possibly reduced when boceprevir given with
  - ETARIVIRINE; avoidance of boceprevir advised by manufacturer of
  - FOSAMPReNAVIR, NEVIRAPINE and TIPRANAvIR; manufacturers advise avoid concomitant use of boceprevir with
  - LOPINAVIR; boceprevir increases plasma concentration of
  - MARAVIroC (consider reducing dose of maraviroc); plasma concentration of both drugs reduced when boceprevir given with
  - RITONAVIR
- Anxiolytics and Hypnotics: boceprevir increases plasma concentration of oral
  - MIDAzoLAM—manufacturer of boceprevir advises avoid concomitant use
- Cardiac Glicosides: boceprevir possibly increases side-effects of
  - DIGOxin
- Ciclosporin: boceprevir increases plasma concentration of
  - CICLOSPORIN
- Cilostazol: boceprevir possibly increases plasma concentration of
  - CILOSTAZOL (see under Cilostazol, p. 221)
- Cocistat: avoidance of boceprevir advised by manufacturer of COBICISTAT
- Cytotoxics: boceprevir possibly increases the plasma concentration of
  - BOSUTiniB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; manufacturer of boceprevir advises avoid concomitant use with
  - DASATiNIB, ERLoTINiB, GEFTiNIB, IMATiNIB, LAPATiNIB, NILOTiNIB, PzAPANiB, SORAFEniB and SUNiTINIB; manufacturer of ruxolitinib advises dose reduction when boceprevir given with
  - RUXoLITINiB—consult ruxolitinib product literature; boceprevir possibly increases plasma concentration of
  - OLAPARiB (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)
- Domperidone: possible increased risk of ventricular arrhythmias when boceprevir given with
  - DOMPERIDONE—avoid concomitant use
- Ergot Alkaloids: manufacturer of boceprevir advises avoid concomitant use with
  - ERGOT ALKALOiDS
- Guanfacine: boceprevir possibly increases plasma concentration of
  - GUANFACiNE (halve dose of guanfacine)
- Lipid-regulating Drugs: boceprevir increases plasma concentration of
  - ATORvASTATIN (reduce dose of atorvastatin); boceprevir increases plasma concentration of
  - PRaVASTATiN; manufacturers advise avoid concomitant use of boceprevir with
  - SIMVASTATIN
- Progestogens: boceprevir increases plasma concentration of
  - DROSPiRENOne (increased risk of toxicity)
- Siromus: boceprevir increases plasma concentration of
  - SIROlUMiS (increased risk of toxicity—reduce sirolimus dose)
- Tacrolimus: boceprevir increases plasma concentration of
  - TACROLiMUS (reduce dose of tacrolimus)
Bosentan

- Antiarrhythmics: plasma concentration of bosentan reduced by • Rifampicin — manufacturer of bosutinib advises avoid concomitant use
- Antidepressants: plasma concentration of bosentan possibly reduced by • ST JOHN’S WORT — manufacturer of bosutinib advises avoid concomitant use
- Anti-epileptics: plasma concentration of bosentan possibly reduced by • Carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone — manufacturer of bosutinib advises avoid concomitant use

Bosutinib

- Analgesics: possible increased risk of ventricular arrhythmias when bosutinib given with • Methadone
- Antacids: manufacturer of bosutinib advises separating administration with antacids by about 12 hours
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when bosutinib given with • Amiodarone and • Disopyramide — plasma concentration of bosutinib possibly increased by • Dronedarone — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Antifungals: plasma concentration of bosutinib possibly increased by • Ciprofloxacin, clarithromycin, erythromycin and • Telithromycin — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; possible increased risk of ventricular arrhythmias when bosutinib given with • Moxifloxacin — plasma concentration of bosutinib possibly reduced by • Rifabutin —

Bosutinib (continued)

- Antidepressants (continued): manufacturer of bosutinib advises avoid concomitant use; plasma concentration of bosutinib reduced by • Rifampicin — manufacturer of bosutinib advises avoid concomitant use
- Antipsychotics: plasma concentration of bosutinib possibly reduced by • ST JOHN’S WORT — manufacturer of bosutinib advises avoid concomitant use
- Antiepileptics: plasma concentration of bosutinib possibly reduced by • Carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone — manufacturer of bosutinib advises avoid concomitant use

Antifungals: plasma concentration of bosutinib increased by

- Bosentan — increased by • Rifampicin

- Cytotoxics:
  - Cobicistat: manufacturer of bosutinib advises separating administration with bosentan by about 24 hours
  - Avoidance of bosentan advised by manufacturer of bosutinib
  - Plasma concentration of bosutinib possibly increased by • Flucanazole, • Itraconazole, • Posaconazole and • Voriconazole — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Antipsychotics: possible increased risk of ventricular arrhythmias when bosutinib given with • Haloperidol; avoid concomitant use of cytotoxics with • Clozapine (increased risk of agranulocytosis)

- Antivirals: plasma concentration of bosutinib possibly increased by • Atazanavir, • Boceprevir, • Darunavir, • Fosamprenavir, • Indinavir, • ritonavir, • Saquinavir and • Telaprevir — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; plasma concentration of bosutinib possibly reduced by • Efavirenz and • Etiravirine — manufacturer of bosutinib advises avoid concomitant use

- Aprepitant: plasma concentration of bosutinib possibly increased by • Aprepitant — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Beta-blockers: possible increased risk of ventricular arrhythmias when bosutinib given with • Sotalol

- Bosentan: plasma concentration of bosutinib possibly reduced by • Bosentan — manufacturer of bosutinib advises avoid concomitant use

- Calcium-channel Blockers: plasma concentration of bosutinib possibly increased by • Diltiazem and • Verapamil — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Cytotoxics: plasma concentration of bosutinib possibly increased by • Matinib — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Darunavir:
  - Manufacturer of bosutinib advises avoid concomitant use with • Domperidone — (risk of ventricular arrhythmias)

- Fosaprepitant: plasma concentration of bosutinib possibly increased by • Fosaprepitant — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Grapefruit juice; plasma concentration of bosutinib possibly increased by • Grapefruit juice — manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Haloperidol; manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib

- Modafinil: plasma concentration of bosutinib possibly reduced by • Modafinil — manufacturer of bosutinib advises avoid concomitant use

- Ulcer-healing Drugs: plasma concentration of bosutinib reduced by • Lansoprazole

Brentuximab vedotin

- Antibacterials: effects of brentuximab vedotin possibly reduced by • Rifampicin

- Antifungals: possible increased risk of neutropenia when brentuximab vedotin given with • Ketoconazole

- Antipsychotics: avoid concomitant use of cytotoxics with • Clozapine (increased risk of agranulocytosis)

- Cytotoxics: increased risk of pulmonary toxicity when brentuximab vedotin given with • Bleomycin — avoid concomitant use

- Vaccines: risk of generalised infections when monoclonal antibodies given with live • Vaccines — avoid concomitant use
Brimonidine

Antidepressants: manufacturer of brimonidine advises avoid concomitant use with MAOIS, TRICYCLIC-RELATED ANTIDEPRESSANTS and TRICYCLICS

Brinzolamide see Diuretics

Brivaracetam

Antibacterials: plasma concentration of brivaracetam reduced by

- Rifampicin

Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIS and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered)

Antiepileptics: plasma concentration of brivaracetam reduced by CARBAMAZEPINE, also plasma concentration of active metabolite of carbamazepine increased; plasma concentration of brivaracetam reduced by FOSPHENYTONE, PHENOBARBITAL, PHENOTYPIN and PRIMIDONE

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by Mefloquine

- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by Antipsychotics (convulsive threshold lowered)

- Oralstat: possible increased risk of convulsions when antiepileptics given with Oralstat

Bromocriptine

- Alcohol: tolerance of bromocriptine reduced by Alcohol

- Antibacterials: plasma concentration of bromocriptine increased by ERYTHROMYCIN (increased risk of toxicity); plasma concentration of bromocriptine possibly increased by MACROLIDES (increased risk of toxicity)

- Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of bromocriptine antagonised by Antipsychotics

- Domperidone: hypoprolactinaemic effect of bromocriptine possibly antagonised by Domperidone

- Antineurotransmitter: bromocriptine concentration of bromocriptine increased by OCTREOTIDE

- Memantine: effects of dopaminergics possibly enhanced by Memantine

- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by Methylodopa

- Metoclopramide: hypoprolactinaemic effect of bromocriptine antagonised by Metoclopramide

- Symptomimetics: risk of toxicity when bromocriptine given with Symptomimetics

Buclozine see Antihistamines

Budesonide see Corticosteroids

Bumetanide see Diuretics

Butapacaine

- Anti-arhythmic: increased myocardial depression when butapacaine given with Anti-arhythmic

- Beta-blockers: increased risk of butapacaine toxicity when given with Propranolol

Buprenorphine see Opioid Analgesics

Buproprion

- Antidepressants: buproprion possibly increases plasma concentration of Citalopram; manufacturer of buproprion advises avoid for 2 weeks after stopping MAOIS; manufacturer of buproprion advises avoid concomitant use with MOLOBEMIDE; buproprion possibly increases plasma concentration of TRICYCLICS (possible increased risk of convulsions); buproprion increases plasma concentration of Vortioxetine (consider reducing dose of vortioxetine)

- Antiepileptics: plasma concentration of buproprion reduced by Carbamazepine, fosphenytoin and phenytoin; metabolism of buproprion inhibited by Sodium Valproate and valproic acid

- Antivirals: metabolism of buproprion accelerated by Efavirenz (reduced plasma concentration); plasma concentration of buproprion reduced by Ritonavir

- Atomoxetine: possible increased risk of convulsions when bupropion given with Atomoxetine

- Dopaminergics: increased risk of side-effects when bupropion given with Amantadine, Co-beneldopa, Co-careldopa or levodopa

- Hormone Antagonists: bupropion possibly inhibits metabolism of Tamoxifen to active metabolite (avoid concomitant use)

Buproprion (continued)

- Methylthioninium: possible risk of CNS toxicity when buproprion given with Methylthioninium — avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Buspirone see Anxiolytics and Hypnotics

Busulfan

- Analgesics: metabolism of intravenous busulfan possibly inhibited by Paracetamol (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol)

- Antibacterials: plasma concentration of busulfan increased by Metronidazole (increased risk of toxicity)

- Antiepileptics: plasma concentration of busulfan possibly reduced by Fosphenytoin and Phenytoin

- Antifungals: metabolism of busulfan inhibited by Itraconazole (increased risk of toxicity)

- Antipsychotics: avoid concomitant use of cytoxics with Clozapine (increased risk of agranulocytosis)

- Cytotoxics: increased risk of hepatotoxicity when busulfan given with Thioguanine

Busulfan

Antipsychotics see Antipsychotics

Cabazitaxel

- Antidepressants: plasma concentration of cabazitaxel possibly increased by Clarithromycin and Telithromycin — manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; manufacturer of cabazitaxel advises concomitant use with Rifabutin; plasma concentration of cabazitaxel reduced by Rifampicin — manufacturer of cabazitaxel advises avoid concomitant use

- Antiepileptics: manufacturer of cabazitaxel advises avoid concomitant use with St John’s Wort

- Antipsychotics: manufacturer of cabazitaxel advises avoid concomitant use with Carbamazepine, fosphenytoin, Phenobarbital, Phenotyphin and Primidone

- Antifungals: manufacturer of cabazitaxel advises avoid concomitant use with Ketoconazole; plasma concentration of cabazitaxel possibly increased by Itraconazole and Voriconazole — manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel

- Antipsychotics: avoid concomitant use of cytoxics with Clozapine (increased risk of agranulocytosis)

- Antivirals: manufacturer of cabazitaxel advises avoid concomitant use with Atazanavir; plasma concentration of cabazitaxel possibly increased by Indinavir, Ritonavir and Saquinavir — manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel

Cabelergone

- Antibacterials: plasma concentration of cabergolone increased by Erythromycin (increased risk of toxicity); plasma concentration of cabergolone possibly increased by MACROLIDES (increased risk of toxicity)

- Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of cabergolone antagonised by Antipsychotics

- Domperidone: hypoprolactinaemic effect of cabergolone antagonised by Domperidone

- Memantine: effects of dopaminergics possibly enhanced by Memantine

- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by Methylodopa

- Metoclopramide: hypoprolactinaemic effect of cabergolone antagonised by Metoclopramide

Caboantinib

- Antibacterials: plasma concentration of caboantinib possibly increased by Clarithromycin and Erythromycin; plasma concentration of caboantinib reduced by Rifampicin — avoid concomitant use

- Antidepressants: plasma concentration of caboantinib possibly reduced by St John’s Wort — manufacturer of caboantinib advises avoid concomitant use

- Antiepileptics: plasma concentration of caboantinib possibly reduced by Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone — avoid concomitant use
Calcitriol see Vitamins

Calcium Salts

NOTE see also Antacids
• Antiarthritics: calcium salts reduce absorption of ciprofloxacin (give at least 2 hours before or 4 hours after ciprofloxacin); calcium salts possibly reduce absorption of tetracyclines (give at least 2 to 3 hours apart)
• Antivirals: calcium salts reduce absorption of dolutegravir — manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after calcium salts; separating administration from calcium salts by 4 hours advised by manufacturer of ledipasvir; manufacturer of rifapentine advises give calcium salts 2 hours before or 4 hours after rifapentine.
• Bisphosphonates: calcium salts reduce absorption of bisphosphonates.
• Cardiac Glysosides: large intravenous doses of calcium salts can precipitate arrhythmias when given with cardiac glycosides.
• Corticosteroids: absorption of calcium salts reduced by corticosteroids.
• Cytotoxics: calcium salts reduce absorption of estramustine (manufacturer of estramustine advises avoid concomitant administration).
• Diuretics: increased risk of hypercalcaemia when calcium salts given with thiazides and related diuretics.
• Etrombopag: calcium salts possibly reduce absorption of etrombopag (give at least 4 hours apart).
• Fluorides: calcium salts reduce absorption of fluorides.
• Iron Salts: calcium salts reduce absorption of oral iron salts.
• Thyroid Hormones: calcium salts reduce absorption of levothyroxine.
• Zinc: calcium salts reduce absorption of zinc.

Calcium-channel Blockers

NOTE Dihydropyridine calcium-channel blockers include amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, and nimodipine.
• ACE Inhibitors: enhanced hypotensive effect when calcium-channel blockers given with ACE inhibitors.
• Adrenergic Neurone Blockers: enhanced hypotensive effect when calcium-channel blockers given with adrenergic neurone blockers.
• Alcohol: enhanced hypotensive effect when calcium-channel blockers given with alcohol; verapamil possibly increases plasma concentration of alcohol.
• Aldesleukin: enhanced hypotensive effect when calcium-channel blockers given with aldesleukin.
• Aminophylline: enhanced hypotensive effect when calcium-channel blockers given with aminophylline; verapamil increases plasma concentration of aminophylline.
• Alpha-blockers: enhanced hypotensive effect when calcium-channel blockers given with alpha-blockers; also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin.
• Aminophylline: calcium-channel blockers possibly increase plasma concentration of aminophylline; enhanced hypotensive effect when calcium-channel blockers given with amiodarone; increased risk of myocardial depression and asystole when verapamil given with disopyramide or flecainide; increased risk of bradycardia and myocardial depression when diltiazem and verapamil given with dronedarone; nifedipine increases plasma concentration of dronedarone.
• Antiarrhythmics: metabolism of calcium-channel blockers possibly inhibited by clarithromycin, erythromycin, telithromycin, and risedronate; metabolism of lercanidipine possibly inhibited by risedronate; effects of dihydropyridines, nicardipine and nimodipine possibly accelerated by rifampicin; increased risk of agranulocytosis; plasma concentration of cabozantinib possibly reduced; effects of dihydropyridines, nicardipine and nimodipine possibly accelerated by rifampicin; increased risk of agranulocytosis; increased risk of bradycardia and myocardial depression when diltiazem and verapamil given with rifampicin; avoidance of verapamil by manufacturer of fidaxomycin; anticoagulants: verapamil possibly increases plasma concentration of dabigatran (see under dabigatran etexilate, p. 128); verapamil increases plasma concentration of edoxaban.
• Antidepressants: metabolism of nifedipine possibly inhibited by fluoxetine (increased plasma concentration); diltiazem and verapamil increase plasma concentration of mirtazapine; enhanced hypotensive effect when calcium-channel blockers given with mirtazapine; plasma concentration of nifedipine reduced by st john’s wort; plasma concentration of amiodarone and nifedipine possibly reduced by st john’s wort; plasma concentration of verapamil significantly reduced by st john’s wort; diltiazem and verapamil possibly increase plasma concentration of tricyclics.
• Antidiabetics: glucose tolerance occasionally impaired when nifedipine given with insulins.
• Antiepileptics: effects of dihydropyridines, nicardipine and nifedipine probably reduced by carbamazepine; diltiazem and verapamil enhance effects of carbamazepine; manufacturer of nimodipine advises avoid concomitant use with carbamazepine, fosphenytoin and phenytoin (plasma concentration of nimodipine possibly reduced); effects of felodipine and isradipine reduced by carbamazepine; effects of felodipine and verapamil reduced by phenytoin; manufacturer of nimodipine advises avoid concomitant use with fosphenytoin; phenobarbital, phenytoin and primidone; diltiazem increases plasma concentration of fosphenytoin and phenytoin but also effect of diltiazem reduced; effects of calcium-channel blockers probably reduced by phenobarbital and primidone; manufacturer of nimodipine advises avoid concomitant use with phenobarbital and primidone (plasma concentration of nimodipine reduced); effects of felodipine and verapamil reduced by phenytoin.
Calcium-channel Blockers (continued)
- Antifungals: metabolism of dihydropyridines possibly inhibited by ITRACANAZOLE and KETOCONAZOLE (increased plasma concentration); metabolism of felodipine is inhibited by KETOCONAZOLE (increased plasma concentration). Manufacturer of ketoconazole advises avoid concomitant use; manufacturer of lercanidipine advises avoid concomitant use with ITRACANAZOLE and KETOCONAZOLE; negative inotropic effect possibly increased when calcium-channel blockers given with ITRACANAZOLE and KETOCONAZOLE; metabolism of felodipine inhibited by ITRACANAZOLE (increased plasma concentration); plasma concentration of nifedipine increased by MICAFUNIC.
- Antimalarials: possible increased risk of bradycardia when calcium-channel blockers given with MELOQUIN.
- Antimuscarinics: enhancement of antimuscarinic effect by guanfacine.

Calcium-channel Blockers (continued)
- Corticosteroids: hypotensive effect of calcium-channel blockers antagonised by CORTICOSTEROIDS; diltiazem increases plasma concentration of METHYLPRERIDINOLS.
- Cytotoxics: verapamil possibly increases plasma concentration of OXORUBICIN; verapamil possibly increases the plasma concentration of AFAFINIB—manufacturer of afatinib advises separating administration of verapamil by 6 to 12 hours; diltiazem and verapamil possibly increase the plasma concentration of BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; possible increased risk of bradycardia when diltiazem or verapamil given with CRIZOTINIB; plasma concentration of both drugs may increase when verapamil given with EVEROLMULUS (consider reducing the dose of everolimus); diltiazem and verapamil possibly increase the plasma concentration of IBRUTINIB—reduce dose of ibritinib (see under Ibrutinib, p. 867); diltiazem and verapamil possibly increase plasma concentration of OLAPARIB (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881); nifedipine possibly inhibits metabolism of VINCIRINE.
- Diphteroids: manufacturer of daphneontilde advises dose reduction when diltiazem and verapamil given with DAPTOXIN (see under Dapoxetine, p. 751).
- Dose: enhanced hypotensive effect when calcium-channel blockers given with DIAZODE.
- Dihydropyridine: diltiazem and verapamil increase plasma concentration of EPLERENONE (reduce dose of eplerenone); enhanced hypotensive effect when calcium-channel blockers given with DURETICS.
- Dopamine: enhanced hypotensive effect when calcium-channel blockers given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA.
- Fingolimod: possible increased risk of bradycardia when diltiazem or verapamil given with FINGOLIMOD.
- Fosaprepitant: plasma concentration of both drugs may increase when diltiazem given with FOSAPREPTANT.
- Grapefruit: plasma concentration of felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil increased by GRAPEFRUIT JUICE.
- Guanfacine: diltiazem and verapamil possibly increase the plasma concentration of GUANFACINE (halve dose of guanfacine).
- Hormone Antagonists: diltiazem and verapamil increase plasma concentration of DUTASTERIDE; possible increased risk of bradycardia when diltiazem or verapamil given with PASIREOTID.
- Ibradine: diltiazem and verapamil increase plasma concentration of IVABRADINE—avoid concomitant use.
- Lenalidomide: verapamil possibly increases plasma concentration of LENALIDOMIDE (increased risk of toxicity).
- Lipid-regulating Drugs: diltiazem increases plasma concentration of ATORVASTATIN—possible increased risk of myopathy; plasma concentration of verapamil increased by ATORVASTATIN, also possible increased risk of myopathy (consider reducing dose of atorvastatin); possible increased risk of myopathy when amiodipine and diltiazem given with SIMVASTATIN (see under Simvastatin, p. 194); increased risk of myopathy when verapamil given with SIMVASTATIN (see under Simvastatin, p. 194); avoidance of diltiazem and verapamil advised by manufacturer of LOMITAPIDE (plasma concentration of lomitapide possibly increased); separating administration from amiodipine and lacidipine by 12 hours advised by manufacturer of LOMITAPIDE.
- Lithium: neurotoxicity may occur when diltiazem or verapamil given with LITHIUM without increased plasma concentration of lithium.
- Magnesium (parenteral): profound hypotension reported with concomitant use of nifedipine and PARENTERAL MAGNESIUM in pre-eclampsia.
- Methyldopa: enhanced hypotensive effect when calcium-channel blockers given with METHYLDOPA.
Calcium-channel Blockers (continued)

- Moxisylyte: enhanced hyotensive effect when calcium-channel blockers with MOXISYLYTE
- Moxonidine: enhanced hyotensive effect when calcium-channel blockers with MOXONIDINE
- Muscle Relaxants: verapamil enhances effects of NON-DEPOLARISING MUSCLE RELAXANTS and SUXAMETHONIUM; enhanced hyotensive effect when calcium-channel blockers given with BACLOFEN or TIZANIDINE; manufacturer of verapamil advises avoid concomitant use of intravenous DANTROLENE; possible increased risk of ventricular arrhythmias when diltiazem given with intravenous DANTROLENE—manufacturer of diltiazem advises avoid concomitant use; calcium-channel blockers possibly enhance effects of NON-DEPOLARISING MUSCLE RELAXANTS
- Naloxegol: diltiazem increases plasma concentration of NALOXEGOL (reduce dose of naloxegol—see under Naloxegol, p. 61); verapamil possibly increases plasma concentration of NALOXEGOL (reduce dose of naloxegol—see under Naloxegol, p. 61)
- Nitrates: enhanced hyotensive effect when calcium-channel blockers with NITRATES
- Oestrogens: hyotensive effect of calcium-channel blockers antagonised by OESTROGENS
- Prostaglandins: enhanced hyotensive effect when calcium-channel blockers given with ALPROSTADIL
- Ranolazine: diltiazem and verapamil increase plasma concentration of RANOLAZINE (consider reducing dose of ranolazine)
- Sildenafil: diltiazem enhances hyotensive effect when amiodipine given with SILDENAFIL
  - Sirolimus: diltiazem increases plasma concentration of SIROLIMUS; plasma concentration of both drugs increased when verapamil given with a SIROLIMUS; nicardipine possibly increases plasma concentration of SIROLIMUS
- Sulfinpyrazone: plasma concentration of verapamil reduced by SULFINPYRAZONE
  - Tacrolimus; diltiazem, nicardipine and nifedipine increase plasma concentration of TACROLIMUS; felodipine and verapamil possibly increase plasma concentration of TACROLIMUS
  - Theophylline: calcium-channel blockers possibly increase plasma concentration of THYMEFOLINE (enhanced effect); diltiazem increases plasma concentration of THYMEFOLINE; verapamil increases plasma concentration of THYMEFOLINE (enhanced effect)
  - Ticagrelor: diltiazem increases plasma concentration of TICAGRELOR
  - Ulcer-healing Drugs: metabolism of calcium-channel blockers possibly inhibited by CIMETIDINE (increased plasma concentration); plasma concentration of isradipine increased by CIMETIDINE (halve dose of isradipine)
  - Ulipristal: avoidance of verapamil advised by manufacturer of low-dose ULIPRISTAL
  - Vardenafil: enhanced hyotensive effect when nifedipine given with VARDENAFIL
  - Vasodilator Antihypertensives: enhanced hyotensive effect when calcium-channel blockers given with HYDRAZALINE, MINOXIDIL or SODIUM NITROPRUSSIDE

Calcium-channel Blockers (dihydropyridines) see Calcium-channel Blockers

Canagliflozin see Antidiabetics

Canakinumab
- Antipsychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

Candesartan see Angiotensin-II Receptor Antagonists

Cannabis Extract
- Antibacterials: plasma concentration of cannabis extract reduced by Rifampicin—manufacturer of cannabis extract advises avoid concomitant use
- Antidepressants: plasma concentration of cannabis extract possibly reduced by ST JOHN’S WORT—manufacturer of cannabis extract advises avoid concomitant use; possible

Cannabis Extract (continued)
- increased risk of hypertension and tachycardia when cannabis extract given with TRICYCLES
- Antiepileptics: plasma concentration of cannabis extract possibly reduced by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE—manufacturer of cannabis extract advises avoid concomitant use
- Antifungals: plasma concentration of cannabis extract increased by KETOCONAZOLE

Capecitabine
- Allopurinol: manufacturer of capecitabine advises avoid concomitant use with ALLOPURINOL
- Antibacterial: metabolism of capecitabine inhibited by METRONIDAZOLE (increased toxicity)
- Anticoagulants: capecitabine enhances anticoagulant effect of COUMARINS
- Antiepileptics: capecitabine possibly inhibits metabolism of FOSPHENYTOIN and PHENYTOIN (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)
- Cytotoxics: capecitabine possibly increases plasma concentration of ERLOTINIB
- Filgrastim: neutropenia possibly exacerbated when capecitabine given with FILGRASTIM
- Folates: toxicity of capecitabine increased by FOLIC ACID—avoid concomitant use
- Lipogfilgrastim: neutropenia possibly exacerbated when capecitabine given with LIPOGFILGRASM
- Ppegfilgrastim: neutropenia possibly exacerbated when capecitabine given with PEGFILGRASM
- Ulcer-healing Drugs: metabolism of capecitabine inhibited by CIMETIDINE (increased plasma concentration)

Capreomycin
- Antibacterials: increased risk of nephrotoxicity when capreomycin given with COLISTIMETHATE SODIUM or POLYMIXINS; increased risk of nephrotoxicity and ototoxicity when capreomycin given with AMINGGLYCOSIDES or VANCOMYCIN
- Cytoxics: increased risk of nephrotoxicity and ototoxicity when capreomycin given with PLATINUM COMPOUNDS
- Vaccines: antibacterials inactive ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Captopril see ACE Inhibitors

Carbamazepine
- Alcohol: CNS side-effects of carbamazepine possibly increased by ALCOHOL
- Aminophylline: carbamazepine accelerates metabolism of AMINOPHYLLINE (reduced effect)
- Analgesics: effects of carbamazepine enhanced by DEXTROPROPXYPHENYE; carbamazepine possibly accelerates metabolism of FENTANYL (reduced effect); carbamazepine reduces plasma concentration of METHADONE; carbamazepine reduces effects of TRAMADOL; carbamazepine possibly accelerates metabolism of PARACETAMOL (also isolated reports of hepatotoxicity)
- Anthelmintics: carbamazepine reduces plasma concentration of ALBINDAZOLE and PRAZIQUENTAL—consider increasing albendazole and praziquantel dose when given for systemic infections
- Anti-arrhythmics: carbamazepine possibly reduces plasma concentration of DRONERADONE—avoid concomitant use
- Antibacterials: plasma concentration of carbamazepine increased by CLARITHROMYCIN (consider reducing dose of carbamazepine); plasma concentration of carbamazepine increased by ERYTHROMYCIN; plasma concentration of carbamazepine reduced by RIFABUTIN; carbamazepine accelerates metabolism of DOXYCYCLINE (reduced effect); carbamazepine possibly reduces plasma concentration of BEDAQUELINE—manufacturer of bedaquiline advises avoid concomitant use; avoidance of carbamazepine advised by manufacturer of DELAMANID; plasma concentration of carbamazepine increased by ISOXAZID (also possibly increased isoniazid hepatotoxicity); carbamazepine reduces
Antiepileptics: carbamazepine possibly reduces plasma concentration of antiepileptics—manufacturer of axitinib advises avoid concomitant use for treatment of deep-vein thrombosis or pulmonary embolism; carbamazepine accelerates thrombolysis mechanism of COUMARINS (reduced anticoagulant effect); carbamazepine possibly reduces plasma concentration of DABIGATRAN—manufacturer of dabigatran advises avoid concomitant use; carbamazepine possibly reduces plasma concentration of EDOXABAN; carbamazepine possibly reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis.

Antidepressants: carbamazepine possibly reduces plasma concentration of tricyclics (reduced plasma concentration and reduced effect); carbamazepine possibly reduces plasma concentration of vortioxetine—consider increasing dose of vortioxetine; carbamazepine possibly reduces plasma concentration of ETHOSUXIMIDE and RETIGABINE; plasma concentration of both drugs often reduced when carbamazepine given with fosphenytoin or phenytoin, also plasma concentration of an active metabolite of oxcarbazepine may be increased; carbamazepine often reduces plasma concentration of lamotrigin, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); possible increased risk of carbamazepine toxicity when given with levetiracetam; plasma concentration of carbamazepine sometimes reduced by oxcarbazepine (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; carbamazepine reduces plasma concentration of perampanel (see under Perampanel, p. 301); carbamazepine possibly increases plasma concentration of phenobarbital and primidone; plasma concentration of both drugs possibly reduced when carbamazepine given with rifampicin; plasma concentration of tiagabine and zonisamide; carbamazepine often reduces plasma concentration of topiramate.

Antifungals: plasma concentration of carbamazepine possibly increased by ketoconazole, also plasma concentration of ketoconazole possibly reduced; plasma concentration of carbamazepine possibly increased by fluconazole and miconazole; carbamazepine possibly reduces plasma concentration of isavuconazole and voriconazole—avoid concomitant use; carbamazepine possibly reduces plasma concentration ofitraconazole and posaconazole; carbamazepine possibly reduces plasma concentration of caspofungin—consider increasing dose of caspofungin.

Antimalarias: avoidance of carbamazepine advised by manufacturer of artequinoxil with piperaquine; antiviral effect of antiepileptics antagonised by mefloquine.

Antimuscarnics: carbamazepine possibly reduces plasma concentration of active metabolite of fesoterodine—manufacturer of fesoterodine advises avoid concomitant use.

Antipsychotics: antipsychotic effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered); carbamazepine accelerates metabolism of haloperidol, olanzapine, quetiapine and risperidone (reduced plasma concentration); carbamazepine reduces plasma concentration of aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); carbamazepine accelerates metabolism of clozapine (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; carbamazepine possibly reduces plasma concentration of luradione—avoid concomitant use; carbamazepine reduces plasma concentration of paliperidone.

Antivirals: avoidance of carbamazepine advised by manufacturer of boceprevir and rilpivirine (plasma concentration of boceprevir and rilpivirine possibly reduced); carbamazepine possibly reduces plasma concentration of darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir, and carbamazepine reduces plasma concentration of dasabuvir, omibasvir and paritaprevir—avoid concomitant use; carbamazepine reduces the plasma concentration of dolastatin (see under Dolastatin, p. 592); plasma concentration of both drugs reduced when carbamazepine given with efavirenz; avoidance of carbamazepine advised by manufacturer of elvitegravir, etravirine, ledipasvir, sofosbuvir and telaprevir; carbamazepine possibly reduces plasma concentration of indinavir, also plasma concentration of carbamazepine possibly increased; carbamazepine reduces plasma concentration of nevirapine, plasma concentration of carbamazepine possibly increased by ritonavir.

Anxiolytics and Hypnotics: carbamazepine often reduces plasma concentration of clonazepam; carbamazepine reduces plasma concentration of midazolam.

Apremilast: carbamazepine possibly reduces plasma concentration of apremilast—avoid concomitant use.

Aprepitant: carbamazepine possibly reduces plasma concentration of aprepitant.

Avanafl: carbamazepine possibly reduces plasma concentration of avanafl—manufacturer of avanafl advises avoid concomitant use.

Bupropion: carbamazepine reduces plasma concentration of bupropion.

Calcium-channel Blockers: carbamazepine reduces effects of felodipine and isradipine; carbamazepine probably reduces effects of dihydropyridines, nicardipine and nifedipine; avoidance of carbamazepine advised by manufacturer of nimodipine (plasma concentration of nimodipine possibly reduced); effects of carbamazepine enhanced by dilizium and verapamil.

Cannabis Extract: carbamazepine possibly reduces plasma concentration of cannabis extract—manufacturer of cannabis extract advises avoid concomitant use.

Ciclosporin: carbamazepine accelerates metabolism of ciclosporin.

Clopidogrel: carbamazepine possibly reduces antiplatelet effect of clopidogrel.

Cobicistat: carbamazepine possibly reduces plasma concentration of cobicistat—manufacturer of cobicistat advises avoid concomitant use.

Corticosteroids: carbamazepine accelerates metabolism of corticosteroids (reduced effect).

Cytotoxics: carbamazepine possibly decreases plasma concentration of axitinib (increase dose of axitinib—consult axitinib product literature); carbamazepine possibly reduces plasma concentration of bortezomib, bosutinib, crizotinib, ibritinib, idelalisib and ponatinib advises avoid concomitant use; carbamazepine possibly reduces plasma concentration of cabozantinib and ceritinib—avoid concomitant use; avoidance of...
Carbamazepine
- Cytotoxics (continued)
  carbamazepine advised by manufacturer of
  CABAZITAXEL, DABRAFENIB, GEPITINIB, OLAPARIB and VEMURAFENIB;
  avoidance of carbamazepine advised by manufacturer of
  DASATINIB, VANDETANIB and VISMODEGIB (plasma concentration of dasatinib, vandetanib and vismodegib possibly reduced);
  carbamazepine reduces plasma concentration of IMATINIB and LAPATINIB—avoid concomitant use;
  carbamazepine possibly reduces plasma concentration of ERIFULIN; carbamazepine reduces plasma concentration of IRINOTECAN and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when carbamazepine given with PROCARBAZINE.
- Diuretics: carbamazepine reduces plasma concentration of
  EPLERENONE—avoid concomitant use; increased risk of hyponatraemia when carbamazepine given with DIURETICS; plasma concentration of carbamazepine increased by
  ACETAZOLAMIDE.
- Fingolimod: carbamazepine reduces plasma concentration of
  FINGOLIMOD.
- Fosaprepitant: carbamazepine possibly reduces plasma concentration of
  FOSAPREPIANT.
- Guanfacine: carbamazepine possibly reduces plasma concentration of
  GUANFACINE—increased dose of guanfacine.
- Hormone Antagonists: carbamazepine possibly reduces plasma concentration of
  ABRITERONE—manufacturer of abiraterone advises avoid concomitant use; metabolism of carbamazepine inhibited by
  DANAZOL (increased risk of toxicity); carbamazepine possibly accelerates metabolism of
toremifene (reduced plasma concentration).
- SH3 receptor Antagonists: carbamazepine accelerates metabolism of
  ONDANSETRON (reduced effect).
- Ixacator: carbamazepine possibly reduces plasma concentration of
  IXACAFOR—manufacturer of ixacator advises avoid concomitant use.
- Lipid-regulating Drugs: carbamazepine reduces plasma concentration of
  SIMVASTATIN—consider increasing dose of simvastatin.
- Lithium: neurotoxicity may occur when carbamazepine given with
  LITHIUM without increased plasma concentration of lithium.
- Lumacaftor: plasma concentration of carbamazepine possibly reduced by
  LUMACAFTOR—manufacturer of lumacaftor advises avoid concomitant use.
- Macitentan: avoidance of carbamazepine advised by manufacturer of
  MACITENTAN.
- Muscle Relaxants: carbamazepine antagonises muscle relaxing effect of
  NON-DEPOLARISING MUSCLE RELAXANTS (accelerated recovery from neuromuscular blockade).
- Naloxegol: carbamazepine possibly reduces plasma concentration of
  NALOXEGOL—avoid concomitant use.
- Oestrogens: carbamazepine accelerates metabolism of
  OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC).
- Orlistat: possible increased risk of convulsions when
  antiepileptics given with
  ORLISTAT.
- Panobinostat: avoidance of carbamazepine advised by manufacturer of
  PANOBINOSTAT.
- Progestogens: carbamazepine accelerates metabolism of
  PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC).
- Retinoids: plasma concentration of carbamazepine possibly reduced by
  ISOTRETINOIN.
- Rol氟米酯: carbamazepine possibly inhibits effects of
  ROFLUMILAST (manufacturer of rolfluimilast advises avoid concomitant use).
- Theophylline: carbamazepine accelerates metabolism of
  THEOPHYLLINE (reduced effect).

Carbamazepine (continued)
- Thyroid Hormones: carbamazepine accelerates metabolism of
  THYROID HORMONES (may increase requirements for thyroid hormones in hypothyroidism).
- Tilibone: carbamazepine accelerates metabolism of
  TIBOLONE (reduced plasma concentration).
- Ticagrelor: carbamazepine possibly reduces plasma concentration of
  TICAGRELOR.
- Ulcer-healing Drugs: metabolism of carbamazepine inhibited by
  CIMETIDINE (increased plasma concentration).
- Ulipristal: avoidance of carbamazepine advised by manufacturer of
  ULIPRISTAL (contraceptive effect of ulipristal possibly reduced).
- Vitamins: carbamazepine possibly increases requirements for
  ALFACALCIDOL, CALCIUM, COLECALCIFEROL, DIIHYDROACHYSTEROL, ERGOCALCIFEROL, PARICALCITOL or VITAMIN D.

Carbapenems see Ertapenem, Imipenem with Cilastatin, and Meropenem.

Carbamazepine
- Anticoagulants: carbamazepine possibly increases anticoagulant effect of
  COUMARDIN.
- Carboplatin see Platinum Compounds.
- Carboprost see Prostaglandins.
- Cardiac Glysides
  - ACE Inhibitors: plasma concentration of digoxin possibly increased by
    Captopril.
  - Alpha-blockers: plasma concentration of digoxin increased by
    PRAZOSIN.
  - Aminosalicylates: absorption of digoxin possibly reduced by
    SULFASALAZINE.
  - Analgesics: plasma concentration of cardiac glycosides possibly increased by
    NSAIDS, also possible exacerbation of heart failure and reduction of renal function.
  - Antacids: absorption of digoxin possibly reduced by
    ANTACIDS.
  - Anti-arrhythmics: plasma concentration of digoxin increased by
    AMIODARONE, DRONEDARONE and PROPafenone (halve dose of digoxin).
  - Antibacterials: plasma concentration of digoxin possibly increased by
    GENTAMICIN, TELITHROMYCIN and TRIMETHOPRIM; absorption of digoxin reduced by
    NEOMYCIN; plasma concentration of digoxin possibly reduced by
    RIFAMPICIN; plasma concentration of digoxin increased by
    MACROLIDES (increased risk of toxicity).
  - Antidepressants: plasma concentration of digoxin reduced by
    ST JOHN’S WORT—avoid concomitant use.
  - Antidiabetics: plasma concentration of digoxin possibly reduced by
    ACARBOSE; plasma concentration of digoxin increased by
    CANAGLIFLOZIN and SITAGLITRIPTIN.
  - Anti-epileptics: plasma concentration of digoxin possibly reduced by
    FOSPHENYTOIN and PHENYTOIN.
  - Antifungals: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with
    AMPHOTERICIN; plasma concentration of digoxin increased by
    ISAVONICAZOLE and
    ITRACONAZOLE.
  - Antimalarials: plasma concentration of digoxin possibly increased by
    CHLOROQUINE and HYDROXYCHLOROQUINE; possible increased risk of bradycardia when digoxin given with
    MEfloQUINE; plasma concentration of digoxin increased by
    QUININE.
  - Antimuscarinics: plasma concentration of digoxin possibly increased by
    DARIFENACIN.
  - Antivirals: side-effects of digoxin possibly increased by
    BOCEPREVIR; plasma concentration of digoxin increased by
    DACLATASVIR, ETARAVIRINE, SIMPREVIR and TELAPREVIR; plasma concentration of digoxin possibly increased by
    PARITAPREVIR (consider reducing dose of digoxin); plasma concentration of digoxin possibly increased by
    RITONAVIR.
  - Anxiolytics and Hypnotics: plasma concentration of digoxin increased by
    ALPRAZOLAM (increased risk of toxicity).
  - Beta-blockers: increased risk of AV block and bradycardia when
    cardiac glycosides given with
    BETABLOCKERS.
  - Calcium Salts: arrhythmias can be precipitated when
    cardiac glycosides given with large intravenous doses of
    CALCIUM SALTS.
Ca**rdiac Glycosides** (continued)

- Calcium-channel Blockers: plasma concentration of digoxin increased by [Diltiazem](#), [Lercanidipine](#) and [Nimodipine](#); plasma concentration of digoxin possibly increased by [Nifedipine](#); plasma concentration of digoxin increased by [Verapamil](#), also increased risk of AV block and bradycardia
- Ciclosporin: plasma concentration of digoxin increased by [Ciclosporin](#) (increased risk of toxicity)
- Ciclosporin: plasma concentration of digoxin possibly increased by [Ciclosporin](#) (increased risk of toxicity)
- Ciclosporin: plasma concentration of digoxin possibly increased by [Ciclosporin](#) (increased risk of toxicity)
- Ciclosporin: plasma concentration of digoxin possibly increased by [Ciclosporin](#) (increased risk of toxicity)
- Colchicine: possible increased risk of myopathy when digoxin given with [Colchicine](#)
- Corticosteroids: increased risk of hypokalaemia when cardiac glycosides given with [Corticosteroids](#)
- Cytoxics: absorption of digoxin **tablets** possibly reduced by [Bleomycin](#), [Carmustine](#), [Cyclophosphamide](#), [Cytarabine](#), [Doxorubicin](#), [Melphalan](#), [Methotrexate](#), [Procarbazine](#) and [Vincristine](#) ; possible increased risk of bradycardia when digoxin given with [Cytotoxins](#); manufacturer of digoxin advises give [Ibrutinib](#) at least 6 hours before or after Ibrutinib; plasma concentration of digoxin increased by [Vandetanib](#) — possible increased risk of bradycardia
- Diuretics: plasma concentration of digoxin possibly increased by [Potassium Canrenoate](#); plasma concentration of digoxin increased by [Spironolactone](#) ; increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with [Acetazolamide](#), [Loop Diuretics](#) or [Thiazides and Related Diuretics](#)
- Icacinac: plasma concentration of digoxin possibly increased by [Ivacaftor](#)
- Lenalidomide: plasma concentration of digoxin possibly increased by [Lenalidomide](#)
- Lipid-regulating Drugs: absorption of cardiac glycosides possibly reduced by [Colistin](#) and [Col Streptomycin](#); plasma concentration of digoxin possibly increased by [Aторвастатин](#)
- Mirabegron: plasma concentration of digoxin increased by [Mirabegron](#) — reduced initial dose of digoxin
- Muscle Relaxants: risk of ventricular arrhythmias when cardiac glycosides given with [Suxamethonium](#); possible increased risk of bradycardia when cardiac glycosides given with [Tizanidine](#)
- Penicillamine: plasma concentration of digoxin possibly reduced by [Penicillamine](#)
- Ranolazine: plasma concentration of digoxin increased by [Ranolazine](#)
- Sympathomimetics: avoidance of digoxin advised by manufacturer of [Midodrine](#)
- Sympathomimetics, Beta: plasma concentration of digoxin possibly reduced by [Salbutamol](#)
- Ticagrelor: plasma concentration of digoxin increased by [Ticagrelor](#)
- Tolvaptan: plasma concentration of digoxin increased by [Tolvaptan](#) (increased risk of toxicity)
- Ulcer-healing Drugs: plasma concentration of digoxin possibly increased by [Proton Pump Inhibitors](#); absorption of cardiac glycosides possibly reduced by [Sucralfate](#)
- Ulipristal: manufacturer of ulipristal advises give digoxin at least 1.5 hours before or after [Ulipristal](#)

**Carmustine**

- Antipsychotics: avoid concomitant use of cytoxics with [Clozapine](#) (increased risk of agranulocytosis)
- Cardiac Glycosides: cardustine possibly reduces absorption of [Digoxin](#) tablets
- Ulcer-healing Drugs: myelosuppressive effects of cardustine possibly enhanced by [Cimetidine](#)

**Carpe**tolol see Beta-blockers

**Carvedilol** see Beta-blockers

**Cephalosporins**

- Antimicrobial: plasma concentration of cephalosporin initially increased and then reduced by [Rifampicin](#) (consider increasing dose of cephalosporin)
- Antiepileptics: plasma concentration of cephalosporin possibly reduced by [Carbamazepine](#), [Fosphenytoin](#) and [Phenytoin](#) — consider increasing dose of cephalosporin
- Antivirals: plasma concentration of cephalosporin possibly reduced by [Efavirenz](#) and [Nevirapine](#) — consider increasing dose of cephalosporin

**Caspofungin** (continued)

- Ciclosporin: plasma concentration of caspofungin increased by [Ciclosporin](#) (manufacturer of caspofungin recommends monitoring liver enzymes)
- Corticosteroids: plasma concentration of caspofungin possibly reduced by [Dexamethasone](#) — consider increasing dose of caspofungin
- Tacrolimus: caspofungin reduces plasma concentration of [Tacrolimus](#)

**Catumaxomab**

- Antipsychotics: avoid concomitant use of cytoxics with [Clozapine](#) (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live [Vaccines](#) — avoid concomitant use

**Cefadroxil** see Cephalosporins

**Cefalexin** see Cephalosporins

**Cefixime** see Cephalosporins

**Cefotaxime** see Cephalosporins

**Ceftriaxone** see Cephalosporins

**Cefuroxime** see Cephalosporins

**Celecoxib** see NSAIDs

**Celiprolol** see Beta-blockers

**Cephalosporins**

- Antacids: absorption of cefalor reduced by [Antacids](#)
- Antibacterials: possible increased risk of nephrotoxicity when cephalosporins given with [Aminoglycosides](#)
- Anticoagulants: cephalosporins possibly enhance anticoagulant effect of [Coumarins](#)
- Teriflunomide: plasma concentration of cefalor increased by [Teriflunomide](#)
- Vaccines: antibacterials inactivate [Oral Typhoid Vaccine](#) — see under Typhoid Vaccine in BNF or NBFC

**Ceritinib**

- Analgesics: manufacturer of ceritinib advises avoid concomitant use with [Alfentanil](#) and [Fentanyl](#); possible increased risk of ventricular arrhythmias when ceritinib given with [Methadone](#) and [Disopyramide](#)
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when ceritinib given with [Amiodarone](#) and [Disopyramide](#)
- Antibacterials: possible increased risk of ventricular arrhythmias when ceritinib given with [Clarithromycin](#) and [Moxifloxacin](#); plasma concentration of ceritinib possibly reduced by [Rifabutin](#) — avoid concomitant use; plasma concentration of ceritinib reduced by [Rifampicin](#) — avoid concomitant use; plasma concentration of ceritinib possibly increased by [Telithromycin](#) — avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 861)
- Anticoagulants: manufacturer of ceritinib advises avoid concomitant use with [Warfarin](#)
- Antidepressants: plasma concentration of ceritinib possibly reduced by [St John’s Wort](#) — avoid concomitant use
- Antiepileptics: plasma concentration of ceritinib possibly reduced by [Carbamazepine](#), [Fosphenytoin](#), [Phenobarbital](#), [Phenytoin](#) and [Primidone](#) — avoid concomitant use
- Antifungals: plasma concentration of ceritinib increased by [Ketoconazole](#) — avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 861); plasma concentration of ceritinib possibly increased by [Itraconazole](#), [Posaconazole](#) and [Voriconazole](#) — avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 861)
- Antimalarials: possible increased risk of ventricular arrhythmias when ceritinib given with [Chloroquine](#)
- Antipsychotics: possible increased risk of ventricular arrhythmias when ceritinib given with [Droperidol](#) and [Haloperidol](#) — avoid concomitant use of cytoxics with...
Ceritinib
- Antipsychotics (continued)
  - **CLOzapine** (increased risk of agranulocytosis); manufacturer of ceritinib advises avoid concomitant use with PIMOZIDE
- Antivirals: plasma concentration of ceritinib possibly increased by **RITONAVIR** and **SAQUINAVIR**—avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 86)
  - Ciclosporin: manufacturer of ceritinib advises avoid concomitant use with CICLOSPORIN
- Domperidone; possible increased risk of ventricular arrhythmias when ceritinib given with **DOMPERIDONE**
- Ergot Alkaloids: manufacturer of ceritinib advises avoid concomitant use with ERGOTAMINE
  - Grapefruit Juice: manufacturer of ceritinib advises avoid concomitant use with GRAPEFRUIT JUICE
  - Sirolimus: manufacturer of ceritinib advises avoid concomitant use with SIROLIMUS
  - Tacrolimus: manufacturer of ceritinib advises avoid concomitant use with TACROLIMUS
Cetilizumab pegol
- Abatacept: avoid concomitant use of cetilizumab pegol with **ABATACEPT**
- Anakinra: avoid concomitant use of cetilizumab pegol with **ANAKINRA**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOzapine** (increased risk of agranulocytosis)
  - Vaccines: risk of generalised infections when monoclonal antibodies given with live **VACCINES**—avoid concomitant use

Chloroquine (continued)
- Agalsidase Alfa and Beta: chloroquine possibly inhibits effects of AGALSIDASE ALFA AND ALFA (manufacturers of agalsidase alfa and beta advise avoid concomitant use)
  - Antacids: absorb proton of chloroquine reduced by **ANTACIDS**
  - Anthelmintics: chloroquine reduces plasma concentration of **PRAZIQUANTEL**—consider increasing praziquantel dose when given for systemic infections
  - Antiarhythmics: increased risk of ventricular arrhythmias when chloroquine given with **AMIODARONE**—avoid concomitant use
  - Antibacterials: increased risk of ventricular arrhythmias when chloroquine given with **MOXIFLOXACIN**—avoid concomitant use
  - Antidepressants: possible increased risk of ventricular arrhythmias when chloroquine given with **DROPERIDOL**—avoid concomitant use

Chloramphenicol
- Antibacterials: metabolism of chloramphenicol accelerated by **RIFAMPICIN** (reduced plasma concentration)
  - Anticoagulants: chloramphenicol enhances anticoagulant effect of **COUMARINS**
  - Antidiabetics: chloramphenicol enhances effects of **SULFINPYRINE**
  - Anti-epileptics: chloramphenicol increases plasma concentration of **FOSPHENYTOIN** and **PHENOTIN** (increased risk of toxicity); metabolism of chloramphenicol possibly accelerated by **PHENOBARBITAL** and **PRIMIDONE** (reduced plasma concentration)
  - Antipsychotics: avoid concomitant use of chloramphenicol with **CLOzapine** (increased risk of agranulocytosis)
  - Ciclosporin: chloramphenicol possibly increases plasma concentration of **CICLOSPORIN**
  - Clopidogrel: chloramphenicol possibly reduces antiplatelet effect of **CLOPIDOGREL**
  - Guanfacine: when given with chloramphenicol manufacturer of GUANFACINE advises halve dose
  - Hydroxocobalamin: chloramphenicol reduces response to HYDROXOCOBALAMIN
  - Iron Salts: chloramphenicol possibly inhibits effects of **IRON SALTS**
  - Tacrolimus: chloramphenicol possibly increases plasma concentration of **TACROLIMUS**
  - Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Chlordiazepoxide see Anxiolytics and Hypnotics

Chlorpropionate
- Antibacterials: chlorpropionate possibly inhibits effects of **SULFONAMIDES** (manufacturer of chlorpropionate advises avoid concomitant use)

Chloroquine
- Adsorbents: absorption of chloroquine reduced by KAOLIN

Chloroplacine
- Antabuse: chloroplacine possibly inhibits effects of **NAPHTHOLS** (manufacturer of chloroplacine advises avoid concomitant use)
Ciclosporin

- Antibacterials: concentration of ciclosporin possibly reduced by:
  - SULFAZIDINE; increased risk of nephrotoxicity when ciclosporin given with:
  - AMINOLGICOSIDES, POLYMYXINS, QUINOLONES, SULFONAMIDES or VANCOMYCIN; plasma concentration of ciclosporin possibly increased by:
  - CHLORAMPHENICOL and TETRITHROMYCIN; increased risk of myopathy when ciclosporin given with:
  - DAPTOMYCIN (preferably avoid concomitant use); avoidance of ciclosporin advised by manufacturer of FIDAXOMICIN; metabolism of ciclosporin possibly inhibited by:
  - MACROLIDES; increased plasma concentration; ciclosporin increases plasma concentration of:
  - RIFAMICIN; increased risk of nephrotoxicity when ciclosporin given with:
  - TRIMETHOPRIM, also plasma concentration of ciclosporin reduced by intravenous trimethoprim
- Anticoagulants: ciclosporin possibly increases plasma concentration of:
  - DABIGATRAN — manufacturer of dabigatran advises avoid concomitant use; ciclosporin increases plasma concentration of:
  - EDOXABAN (reduce dose of edoxaban — see under Edoxaban, p. 118)
- Antidepressants: plasma concentration of ciclosporin reduced by:
  - ST JOHN'S WORT — avoid concomitant use
- Antidiabetics: ciclosporin possibly enhances hypoglycaemic effect of REPAGLITINIDE
- Antiepileptics: metabolism of ciclosporin accelerated by:
  - CARBAMAZEPINE, FOSPHENYTIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by:
  - DXCABAZEPINE
- Antiinflamnals: metabolism of ciclosporin inhibited by:
  - FLUCONAZOLE, ITRACONAZOLE, KETOCONAZOLE, POSaconazole and VORICONAZOLE (increased plasma concentration); metabolism of ciclosporin possibly inhibited by:
  - MICANOZOLE (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with:
  - AMPHOTERICIN; plasma concentration of ciclosporin increased by:
  - ISAVONAZOLE; ciclosporin increases plasma concentration of:
  - CASPOFUNGIN (manufacturer of caspofungin recommends monitoring liver enzymes); plasma concentration of ciclosporin possibly reduced by:
  - GRISOFULVIN and TERBINAFINE; ciclosporin concentration of ciclosporin possibly increased by:
  - MICAFUNGIN
- Antimalarials: plasma concentration of ciclosporin increased by:
  - CHLOROQUINE and HYDROXYCHLOROQUINE (increased risk of toxicity)
- Antimuscarnics: avoidance of ciclosporin advised by manufacturer of:
  - DARIFENACIN
- Antibacterials: increased risk of nephrotoxicity when ciclosporin given with:
  - ACICLOVIR or VALACLOVIR; plasma concentration of ciclosporin possibly increased by:
  - ATAZANAVIR and RITONAVIR; plasma concentration of ciclosporin increased by:
  - BOCEPREVIR, FOSAMPRENARVIR and INIDINAVIR; plasma concentration of ciclosporin possibly reduced by:
  - EFAVIRENZ; plasma concentration of both drugs increased when ciclosporin given with:
  - SACAQINAVIR; plasma concentration of both drugs increased when ciclosporin given with:
  - TELAPREVIR (reduce dose of ciclosporin)
- Beta-blockers: plasma concentration of ciclosporin increased by:
  - CARVEDIOL
- Bile Acids: avoidance of ciclosporin advised by manufacturer of:
  - CHOLIC ACID; absorption of ciclosporin increased by:
  - URSODEOXYCHOLIC ACID
- Bosentan: ciclosporin increases plasma concentration of:
  - BOSENTAN (also plasma concentration of ciclosporin reduced—avoid concomitant use)
- Calcium-channel Blockers: combination of ciclosporin with:
  - LERCANDIPINE may increase plasma concentration of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by:
  - DILTIAZEM, NICARDIPINE and VERAPAMIL; ciclosporin possibly increases plasma concentration of:
  - NIFEDIPINE (increased risk of toxicity including gingival hyperplasia)
- Cardiac Glycosides: ciclosporin increases plasma concentration of:
  - DIGOXIN (increased risk of toxicity)

Ciclosporin (continued)

- Colchicine: possible increased risk of nephrotoxicity and myotoxicity when ciclosporin given with:
  - COLCHICINE — suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: plasma concentration of ciclosporin increased by high-dose:
  - METHYLPREDNISOLONE (risk of convulsions); ciclosporin increases plasma concentration of:
  - PRENISOLONE
- Cytotoxics: increased risk of nephrotoxicity when ciclosporin given with:
  - MELPHALAN; increased risk of neurotoxicity when ciclosporin given with:
  - DOXORUBICIN; ciclosporin increases plasma concentration of:
  - EPIRUBICIN and IDARUBICIN; ciclosporin reduces excretion of:
  - MITOXANTRONE (increased plasma concentration); risk of toxicity when ciclosporin given with:
  - METHOTREXATE; ciclosporin possibly increases the plasma concentration of:
  - AFATINIB — manufacturer of afatinib advises separating administration of ciclosporin by 6 to 12 hours; avoidance of ciclosporin advised by manufacturer of:
  - CERITINIB; caution with ciclosporin advised by manufacturer of:
  - CRIZOTINIB; ciclosporin increases plasma concentration of:
  - EVEROLIMUS (consider reducing the dose of everolimus — consult everolimus product literature); plasma concentration of ciclosporin possibly increased by:
  - IMATINIB; in vitro studies suggest a possible interaction between ciclosporin and:
  - DOXETAXEL (consult doxetaxel product literature); ciclosporin possibly increases plasma concentration of:
  - ETOPOSIDE (increased risk of toxicity)
- Dexamethasone: increased risk of immunosuppression with ciclosporin advised by manufacturer of:
  - DEXRAXOZANE
- Diuretics: plasma concentration of ciclosporin possibly increased by:
  - ACETAZOLAMIDE; increased risk of hyperkalaemia when ciclosporin given with:
  - ALDOSTERONE ANTAGONISTS or POTASSIUM-SPARING DIURETICS; increased risk of nephrotoxicity and possibly hypermagnesaemia when ciclosporin given with:
  - THIAZIDES AND RELATED DIURETICS
- Grapefruit Juice: plasma concentration of ciclosporin increased by:
  - GRAPEFRUIT JUICE (increased risk of toxicity)
- Hormone Antagonists: metabolism of ciclosporin inhibited by:
  - GALANZOL (increased plasma concentration); plasma concentration of ciclosporin reduced by:
  - LAMOTRIGINE and OXCARBAZEPINE; increased risk of nephrotoxicity when ciclosporin given with:
  - PASIREOTIDE
- Lenalidomide: ciclosporin possibly increases plasma concentration of:
  - LENALIDOMIDE (increased risk of toxicity)
- Lipid-regulating Drugs: absorption of ciclosporin reduced by:
  - COLESSELAM; increased risk of renal impairment when ciclosporin given with:
  - BEZAFIBRATE or FENOFLIBRATE; increased risk of myopathy when ciclosporin given with:
  - ATORVASTATIN (see under Atorvastatin, p. 191); increased risk of myopathy when ciclosporin given with:
  - FLUVASTATIN or PRAVASTATIN; increased risk of myopathy when ciclosporin given with:
  - ROSUVASTATIN or SIMVASTATIN (avoid concomitant use); plasma concentration of both drugs may increase when ciclosporin given with:
  - EZETIMIBE; separating administration from ciclosporin by 12 hours advised by manufacturer of:
  - LOMITAPIDE
- Lumacaftor: avoidance of ciclosporin advised by manufacturer of:
  - LUMACTAUR
- Mannitol: possible increased risk of nephrotoxicity when ciclosporin given with:
  - MANNITOL
- Metoclopimamide: plasma concentration of ciclosporin increased by:
  - METOCLOPRAMIDE
- Mifamurtide: avoidance of ciclosporin advised by manufacturer of:
  - MIFAMURTIDE
- Modafinil: plasma concentration of ciclosporin reduced by:
  - MODAFINIL
- Oestrogens: plasma concentration of ciclosporin possibly increased by:
  - OESTROGENS
- Orlistat: absorption of ciclosporin possibly reduced by:
  - ORLISTAT
- Potassium Salts: increased risk of hyperkalaemia when ciclosporin given with:
  - POTASSIUM SALTS
- Progestogens: plasma concentration of ciclosporin possibly increased by:
  - PROGESTOGENS
- Ranolazine: plasma concentration of both drugs may increase when ciclosporin given with:
  - RANOLAZINE

Interactions

Appendix 1

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Ciclosporin — Ciclosporin 1257
Clonidine (continued)

- Adrenergic Neurone Blockers: enhanced hypotensive effect when clonidine given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypotensive effect when clonidine given with ALCOHOL
- Aldesleukin: enhanced hypotensive effect when clonidine given with ALDESLEUKIN
- Alpha-blockers: enhanced hypotensive effect when clonidine given with ALPHA-BLOCKERS
- Anaesthetics, General: enhanced hypotensive effect when clonidine given with GENERAL ANAESTHETICS
- Analgesics: hypotensive effect of clonidine antagonised by NSAIDS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when clonidine given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antidepressants: enhanced hypotensive effect when clonidine given with MAOIS; hypotensive effect of clonidine possibly antagonised by MIRTAZAPINE; hypotensive effect of clonidine antagonised by TRICYCLICS, also increased risk of hypertension on clonidine withdrawal
- Antipsychotics: enhanced hypotensive effect when clonidine given with PHENOTHIAZINES
- Anxiolytics and Hypnotics: enhanced hypotensive effect when clonidine given with ANXIOLYTICS AND HYPNOTICS
- Beta-blockers: increased risk of withdrawal hypertension when clonidine given with BETA-BLOCKERS (withdraw beta-blockers several days before slowly withdrawing clonidine)
- Calcium-channel Blockers: enhanced hypotensive effect when clonidine given with CALCIUM-CHANNEL BLOCKERS
- Corticosteroids: hypotensive effect of clonidine antagonised by CORTICOSTEROIDS
- Cytoxics: possible increased risk of bradycardia when clonidine given with CRIZOTINIB
- Diazoxide: enhanced hypotensive effect when clonidine given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when clonidine given with DIURETICS
- Dopaminergics: enhanced hypotensive effect when clonidine given with DOPAMINE
- Oestrogens: hypotensive effect of clonidine antagonised by OESTROGENS
- Prostaglandins: enhanced hypotensive effect when clonidine given with ALPROSTADIL
- Sympathomimetcs: possible risk of hypertension when clonidine given with ADRENALINE (EPINEPHRINE) or NORADEXALINE (NOREPINEPHRINE); serious adverse events reported with concomitant use of clonidine and METHYLPHENIDATE (causality not established)
- Vasodilator Antihypertensives: enhanced hypotensive effect when clonidine given with HYDRAZALINE, MINOXIDIL or SODIUM NITROPRUSIDE

Clopidogrel

- Analgesics: increased risk of bleeding when clopidogrel given with NSAIDS or ASPIRIN
- Antibacterials: antiplatelet effect of clopidogrel possibly reduced by CHLORAMPHENICOL, CIPROFLOXACIN and ERYTHROMYCIN
- Anticoagulants: manufacturer of clopidogrel advises avoid concomitant use with WARFARIN; antiplatelet action of clopidogrel enhances anticoagulant effect of COUMARINS and PHENINDIONE; increased risk of bleeding when clopidogrel given with HEPARINS

Clindamycin

- Adverse effects: Clindamycin increases plasma concentration of SIROLIMUS
- Sulfonpyrazone: plasma concentration of clindamycin possibly reduced by SULFONPYRAZONE
- Tacrolimus: plasma concentration of clindamycin increased by TACROLIMUS (increased risk of nephrotoxicity)—avoid concomitant use
- Ticagrelor: clopidogrel increases plasma concentration of TICAGRELOR
- Ulcer-healing Drugs: plasma concentration of clindamycin possibly increased by Cimetidine; plasma concentration of clindamycin possibly affected by Omeprazole
- Vitamins: plasma concentration of clindamycin possibly affected by VITAMIN E

Clonazepam

- Anxiolytics and Hypnotics
- Antidepressants, SSRI
- Antihistamines
- Histamine: avoid concomitant use of clonidine with Antiplatelet action of clopidogrel possibly reduced by CHLORAMPHENICOL, CIPROFLOXACIN and ERYTHROMYCIN
Clozapine see Co-amoxiclav

▶ Memantine:

▶ Iron Salts:

▶ Diuretics:

▶ Clonidine:

▶ Calcium-channel Blockers:

▶ Anxiolytics and Hypnotics:

▶ Antimuscarinics:

▶ Antidepressants:

▶ Alpha-blockers:

▶ Adrenergic Neurone Blockers:

▶ Ulcer-healing Drugs: clopidogrel

ANTAGONISTS after stopping MAOIs; increased risk of side-effects when co-given with beneldopa when given with

enhanced hypotensive effect when co-beneldopa given with

increased risk of side-effects when co-beneldopa given with

absorption of co-beneldopa possibly reduced

risk of hypertensive crisis when co-beneldopa given with

ISONIAZID

Antidepressants: risk of hypertensive crisis when co-beneldopa given with MAOIs; increased risk of side-effects when co-beneldopa given with moclobemide

Antiepileptics: effects of co-beneldopa possibly reduced by fosphenytoin and phenytoin

Antimuscarinics: absorption of co-beneldopa possibly reduced by antimuscarinics

Antipsychotics: effects of co-beneldopa antagonised by antipsychotics; avoidance of co-beneldopa advised by manufacturer of amisulpride (agonist of effect)

Anxiolytics and Hypnotics: effects of co-beneldopa possibly antagonised by benzodiazepines

Beta-blockers: enhanced hypotensive effect when co-beneldopa given with beta-blockers

Bupropion: increased risk of side-effects when co-beneldopa given with bupropion

Calcium-channel Blockers: enhanced hypotensive effect when co-beneldopa given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when co-beneldopa given with clonidine

Diazoxide: enhanced hypotensive effect when co-beneldopa given with diazoxide

Diuretics: enhanced hypotensive effect when co-beneldopa given with diuretics

Dopaminergics: enhanced effects and increased toxicity of co-beneldopa when given with selegiline (reduce dose of co-beneldopa)

Iron Salts: absorption of co-beneldopa possibly reduced by oral iron salts

Mecamylamine: effects of dopaminergics possibly enhanced by mecamylamine

Methyldopa: enhanced hypotensive effect when co-beneldopa given with methyldopa; antiparkinsonian effect of dopaminergics antagonised by methyldopa

Clopidogrel (continued) All interactions are described below. 

Clopidogrel (continued) Antidepressants: antplatelet effect of clopidogrel possibly reduced by fluoxetine, fluvoxamine and moclobemide

Antiepileptics: antplatelet effect of clopidogrel possibly reduced by carbamazepine and oxcarbazepine

Antifungals: antplatelet effect of clopidogrel possibly reduced by fluconazole, itraconazole, ketoconazole and voriconazole

Antivirals: antplatelet effect of clopidogrel possibly reduced by etravirine

Dipyriramole: increased risk of bleeding when clopidogrel given with dipyriramole

Iloprost: increased risk of bleeding when clopidogrel given with iloprost

Lipid-regulating Drugs: clopidogrel increases plasma concentration of rosuvastatin — adjust dose of rosuvastatin (consult product literature)

Prasugrel: possible increased risk of bleeding when clopidogrel given with prasugrel

Ulcer-healing Drugs: clopidogrel increases plasma concentration of omeprazole and esomeprazole

Clotrimazole see Antifungals, imidazole

Clozapine see Antipsychotics

Co-amoxiclav see Penicillins

Co-beneldopa ▶ ACE Inhibitors: enhanced hypotensive effect when co-beneldopa given with ACE INHIBITORS

Adrenergic Neurone Blockers: enhanced hypotensive effect when co-beneldopa given with adrenergic neurone blockers

Alpha-blockers: enhanced hypotensive effect when co-beneldopa given with alpha-blockers

Anaesthetics, General: increased risk of arrhythmias when co-beneldopa given with volatile liquid general anaesthetics

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when co-beneldopa given with angiotensin-II receptor antagonists

Redbloodcell: effects of co-beneldopa possibly reduced by isoniazid

Antidepressants: risk of hypertensive crisis when co-beneldopa given with madopar, avoid co-beneldopa for at least 2 weeks after stopping MAOIs; increased risk of side-effects when co-beneldopa given with moclobemide

Antiepileptics: effects of co-beneldopa possibly reduced by fosphenytoin and phenytoin

Pharmacokinetic Interactions: absorption of co-beneldopa possibly reduced by antimuscarinics

Antipsychotics: effects of co-beneldopa antagonised by antipsychotics; avoidance of co-beneldopa advised by manufacturer of amisulpride (agonist of effect)

Anxiolytics and Hypnotics: effects of co-beneldopa possibly antagonised by benzodiazepines

Beta-blockers: enhanced hypotensive effect when co-beneldopa given with beta-blockers

Bupropion: increased risk of side-effects when co-beneldopa given with bupropion

Calcium-channel Blockers: enhanced hypotensive effect when co-beneldopa given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when co-beneldopa given with clonidine

Diazoxide: enhanced hypotensive effect when co-beneldopa given with diazoxide

Diuretics: enhanced hypotensive effect when co-beneldopa given with diuretics

Dopaminergics: enhanced effects and increased toxicity of co-beneldopa when given with selegiline (reduce dose of co-beneldopa)

Iron Salts: absorption of co-beneldopa possibly reduced by oral iron salts

Mecamylamine: effects of dopaminergics possibly enhanced by mecamylamine

Methyldopa: enhanced hypotensive effect when co-beneldopa given with methyldopa; antiparkinsonian effect of dopaminergics antagonised by methyldopa

Co-beneldopa (continued) ▶ Moxonidine: enhanced hypotensive effect when co-beneldopa given with moxonidine

Muscle Relaxants: possible agitation, confusion and hallucinations when co-beneldopa given with baclofen

Nitrates: enhanced hypotensive effect when co-beneldopa given with nitrates

Vasodilator Antihypertensives: enhanced hypotensive effect when co-beneldopa given with hydralazine, minoxidil or sodium nitroprusside

Cobicistat • Alpha-blockers: cobicistat possibly increases plasma concentration of alfuzosin — manufacturer of cobicistat advises avoid concomitant use

Anti-arrhythmics: cobicistat possibly increases plasma concentration of amiodarone — manufacturer of cobicistat advises avoid concomitant use

Antiinfectives: cobicistat possibly increases plasma concentration of rifabutin (adjust dose — consult product literature); plasma concentration of cobicistat possibly reduced by rifampicin — manufacturer of cobicistat advises avoid concomitant use

Anticoagulants: avoidance of cobicistat advised by manufacturer of apixaban; cobicistat possibly enhances anticoagulant effect of rivaroxaban — avoid concomitant use

Antidepressants: plasma concentration of cobicistat possibly reduced by st john’s wort — manufacturer of cobicistat advises avoid concomitant use

Antiepileptics: plasma concentration of cobicistat possibly reduced by carbamazepine, fosphenytoin, phenobarbital and primidone — manufacturer of cobicistat advises avoid concomitant use

Antifungals: cobicistat possibly increases plasma concentration of itraconazole and ketoconazole — manufacturer of cobicistat advises reduce dose of itraconazole and ketoconazole

Antipsychotics: cobicistat possibly increases plasma concentration of lurasidone — avoid concomitant use; cobicistat possibly increases plasma concentration of pimozide — manufacturer of cobicistat advises avoid concomitant use

Antivirals: manufacturer of cobicistat advises avoid concomitant use with boceprevir and ritonavir; cobicistat possibly increases the plasma concentration of daclatasvir — reduce dose of daclatasvir (see under daclatasvir, p. 577); avoidance of cobicistat advised by manufacturer of dasabuvir, nevirapine, ombitasvir and paritaprevir; cobicistat possibly increases plasma concentration of maraviroc (reduce dose of maraviroc); cobicistat possibly increases plasma concentration of simprevir — manufacturer of simprevir advises avoid concomitant use; plasma concentration of both drugs reduced when cobicistat given with tipranavir (avoid concomitant use)

Anxiolytics and Hypnotics: manufacturer of cobicistat advises avoid concomitant use with oral midazolam

Avanafil: cobicistat possibly increases plasma concentration of avanafil — avoid concomitant use

Boventan: manufacturer of cobicistat advises avoid concomitant use with boventan

Cardiac Glycosides: cobicistat possibly increases plasma concentration of digoxin — reduce initial dose of digoxin

Cytotoxics: cobicistat possibly increases the plasma concentration of ibritinib — reduce dose of ibritinib (see under ibritinib, p. 867); cobicistat possibly increases plasma concentration of olaparib (avoid concomitant use or reduce dose of olaparib — see under olaparib, p. 881)

Dorperidone: possible increased risk of venricular arrhythmias when cobicistat given with domperidone — avoid concomitant use

Ergot Alkaloids: cobicistat possibly increases plasma concentration of ergot alkaloids — manufacturer of cobicistat advises avoid concomitant use

Lipid-regulating Drugs: cobicistat possibly increases plasma concentration of atorvastatin — manufacturer of cobicistat
Cobicistat

- Lipid-regulating Drugs: co-careldopa given with Cobicistat increases plasma concentration of NORGESTIMATE.
- Sildenafil: co-careldopa given with Cobicistat increases plasma concentration of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction—consult cobicistat product literature.
- Sympathomimetics, Beta2: manufacturer of cobicistat avoids concomitant use with SALMETEROL.
- Tadalafil: manufacturer of cobicistat advises avoid concomitant use with antidepressants, anticoagulants, anticonvulsants, calcium channel blockers, combination products, cyclosporin, dopamine agonists, dopamine antagonists, dopaminergics, fluoxetine, interferon beta, ketoconazole, lurasidone, milnacipran, moclobemide, nortriptyline, paroxetine, quetiapine, TCAs.
- Vardenafil: manufacturer of cobicistat advises reduce dose of vardenafil (consult cobicistat product literature).
- Vardenafil: manufacturer of cobicistat advises reduce dose of vardenafil (consult cobicistat product literature).
- Alpha-blockers: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Alpha-blockers: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Beta-blockers: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Beta-blockers: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Clonidine: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Diazoxide: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Diuretics: enhanced hypertensive effect when co-careldopa given with Cobicistat advised.
- Dopaminergics: enhanced effects and increased toxicity of co-careldopa when given with Cobicistat advised.
- Iron Salts: absorption of co-careldopa possibly reduced by oral IRON SALTS.
- Memantine: effects of dopamineergics possibly enhanced by Memantine.
- Methyldopa: enhanced hypertensive effect when co-careldopa given with Methyldopa; antiparkinsonian effect of dopamineergics antagonised by Methyldopa.
- Muscle Relaxants: possible agitation, confusion and hallucinations when co-careldopa given with Baclofen.

Colestipol

- Antidiabetics: canagliflozin and dapagliflozin (give at least 4 hours apart).
- Calcium channel blockers: possible increased risk of myopathy when given with Fosphenytoin and Phenytoin.
- Antiepileptics: effects of co-careldopa possibly reduced by Phenytoin.
- Antidepressants: risk of hypertensive crisis when co-careldopa given with MAOIs, avoid co-careldopa for at least 2 weeks after stopping MAOIs; increased risk of side-effects when co-careldopa given with moclobemide.
- Antipsychotics: effects of co-careldopa possibly antagonised by Benzodiazepines.
- Beta-blockers: enhanced hypertensive effect when co-careldopa given with Beta-blockers.
- Bupropion: increased risk of side-effects when co-careldopa given with Bupropion.
- Calcium channel blockers: enhanced hypertensive effect when co-careldopa given with Calcium-channel blockers.
- Cholecalciferol see Vitamins.
- Colesevelam

- Antidiabetics: colesevelam reduces absorption of Glimepiride and Glipizide; colesevelam reduces absorption of Glimepiride—manufacturer of glimepiride advises given at least 4 hours before colchicine; manufacturer of canagliflozin advises give bile acid sequestrants at least 1 hour after or 4–6 before Canagliflozin.
- Antiepileptics: colesevelam possibly reduces absorption of Fosphenytoin and Phenytoin.
- Bile Acids: colesevelam probabaly reduces effects of Cholic Acid (manufacturer of cholic acid advises give at least 5 hours apart).
- Calcium channel blockers: possible increased risk of myopathy when given with Lipid-regulating Drugs: bile acid sequestrants possibly reduce absorption of Lomitapide (give at least 4 hours apart).
- Colesevelam

- Other drugs should be taken at least 4 hours before or after colesevelam to reduce possible interference with absorption.

Colestipol

- Note other drugs should be taken at least 1 hour before or 4–6 hours after colesevelam to reduce possible interference with absorption.
- Antidiabetics: colesevelam reduces absorption of Cholic Acid (manufacturer of cholic acid advises give at least 5 hours apart).
- Bile Acids: colesevelam possibly reduces absorption of Bile Acids; colesevelam probably reduces effects of Cholic Acid (manufacturer of cholic acid advises give at least 5 hours apart).
Colestipol — Corticosteroids 1261

Corticosteroids (continued)
- Anthelmintics: dexamethasone increases plasma concentration of active metabolite of ALBENDAZOLE; continuous use of dexamethasone possibly reduces plasma concentration of ALBENDAZOLE.
- Anticholinergics: plasma concentration of methylprednisolone possibly increased by CLARITHROMYCIN; metabolism of corticosteroids possibly inhibited by ERYTHROMYCIN; metabolism of methylprednisolone inhibited by ERYTHROMYCIN; corticosteroids possibly reduce plasma concentration of ISONIAZID; metabolism of corticosteroids accelerated by rifampicin (reduced effect).
- Anticoagulants: corticosteroids may enhance or reduce anticoagulant effect of coumarins (high-dose corticosteroids enhance anticoagulant effect); corticosteroids may enhance or reduce anticoagulant effect of phenindione.
- Antiangiotics: corticosteroids antagonise hypoglycaemic effect of antidiabetics.
- Antiepileptics: metabolism of corticosteroids accelerated by gabapentin, lamotrigine, phenytoin, primidone (reduced effect).
- Antifungals: metabolism of corticosteroids possibly inhibited by itraconazole and ketoconazole; plasma concentration of active metabolite of ciclosporine increased by ketoconazole; plasma concentration of intranasal mometasone increased by ketoconazole; plasma concentration of intranasal and oral (and possibly also intranasal and rectal) budesonide increased by itraconazole and ketoconazole; plasma concentration of fluticasone increased by itraconazole; metabolism of methylprednisolone inhibited by ketoconazole; increased risk of hypokalaemia when corticosteroids given with amphotericin — avoid unless drug concomitant use unless corticosteroids needed to control reactions; plasma concentration of intranasal fluticasone increased by itraconazole; metabolism of methylprednisolone possibly inhibited by itraconazole; dexamethasone possibly reduces plasma concentration of caspofungin — consider increasing dose of caspofungin.
- Antivirals: dexamethasone possibly reduces plasma concentration of daclatasvir and simprevir — manufacturer of daclatasvir and simprevir advises avoid concomitant use; dexamethasone possibly reduces plasma concentration of indinavir, lopinavir, saquinavir and telaprevir; avoidance of dexamethasone (except when given as a single dose) advised by manufacturer of rilpivirine; plasma concentration of budesonide (including intranasal, intranasal, and rectal budesonide) possibly increased by ritonavir — increased risk of adrenal suppression; plasma concentration of corticosteroids possibly increased by ritonavir — increased risk of adrenal suppression; plasma concentration of triamcinolone injection increased by ritonavir — increased risk of adrenal suppression; plasma concentration of intranasal and intranasal fluticasone increased by ritonavir — increased risk of adrenal suppression; plasma concentration of intranasal and intranasal budesonide and fluticasone possibly increased by telaprevir.
- Aprepitant: metabolism of dexamethasone and methylprednisolone inhibited by aprepitant (reduce dose of dexamethasone and methylprednisolone).
- Beta-blockers: corticosteroids antagonise hypotensive effect of beta-blockers.
- Calcium salts: corticosteroids reduce absorption of calcium salts.
- Calcium-channel blockers: corticosteroids antagonise hypotensive effect of calcium-channel blockers; plasma concentration of methylprednisolone increased by diltiazem.
- Cardiac glycosides: increased risk of hypokalaemia when corticosteroids given with cardiac glycosides.
- Ciclosporin: high-dose methylprednisolone increases plasma concentration of ciclosporin (risk of convulsions); plasma concentration of prednisolone increased by ciclosporin.
- Clonidine: corticosteroids antagonise hypotensive effect of clonidine.
- Cytotoxics: possible increased risk of hepatotoxicity when dexamethasone given with high-dose methotrexate; dexamethasone possibly decreases plasma concentration of...
Corticosteroids — Coumarins

Corticosteroids
Cytoxics (continued)
AXITINIB (increase dose of axitinib—consult axitinib product literature); dexamethasone possibly reduces plasma concentration of CABOZANTINIB—manufacturer of cabozantinib advises avoid concomitant use
• Diazoxide; corticosteroids antagonise hypothensive effect of DIAZoxide
• Diuretics: corticosteroids antagonise diuretic effect of DIURETICS; increased risk of hypokalaemia when corticosteroids given with ACETAZOLAMIDE, LOOP DIURETICS or THIAZIDES AND RELATED DIURETICS
• Fosaprepitant: metabolism of dexamethasone and methylprednisolone inhibited by FOSAPREPITANT (reduce dose of dexamethasone and methylprednisolone)
• Grapefruit Juice: plasma concentration of oral budesonide increased by GRAPEFRUIT JUICE—avoid concurrent use or separate administration by as much as possible and consider reducing oral budesonide dose
• Histamine: avoidance of corticosteroids advised by manufacturer of HISTAMINE
• Methylprednisolone: corticosteroids antagonise hypothensive effect of METHYLPREDNISOLONE
• Mifepristone: effect of corticosteroids (including inhaled corticosteroids) may be reduced for 3–4 days after MIFEPRISTONE
• Moxonidine: corticosteroids antagonise hypothensive effect of MOXONIDINE
• Muscle Relaxants: corticosteroids possibly antagonise effects of PANCURONIUM and VEкрыRONIUM
• Netupitant: plasma concentration of dexamethasone increased by NETUPITANT (halve dose of dexamethasone)
• Niconardil: increased risk of gastro-intestinal bleeding and ulceration when corticosteroids given with NICORANDIL
• Nitrates: corticosteroids antagonise hypothensive effect of NITRATES
• Oestrogens: plasma concentration of corticosteroids increased by oral contraceptive containing OESTROGENS
• Panobinostat: dexamethasone reduces plasma concentration of PANOBINOSTAT
• Sodium Benzoate: corticosteroids possibly reduce effects of SODIUM BENZOATE
• Sodium Phenylbutyrate: corticosteroids possibly reduce effects of SODIUM PHENYL BUTYRATE
• Somatropin: corticosteroids may inhibit growth-promoting effect of SOMATROPIN
• Symptomimetics: metabolism of dexamethasone accelerated by EPHEDRINE; possible risk of hypertension when corticosteroids given with MIDODRINE
• Symptomimetics, Beta₂: increased risk of hypokalaemia when corticosteroids given with high doses of BETA₂ SYMPTOMIMETICS
• Theophylline: increased risk of hypokalaemia when corticosteroids given with THEOPHYLLINE
• Vaccines: high doses of corticosteroids impair immune response to VACCINES—avoid concomitant use with live vaccines
• Vasodilator Antihypertensives: corticosteroids antagonise hypothensive effect of HYDRALAZINE, MINOXIDIL and SODIUM NITROPRUSSIDE

Co-trimoxazole see Trimethoprim and Sulfamethoxazole

Coumarins
NOTE Change in patient’s clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control
• Alcohol: anticoagulant control with coumarins may be affected by major changes in consumption of ALCOHOL
• Allopurinol: anticoagulant effect of coumarins possibly enhanced by ALLOPURINOL
• Anabolic Steroids: anticoagulant effect of coumarins enhanced by ANABOLIC STEROIDS

Coumarins (continued)
• Analgesics: anticoagulant effect of coumarins possibly enhanced by NSAIDS; increased risk of haemorrhage when anticoagulants given with intravenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with ETOROLAC (avoid concomitant use, including low-dose heparins); anticoagulant effect of coumarins enhanced by TRAMADOL; increased risk of bleeding when coumarins given with ASPIRIN (due to antiplatelet effect); anticoagulant effect of coumarins possibly enhanced by prolonged regular use of PARACETAMOL

Antihelminths: anticoagulant effect of coumarins possibly enhanced by IVERMECTIN; anticoagulant effect of warfarin possibly enhanced by LEVAMISOLE
• Anti-arrhythmics: metabolism of coumarins inhibited by AMIODARONE (enhanced anticoagulant effect); anticoagulant effect of warfarin may be enhanced or reduced by DISOPYRAMIDE; anticoagulant effect of coumarins possibly enhanced by DRONEDARONE; anticoagulant effect of coumarins enhanced by PROPafenONE

Antibacterials: experience in anticoagulant clinics suggests that INR possibly altered when coumarins are given with NEOMYCIN (given for local action on gut); anticoagulant effect of coumarins possibly enhanced by AZITHROMYCIN, AZTREONAM, CEPHALOSPORINS, CIPROFLOXACIN, LEVOFLOXACIN, TETRACYCLINES, TIGECYCLINE and TRIMETHOPRIM; anticoagulant effect of coumarins enhanced by CHLORAMPHENICOL, CLARITHROMYCIN, ERYTHROMYCIN, METRONIDAZOLE, NALIDIXIC ACID, NORFLOXACIN, OFLOXACIN and SULFONAMIDES; plasma concentration of warfarin possibly increased by ORITAVANCIN; an interaction between coumarins and broad-spectrum PENICILLINS has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered; metabolism of coumarins accelerated by RIFAMYCINS (reduced anticoagulant effect); anticoagulant effect of warfarin possibly reduced by RIFAXIMIN

Anticoagulants: increased risk of haemorrhage when other anticoagulants given with APIXABAN, DABIGATRAN, EDOXABAN and RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
• Antidepressants: anticoagulant effect of warfarin possibly enhanced by VENLAFAXINE; anticoagulant effect of warfarin may be enhanced or reduced by TRAZODONE; anticoagulant effect of coumarins possibly enhanced by SSRI'S; anticoagulant effect of coumarins reduced by ST JOHN’S WORT (avoid concomitant use); anticoagulant effect of warfarin enhanced by MIRTAZAPINE; anticoagulant effect of coumarins may be enhanced or reduced by TRICYCLICS

Antidiabetics: anticoagulant effect of warfarin possibly enhanced by EXENATIDE; coumarins possibly enhance hypoglycaemic effect of SULFONYLUREAS, also possible changes to anticoagulant effect
• Antiepileptics: metabolism of coumarins accelerated by CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE (reduced anticoagulant effect); plasma concentration of warfarin reduced by ESICARBAZEPINE; metabolism of coumarins accelerated by FOSPHENOTIN and PHENOTIN (possibility of reduced anticoagulant effect, but enhancement also reported); anticoagulant effect of coumarins possibly enhanced by SODIUM VALPROATE and VALPROIC ACID

Antifungals: anticoagulant effect of coumarins enhanced by FLUCONAZOLE, ITRACONAZOLE, KETOCONAZOLE and VORICONAZOLE; anticoagulant effect of coumarins greatly enhanced by MICANAZOLE (including oral gel and possibly vaginal and topical formulations)—avoid concomitant use if possible; anticoagulant effect of coumarins reduced by GRISEOFULVIN
• Antimalarials: isolated reports that anticoagulant effect of warfarin may be enhanced by PROGUANIL; plasma concentration of both drugs increased when warfarin given with QUININE
• Antivirals: anticoagulant effect of warfarin may be enhanced or reduced by ATAZANAVIR, NEVIRAPINE and RITONAVIR; plasma concentration of both drugs increased when warfarin given with
Interactions | Appendix 1

**Cumarins**
- Antivirals (continued)
  - concentration of cumarins possibly affected by EFAVIREN,
  - anticoagulant effect of cumarins may be enhanced or reduced by FOSAMPRENAVIR
  - anticoagulant effect of cumarins possibly enhanced by RITONAVIR
  - anticoagulant effect of warfarin possibly enhanced by SAQUINAVIR
  - plasma concentration of warfarin possibly affected by TELAPRE
  - Anxiolytics and Hypnotics: anticoagulant effect of cumarins may transiently be enhanced by CHLORAL
  - Aprepitant: anticoagulant effect of warfarin possibly reduced by APREPI
  - Azathioprine: anticoagulant effect of acenocoumarol possibly enhanced by AZATHIOPRINE
  - anticoagulant effect of warfarin reduced by AZATHIOPRINE
  - Bosentan: monitoring anticoagulant effect of cumarins recommended by manufacturer of BOSENTAN
  - Carbimazole: anticoagulant effect of cumarins possibly enhanced by CARBIMAZOLE
  - Clopidogrel: anticoagulant effect of cumarins enhanced due to antiplatelet action of CLOPIDOGREL
  - Enteral Feeds: anticoagulant effect of cumarins may be enhanced or reduced by CORTICOSTEROIDS (high-dose corticosteroids enhance anticoagulant effect)
  - Cranberry Juice: anticoagulant effect of cumarins possibly enhanced by CRANBERRY JUICE
  - Cytoxotics: anticoagulant effect of cumarins possibly enhanced by ETOPOSIDE, IFOSFAMIDE and SORAFENIB
  - anticoagulant effect of cumarins enhanced by CAPECITABINE, FLUPROURACIL and TEGAFUR: anticoagulant effect of warfarin possibly enhanced by GEPITINIB, GEMCITABINE and VEMURAFENIB: anticoagulant effect of cumarins possibly reduced by MERCAPTOPURINE and MITOTANE: avoidance of warfarin advised by manufacturer of CERITINIB: plasma concentration of warfarin reduced by DABRAFENIB: increased risk of bleeding when cuminars given with ERLOTINIB: avoidance of warfarin advised by manufacturer of IBRUTINIB: replacement of warfarin with a heparin advised by manufacturer of IMATINIB (possibility of enhanced warfarin effect): increased risk of bleeding when warfarin given with REGORAFENIB
  - Dipryidamole: anticoagulant effect of cumarins enhanced due to antiplatelet action of DIPYRIDAMOLE
  - Disulfiram: anticoagulant effect of cumarins enhanced by DISULFIRAM
  - Dopaminergics: anticoagulant effect of warfarin enhanced by ENTACONE
  - Enteral Feeds: anticoagulant effect of cumarins antagonised by vitamin K (present in some ENTERAL FEEDS)
  - Fosaprepitant: anticoagulant effect of warfarin possibly reduced by FOSAPREPI
  - Glucosamine: anticoagulant effect of warfarin enhanced by GLUCOSAMINE (avoid concomitant use)
  - Hormone Antagonists: anticoagulant effect of cumarins possibly enhanced by BICALUTAMIDE and TROPEMIFENE
  - metabolism of cumarins inhibited by DANAZOL (enhanced anticoagulant effect): plasma concentration of cumarins possibly reduced by ENZALUTAMIDE: anticoagulant effect of cumarins enhanced by FLUTAMIDE and TAMOXIFEN
  - Ilprost: anticoagulant effect of cumarins possibly enhanced by ILPROST
  - Lactulose: anticoagulant effect of cumarins possibly enhanced by LACTULOSE
  - Leflunomide: anticoagulant effect of warfarin possibly enhanced by LEFLUNOMIDE
  - Levoketiene Receptor Antagonists: anticoagulant effect of warfarin enhanced by ZAFIRLUKAST
  - Levocarnitine: anticoagulant effect of cumarins possibly enhanced by LEVOCAR
  - Lipid-regulating Drugs: anticoagulant effect of cumarins may be enhanced or reduced by COLESTYRAMINE: anticoagulant effect of warfarin may be transiently reduced by ATORVASTATIN: anticoagulant effect of cumarins enhanced by FIBRATES and FLUVASTATIN: anticoagulant effect of cumarins possibly enhanced by EZETIMIBE

**Cumarins**
- Lipid-regulating Drugs (continued)
  - RosuVASTATIN: anticoagulant effect of cumarins can be enhanced by SIMVASTATIN: anticoagulant effect of warfarin possibly enhanced by LOMITAPIDE
  - Memantine: anticoagulant effect of warfarin possibly enhanced by MEMANTINE
  - Oestrogens: anticoagulant effect of cumarins may be enhanced or reduced by OESTROGENS
  - Orlstat: monitoring anticoagulant effect of cumarins recommended by manufacturer of ORLISTAT
  - Prasugrel: possible increased risk of bleeding when cumarins given with PRASUGREL
  - Protogestogens: anticoagulant effect of cumarins may be enhanced or reduced by PROGESTOGENS
  - Raloxifene: anticoagulant effect of cumarins antagonised by RALOXIFENE
  - Retinooids: anticoagulant effect of cumarins possibly reduced by ACITRETIN
  - Sulfipyrazone: anticoagulant effect of cumarins enhanced by SULFINDPAZONE
  - Sympathomimetics: anticoagulant effect of cumarins possibly enhanced by METHYLPHENIDATE
  - Testolactone: anticoagulant effect of cumarins enhanced by TESTOLACTONE
  - Testosterone: anticoagulant effect of cumarins enhanced by TESTOSTERONE
  - Thyroid Hormones: anticoagulant effect of cumarins enhanced by THYROID HORMONES
  - Ubidecarenone: anticoagulant effect of warfarin may be enhanced or reduced by UBIDECARENONE
  - Ulcer-healing Drugs: metabolism of cumarins inhibited by CIMITIDINE (enhanced anticoagulant effect): anticoagulant effect of cumarins possibly enhanced by ESOMEPRAZOLE and OMEPRAZOLE: anticoagulant effect of cumarins might be enhanced by PANTOPRAZOLE: absorption of cumarins possibly reduced by SUCRALFATE (reduced anticoagulant effect)
  - Vaccines: anticoagulant effect of warfarin possibly enhanced by INFLUENZA VACCINE
  - Vitamins: anticoagulant effect of cumarins possibly enhanced by VITAMIN E: anticoagulant effect of cumarins antagonised by VITAMIN K

**Cranberry Juice**
- Anticoagulants: cranberry juice possibly enhances anticoagulant effect of CUMARINS—avoid concomitant use

**Crizotinib**
- Analogics: manufacturer of crizotinib advises caution with ALFENTANIL and FENTANYL
- Antibacterials: plasma concentration of crizotinib possibly increased by CLARITHROMYCIN and TLTHROMYCIN—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib possibly reduced by RIFAPUTIN—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib reduced by RIFAMPICIN—manufacturer of crizotinib advises avoid concomitant use
- Antidepressants: plasma concentration of crizotinib possibly reduced by ST JOHN’S WORT—manufacturer of crizotinib advises avoid concomitant use
- Antiepileptics: plasma concentration of crizotinib possibly reduced by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE—manufacturer of crizotinib advises avoid concomitant use
- Antifungals: plasma concentration of crizotinib increased by KETOCONAZOLE—avoid concomitant use; plasma concentration of crizotinib possibly increased by ITRACONAZOLE and VORICONAZOLE—manufacturer of crizotinib advises avoid concomitant use
- Antimalarials: possible increased risk of bradycardia when crizotinib given with MEFLOQUINE
- Antipsychotics: avoid concomitant use of cytoxics with CLOZAPINE (increased risk of agranulocytosis); manufacturer of crizotinib advises caution with PIMOZIDE
- Antivirals: plasma concentration of crizotinib possibly increased by ATAZANAVIR, INDINAVIR, RITONAVIR and
Crizotinib

- Antivirals (continued)
  - SAQUINAVIR — manufacturer of crizotinib advises avoid concomitant use
  - Antioxidants and Hypnotics: crizotinib increases plasma concentration of ▶ MIAZOLAM
  - Beta-blockers: possible increased risk of bradycardia when crizotinib given with ▶ BETA-BLOCKERS
  - Calcium-channel Blockers: possible increased risk of bradycardia when crizotinib given with ▶ DILTIAZEM or ▶ VERAPAMIL
  - Cardiac Glycosides: possible increased risk of bradycardia when crizotinib given with ▶ DIGOXIN
  - Ciclosporin: manufacturer of crizotinib advises caution with ▶ CICLOSPORIN
  - Clonidine: possible increased risk of bradycardia when crizotinib given with ▶ CLONIDINE
  - Cycloheximide: crizotinib possibly increases the plasma concentration of ▶ IBRUTINIB — reduce dose of ibritunib (see under Ibrutinib, p. 867)
  - Ergot Alkaloids: manufacturer of crizotinib advises caution with ▶ ERGOT ALKALOIDS
  - Grapefruit Juice: plasma concentration of crizotinib possibly increased by ▶ GRAPEFRUIT JUICE — manufacturer of crizotinib advises avoid concomitant use
  - Guanfacine: crizotinib possibly increases plasma concentration of ▶ GUANFACINE (halve dose of guanfacine)
  - Oestrogens: manufacturer of crizotinib advises contraceptive effect of ▶ OESTROGENS possibly reduced
  - Parasympathomimetics: possible increased risk of bradycardia when crizotinib given with ▶ PILOCARPINE
  - Progestogens: manufacturer of crizotinib advises contraceptive effect of ▶ PROGESTOGENS possibly reduced
  - Sirolimus: manufacturer of crizotinib advises caution with ▶ SIROLIMUS
  - Tacrolimus: manufacturer of crizotinib advises caution with ▶ TACROLIMUS

Cyclophosphamide

- Antifungals: side-effects of cyclophosphamide possibly increased by ▶ FLUCONAZOLE and ▶ ITRACONAZOLE
- Antipsychotics: avoid concomitant use of cytoxotics with ▶ CLOZAPINE (increased risk of agranulocytosis)
- Cardiac Glycosides: cyclophosphamide possibly reduces absorption of ▶ DIGOXIN tablets
- Cyclophosphamide: increased toxicity when high-dose cyclophosphamide given with ▶ PENTOSTATIN — avoid concomitant use
- Muscle Relaxants: cyclophosphamide enhances effects of ▶ SUXAMETHONIUM

Cycloserine

- Alcohol: increased risk of convulsions when cycloserine given with ▶ ALCOHOL
- Antibacterials: increased risk of CNS toxicity when cycloserine given with ▶ ISONIAZID
- Vaccines: antibacterials inactivate ▶ ORAL TYPHOID VACCINE — see under Typhoid Vaccine in BNF or BNFC

Cyproheptadine see Antihistamines

Cytarabine

- Antifungals: cytarabine possibly reduces plasma concentration of ▶ FLUCYTOSINE
- Antipsychotics: avoid concomitant use of cytoxotics with ▶ CLOZAPINE (increased risk of agranulocytosis)
- Cardiac Glycosides: cytarabine possibly reduces absorption of ▶ DIGOXIN tablets
- Cyclophosphamide: intracellular concentration of cytarabine increased by ▶ FLUIDARABINE

Cytotoxics see individual drugs

Dabigatran (continued)

- Anti-arrhythmics: plasma concentration of dabigatran increased by ▶ AMIODARONE (see under Dabigatran Etxetilale, p. 128); plasma concentration of dabigatran increased by ▶ DRONERADONE — avoid concomitant use
- Anticoagulants: possible increased risk of bleeding when dabigatran given with ▶ CLARITHROMYCIN; plasma concentration of dabigatran reduced by ▶ RIFAMPICIN — manufacturer of dabigatran advises avoid concomitant use
- Antiaggregants: increased risk of haemorrhage when dabigatran given with other ▶ ANTICOAGULANTS (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with ▶ APIXABAN, ▶ RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antidepressants: possible increased risk of bleeding when dabigatran given with ▶ SSRI-RELATED ANTIDEPRESSANTS or ▶ SSRIS; plasma concentration of dabigatran possibly reduced by ▶ ST JOHN’S WORT — manufacturer of dabigatran advises avoid concomitant use
- Antiepileptics: plasma concentration of dabigatran possibly reduced by ▶ CARBAMAZEPINE, ▶ PHOSPHENYTOIN and ▶ PHENOTYIN — manufacturer of dabigatran advises avoid concomitant use
- Antifungals: plasma concentration of dabigatran increased by ▶ KETOCONAZOLE — avoid concomitant use; manufacturer of dabigatran advises avoid concomitant use with ▶ ITRACONAZOLE
- Antivirals: manufacturers advise avoid concomitant use of dabigatran with ▶ DARUNAVIR; plasma concentration of dabigatran possibly increased by ▶ RILPIVIRINE and ▶ TELAPREVIR
- Calcium-channel Blockers: plasma concentration of dabigatran possibly increased by ▶ VERAPAMIL (see under Dabigatran Etxetilale, p. 128)
- Ciclosporin: manufacturer of dabigatran advises avoid concomitant use
- Netupitant: caution with dabigatran advised by manufacturer of ▶ NETUPITANT
- Sulfipyrazone: possible increased risk of bleeding when dabigatran given with ▶ SULFONYLURIA

Dabrafenib

- Antibacterials: manufacturer of dabrafenib advises avoid concomitant use with ▶ RIFAMPICIN
- Anticoagulants: dabrafenib reduces plasma concentration of ▶ WARFARIN
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with ▶ ST JOHN’S WORT
- Antiepileptics: manufacturer of dabrafenib advises avoid concomitant use with ▶ CARBAMAZEPINE, ▶ PHOSPHENYTOIN, ▶ PHENOBARBITAL, ▶ PHENOTYIN and ▶ PRIMIDONE
- Antifungals: plasma concentration of dabrafenib increased by ▶ KETOCONAZOLE
- Antipsychotics: avoid concomitant use of cytoxotics with ▶ CLOZAPINE (increased risk of agranulocytosis)
- Lipid-regulating Drugs: plasma concentration of dabrafenib increased by ▶ Gemfibrozil
- Oestrogens: manufacturer of dabrafenib advises contraceptive effect of hormonal contraceptives containing ▶ OESTROGENS possibly reduced (alternative contraceptive recommended)
- Progestogens: manufacturer of dabrafenib advises contraceptive effect of hormonal contraceptives containing ▶ PROGESTOGENS possibly reduced (alternative contraceptive recommended)
- Ulcer-healing Drugs: manufacturer of dabrafenib advises avoid concomitant use with ▶ PROTON PUMP INHIBITORS (plasma concentration of dabrafenib possibly reduced)
Dacarbazine

- Aldesleukin: avoidance of dacarbazine advised by manufacturer of ALDELEUKIN
- Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)

Dacarbazin

- Anti-arhythmic: possible increased risk of atrial fibrillation when dacarbazin (with fosforbivin) given with AMIODARONE — see under Amiodarone, p. 99
- Antibacterials: plasma concentration of dacarbazin possibly increased by CLARITHROMYCIN and TELOTHROMYCIN — reduce dose of dacarbazin (see under Dacarbazin, p. 577); plasma concentration of dacarbazin possibly reduced by Rifabutin — manufacturer of dacarbazin advises avoid concomitant use; plasma concentration of dacarbazin reduced by Rifampicin — avoid concomitant use
- Antidepressants: plasma concentration of dacarbazin possibly reduced by ST. JOHN'S WORT — manufacturer of dacarbazin advises avoid concomitant use
- Antiepileptics: plasma concentration of dacarbazin possibly reduced by Carbamazepine, Phosphenytoin, Oxcarbazepine, Phenytoin and Primidone — manufacturer of dacarbazin advises avoid concomitant use
- Antifungals: plasma concentration of dacarbazin increased by Ketoconazole — reduce dose of dacarbazin (see under Dacarbazin, p. 577); plasma concentration of dacarbazin possibly increased by Itraconazole, Posaconazole and Voriconazole — reduce dose of dacarbazin (see under Dacarbazin, p. 577)
- Antivirals: plasma concentration of dacarbazin increased by Atazanavir and Teleprrevir — reduce dose of dacarbazin (see under Dacarbazin, p. 577); plasma concentration of dacarbazin possibly increased by Boceprrevir — reduce dose of dacarbazin (see under Dacarbazin, p. 577); manufacturer of dacarbazin advises avoid concomitant use with Darunavir (plasma concentration of dacarbazin possibly increased); plasma concentration of dacarbazin reduced by Efavirenz — increase dose of dacarbazin (see under Dacarbazin, p. 577); manufacturer of dacarbazin advises avoid concomitant use with Etiravirine and Nevirapine (plasma concentration of dacarbazin possibly reduced)
- Cardiac Glycosides: dacarbazin increases plasma concentration of Digoxin
- Cobicitstat: plasma concentration of dacarbazin possibly increased by Cobicitstat — reduce dose of dacarbazin (see under Dacarbazin, p. 577)
- Corticosteroids: plasma concentration of dacarbazin possibly reduced by Dexamethasone — manufacturer of dacarbazin advises avoid concomitant use
- Lipid-regulating Drugs: dacarbazin increases plasma concentration of Rosuvastatin

Dactinomycin

- Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
- Cytotoxics: increased risk of haematotoxicity when dactinomycin given with Vincristine
- Vaccines: risk of generalised infections when cytotoxic antibiotics given with Live VACCINES — avoid concomitant use
- Vitamins: dactinomycin possibly reduces effects of Alfalfacidd, Calcitriol, Colecalciferol, Dihydropotachysterol, Ergocaliferol, Paricalcit and Vitamin D

Dairy Products

- Antibacterials: dairy products reduce absorption of Ciprofloxacin; dairy products reduce absorption of Tetracyclines (except doxycycline and minocycline)
- Cytotoxics: dairy products possibly reduce plasma concentration of Mercaptopurine — manufacturer of mercaptopurine advises give at least 1 hour before or 3 hours after dairy products
- Eliptrombapag: dairy products possibly reduce absorption of Eliptrombapag (give at least 4 hours apart)

Dalteparin see Heparins

Danaparoid

- Analgesics: increased risk of haemorrhage when anticoagulants given with Intravenous Diclofenac (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with Ketorolac (avoid concomitant use, including low-dose heparins)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with Apixaban, Dabigatran, Edoxaban and Rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Danazol

- Anticoagulants: danazol inhibits metabolism of COUMARINS (enhanced anticoagulant effect)
- Antiepileptics: danazol inhibits metabolism of Carbamazepine (increased risk of toxicity)
- Ciclosporin: danazol inhibits metabolism of Ciclosporin (increased plasma concentration)
- Lipid-regulating Drugs: possible increased risk of myopathy when danazol given with Simvastatin — avoid concomitant use
- Tacrolimus: danazol possibly increases plasma concentration of Tacrolimus

Dantrolene see Muscle Relaxants

Dapagliflozin see Antidiabetics

Dapoxetine

- Alcohol: increased sedative effect when dapoxetine given with Alcohol
- Analgesics: possible increased risk of serotoninergic effects when dapoxetine given with Tramadol (manufacturer of dapoxetine advises tramadol should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol)
- Antibacterials: manufacturer of dapoxetine advises dose reduction when dapoxetine given with Clarithromycin and Erythromycin (see under Dapoxetine, p. 751); manufacturer of dapoxetine advises avoid concomitant use with Telithromycin (increased risk of toxicity)
- Antidepressants: possible increased risk of serotoninergic effects when dapoxetine given with SSRIs, St John's Wort, Duloxetine, Tricyclines and Venlafaxine (manufacturer of dapoxetine advises SSRIs, St John's wort, duloxetine, tricyclines and venlafaxine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol)
- Anticoagulants: manufacturer of dapoxetine advises dose reduction when dapoxetine given with Clarithromycin and Erythromycin (see under Dapoxetine, p. 751); manufacturer of dapoxetine advises dose reduction when dapoxetine given with Flucanazole (see under Dapoxetine, p. 751); manufacturer of dapoxetine advises avoid concomitant use with Itraconazole (increased risk of toxicity)
- Antivirals: manufacturer of dapoxetine advises avoid concomitant use with Atazanavir, Ritonavir and Saquinavir (increased risk of toxicity); manufacturer of dapoxetine advises dose reduction when dapoxetine given with Fosamprenavir (see under Dapoxetine, p. 751)
- Appriant: manufacturer of dapoxetine advises dose reduction when dapoxetine given with Appriant (see under Dapoxetine, p. 751)
- Calcium-channel Blockers: manufacturer of dapoxetine advises dose reduction when dapoxetine given with Dilatiazem and Verapamil (see under Dapoxetine, p. 751)
- 5HT-Receptor Agonists: possible increased risk of serotoninergic effects when dapoxetine given with 5HT, Agonists (manufacturer of dapoxetine advises 5HT, agonists should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping 5HT1 agonists)
- Lithium: possible increased risk of serotoninergic effects when dapoxetine given with Lithium (manufacturer of dapoxetine advises lithium should not be started until 1 week after stopping
Dapoxetine
- Lithium (continued)
  stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping lithium)
- Sildenafil: manufacturer of dapoxetine advises avoid concomitant use with SILDENAFIL
- Tadalafil: manufacturer of dapoxetine advises avoid concomitant use with TADALAFIL
- Vardenafil: manufacturer of dapoxetine advises avoid concomitant use with VARDENAFIL

Dapsone
- Antibacterials: plasma concentration of dapsone reduced by RIFAMYCINS; plasma concentration of both drugs may increase when dapsone given with TRIMETHOPRIM
- Antivirals: increased risk of ventricular arrhythmias when dapsone given with SAQUINAVIR—avoid concomitant use
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Daptomycin
- Ciclosporin: increased risk of myopathy when daptomycin given with CICLOSPORIN (preferably avoid concomitant use)
- Lipid-regulating Drugs: increased risk of myopathy when daptomycin given with FIBRATES or STATINS (preferably avoid concomitant use)
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Darifenacin see Antimuscarinics

Darunavir
- Anti-arrhythmics: darunavir possibly increases plasma concentration of LIDOCAINE—avoid concomitant use
- Antibacterials: darunavir increases plasma concentration of DAPSONE; plasma concentration of darunavir significantly reduced by DAUCAMBIN—avoid concomitant use
- Anticoagulants: avoidance of darunavir advised by manufacturer of ARIXIBAN and RIVAROXABAN; manufacturers advise avoid concomitant use of darunavir with BABIGATAN
- Antidepressants: darunavir possibly reduces plasma concentration of PAROXETINE and SERTRALINE; plasma concentration of darunavir reduced by ST JOHN’S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of darunavir possibly reduced by CARBAMAZEPINE, FOSPHENTOIN, PHENOBARTAL, PHENYTOIN and PRIMIDONE
- Antifungals: plasma concentration of both drugs increased when darunavir given with KETOCONAZOLE; darunavir possibly affects plasma concentration of VORICONAZOLE
- Antimalarials: plasma concentration of lumefantrine increased when darunavir given with ARTEMETHER with LUMEFANTRINE; darunavir possibly increases plasma concentration of QUININE (increased risk of toxicity)
- Antipsychotics: darunavir possibly increases plasma concentration of ARIPIPRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); darunavir possibly increases plasma concentration of QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: avoid concomitant use of darunavir with BOCEPREVIR or TELAPREVIR; avoidance of darunavir advised by manufacturer of DACLATASVIR (plasma concentration of daclatasvir possibly increased); manufacturer of darunavir advises take DIDANOSONE 1 hour before or 2 hours after darunavir; plasma concentration of darunavir reduced by EFAVIRENZ (adjust dose—consult product literature); plasma concentration of both drugs increased when darunavir given with INDINAVIR; plasma concentration of darunavir reduced by LOPINAVIR and SAQUINAVIR—avoid concomitant use; darunavir increases plasma concentration of MARAVIROC (consider reducing dose of maraviroc); darunavir increases plasma concentration of PARITAPREVIR and plasma concentration of darunavir decreased; increased risk of rash when darunavir given with Raltegravir; plasma concentration of both drugs increased when darunavir given with SIMPREVIR—manufacturer of simprevir advises avoid concomitant use

Darunavir (continued)
- Cytotoxics: darunavir possibly increases the plasma concentration of BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; darunavir possibly increases plasma concentration of EVEROLIMUS—manufacturer of everolimus advises avoid concomitant use; darunavir possibly increases the plasma concentration of IBRUTINIB—reduce dose of ibritunib (see under Ibrutinib, p. 867)
- Ergot Alkaloids: increased risk of ergotism when darunavir given with ERGOT ALKALOIDS—manufacturer of darunavir advises avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when darunavir given with ATORVASTATIN; darunavir possibly increases plasma concentration of PRAVASTATIN (use lowest possible dose of pravastatin); darunavir increases plasma concentration of ROSUVASTATIN—adjust dose of rosuvastatin (consult product literature); avoidance of darunavir advised by manufacturer of LOMITAPIDE (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of darunavir possibly reduced by ORLISTAT
- Ranolazine: darunavir possibly increases plasma concentration of RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use

Dasabuvir
- Antibacterials: manufacturer of dasabuvir advises avoid concomitant use with CLARITHROMYCIN and TELITHROMYCIN; plasma concentration of dasabuvir possibly reduced by RIFAMPICIN—avoid concomitant use
- Antidepressants: plasma concentration of dasabuvir possibly reduced by ST JOHN’S WORT—manufacturer of dasabuvir advises avoid concomitant use
- Antiepileptics: plasma concentration of dasabuvir reduced by CARBAMAZEPINE—avoid concomitant use; plasma concentration of dasabuvir possibly reduced by FOSPHENTOIN, PHENOBARTAL, PHENYTOIN and PRIMIDONE—avoid concomitant use
- Antifungals: plasma concentration of both drugs increased when dasabuvir given with KETOCONAZOLE—avoid concomitant use; plasma concentration of both drugs possibly increased when dasabuvir given with TRICARAZOLE and POSACONAZOLE—avoid concomitant use
- Antivirals: manufacturer of dasabuvir advises avoid concomitant use with EFAVIRENZ, ETRAVIRINE and NEVIRAPINE
- Cobicitat: manufacturer of dasabuvir advises avoid concomitant use with COBICISTAT
- Cytotoxics: manufacturer of dasabuvir advises avoid concomitant use with MITOTANE
- Diuretics: dasabuvir increases plasma concentration of FUROSEMIDE (reduce dose of furosemide)
- Hormone Antagonists: manufacturer of dasabuvir advises avoid concomitant use with ENZALUTAMIDE
- Lipid-regulating Drugs: manufacturer of dasabuvir advises avoid concomitant use with ATORVASTATIN, GEMFIBROZIL and SIMVASTATIN; dasabuvir increases plasma concentration of ROSUVASTATIN (reduce dose of rosuvastatin—see under Rosuvastatin, p. 195)
- Oestrogens: manufacturer of dasabuvir advises avoid concomitant use of ETHINYLESTRADIAL—use alternative form of contraception

Dasatinib
- Antacids: absorption of dasatinib possibly reduced by ANTACIDS (give at least 2 hours apart)
- Antibacterials: manufacturer of dasatinib advises avoid concomitant use with CLARITHROMYCIN, ERYTHROMYCIN and TELITHROMYCIN (plasma concentration of dasatinib possibly increased); metabolism of dasatinib accelerated by RIFAMPICIN (reduced plasma concentration—avoid concomitant use)
- Antiepileptics: manufacturer of dasatinib advises avoid concomitant use with CARBAMAZEPINE, FOSPHENTOIN, PHENOBARTAL, PHENYTOIN and PRIMIDONE (plasma concentration of dasatinib possibly reduced)
- Antifungals: plasma concentration of dasatinib possibly increased by KETOCONAZOLE; manufacturer of dasatinib
Dasatinib
Antifungals (continued)
advise avoid concomitant use with ITRACONAZOLE (plasma concentration of dasatinib possibly increased)
• Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
• Antivirals: avoidance of dasatinib advised by manufacturer of BOCPREVIR; manufacturer of dasatinib advises avoid concomitant use with RITONAVIR (plasma concentration of dasatinib possibly increased)
• Grapefruit Juice: manufacturer of dasatinib advises avoid concomitant use with GRAPEFRUIT JUICE (plasma concentration of dasatinib possibly increased)
• Lipid-regulating Drugs: dasatinib possibly increases plasma concentration of SIMVASTATIN
• Ulcer-healing Drugs: plasma concentration of dasatinib reduced by • FAMOTIDINE and • OMEPRAZOLE—consider using an antacid as an alternative; manufacturer of dasatinib advises avoid concomitant use with • HISTAMINE H2-ANTAGONISTS and • PROTON PUMP INHIBITORS—consider using an antacid as an alternative
Daunorubicin
• Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
• Cytoxotics: possible increased risk of cardiotoxicity when daunorubicin given with • TRASTUZUMAB—avoid concomitant use for up to 28 weeks after stopping trastuzumab
• Vaccines: risk of generalised infections when cytotoxic antibiotics given with live • VACCINES—avoid concomitant use
Decitabine
• Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
Deferasirox
• Antipsychotics: deferasirox increases plasma concentration of AMINOPHYLLINE (consider reducing dose of aminophylline)
• Antacids: absorption of deferasirox possibly reduced by ANTACIDS containing aluminium (manufacturer of deferasirox advises avoid concomitant use)
• Antibacterials: plasma concentration of deferasirox reduced by RIFAMPICIN
• Antidiabetics: deferasirox increases plasma concentration of REPAGLINIDE
• Antipsychotics: manufacturer of deferasirox advises avoid concomitant use with CLOZAPINE
• Anxiolytics and Hypnotics: deferasirox possibly reduces plasma concentration of MIDAZOLAM
• Muscle Relaxants: manufacturer of deferasirox advises avoid concomitant use with TIZANIDINE
• Theophylline: deferasirox increases plasma concentration of THEOPHYLLINE (consider reducing dose of theophylline)
Deferiprone
• Antacids: absorption of deferiprone possibly reduced by ANTACIDS containing aluminium (manufacturer of deferiprone advises avoid concomitant use)
Deflazacort see Corticosteroids
Delamandin
• Analgesics: increased risk of ventricular arrhythmias when delamandin given with • METHADONE
• Anti-arrhythmics: increased risk of ventricular arrhythmias when delamandin given with • AMIODARONE or • DISOPYRAMIDE
• Antibacterials: possible increased risk of ventricular arrhythmias when delamandin given with • CLARITHROMYCIN and •ERYTHROMYCIN; increased risk of ventricular arrhythmias when delamandin given with • MOXIFLOXACIN; plasma concentration of delamandin reduced by • RIFAMPICIN; delamandin increases plasma concentration of ETHAMBUTOL
• Antidepressants: possible increased risk of ventricular arrhythmias when delamandin given with • TRICYCLICS that prolong the QT interval
• Antiepileptics: manufacturer of delamandin advises avoid concomitant use with CARBAMAZEPINE
• Antipsychotics: increased risk of ventricular arrhythmias when delamandin given with • DROPERIDOL, • HALOPERIDOL or • PIMOZIDE; increased risk of ventricular arrhythmias when delamandin given with • PHENOTHIAZINES that prolong the QT interval
Delamanid (continued)
• Antivirals: plasma concentration of delamanid increased by LOPINAVIR and RITONAVIR; increased risk of ventricular arrhythmias when delamanid given with • SAQUINAVIR
• Beta-blockers: increased risk of ventricular arrhythmias when delamanid given with • SOTALOL
• Cytoxotics: increased risk of ventricular arrhythmias when delamanid given with • ARSENIC TRIOXIDE or • VINFLUNINE; possible increased risk of ventricular arrhythmias when delamanid given with • VINBLASTINE, • VINCristINE, • VindesINE and • VINoreBINE
• Domperidone: possible increased risk of ventricular arrhythmias when delamanid given with • DOMPERIDONE
• Pentamidine isetionate: increased risk of ventricular arrhythmias when delamanid given with • PENTAMIDINE ISETIONATE
• Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC
Demeclocycline see Tetracyclines
Desferroxamine
• Antipsychotics: avoidance of desferroxamine advised by manufacturer of LEVOMEPROMAZINE; manufacturer of desferroxamine advises avoid concomitant use with PROCHLORPERAZINE
Desflurane see Anaesthetics, General
Desloratadine see Antihistamines
Desmopressin
• Analgesics: effects of desmopressin enhanced by INDOMETACIN
• Loperamide: plasma concentration of oral desmopressin increased by LOPERAMIDE
Desogestrel see Progestogens
Dexamethasone see Corticosteroids
Dexamfetamine see Sympathomimetics
Dexibuprofen see NSAIDs
Dextroketoprofen see NSAIDs
Dexrazoxane
• Antiepileptics: dexrazoxane possibly reduces absorption of • FOSPHENYTOIN and • PHENYTOIN
• Ciclosporin: manufacturer of dexrazoxane advises increased risk of immunosuppression with CICLOSPORIN
• Tacrolimus: manufacturer of dexrazoxane advises increased risk of immunosuppression with TACROLIMUS
• Vaccines: risk of generalised infections when dexrazoxane given with live • VACCINES—avoid concomitant use
Dextromethorphan see Opioid Analgesics
Dextropropoxyphene see Opioid Analgesics
Diamorphine see Opioid Analgesics
Diazepam see Anxiolytics and Hypnotics
Diazoxide
• ACE Inhibitors: enhanced hypotensive effect when diazoxide given with ACE INHIBITORS
• Adrenergic Neurone Blockers: enhanced hypotensive effect when diazoxide given with ADRENERGIC NEURONE BLOCKERS
• Alcohol: enhanced hypotensive effect when diazoxide given with ALCOHOL
• Aldesleukin: enhanced hypotensive effect when diazoxide given with ALDESLEUKIN
• Alpha-blockers: enhanced hypotensive effect when diazoxide given with ALPHA-BLOCKERS
• Anaesthetics, General: enhanced hypotensive effect when diazoxide given with GENERAL ANAESTHETICS
• Analgesics: hypotensive effect of diazoxide antagonised by NSAIDS
• Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diazoxide given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
• Antidepressants: enhanced hypotensive effect when diazoxide given with MAOIS or TRICYCLIC-RELATED ANTIDEPRESSANTS
• Antidiabetics: diazoxide antagonises hypoglycaemic effect of ANTIDIABETICS
• Antiepileptics: diazoxide reduces plasma concentration of FOSPHENYTOIN and PHENYTOIN, also effect of diazoxide may be reduced
• Antipsychotics: enhanced hypotensive effect when diazoxide given with PHENOTHIAZINES
Diazoxide – Disopyramide

Diazoxide (continued)

» Anxiolytics and Hypnotics: enhanced hypotensive effect when diazoxide given with ANXIOLYTICS AND HYPNOTICS
» Beta-blockers: enhanced hypotensive effect when diazoxide given with BETA-BLOCKERS
» Calcium-channel Blockers: enhanced hypotensive effect when diazoxide given with CALCIUM-CHANNEL BLOCKERS
» Clonidine: enhanced hypotensive effect when diazoxide given with CLONIDINE
» Corticosteroids: hypotensive effect of diazoxide antagonised by CORTICOSTEROIDS
» Diuretics: enhanced hypotensive and hyperglycaemic effects when diazoxide given with DIURETICS
» Dopaminergics: enhanced hypotensive effect when diazoxide given with BACLOFEN or TIZANIDINE
» Methyldopa: enhanced hypotensive effect when diazoxide given with METHYLOPA
» Moxisylyte: enhanced hypotensive effect when diazoxide given with MOXISYLYTE
» Moxonidine: enhanced hypotensive effect when diazoxide given with MOXONIDINE
» Muscle Relaxants: enhanced hypotensive effect when diazoxide given with BACLOFEN or TIZANIDINE
» Nitrates: enhanced hypotensive effect when diazoxide given with NITRATES
» Prostaglandins: enhanced hypotensive effect when diazoxide given with ALPROSTADIL
» Vasodilator Antihypertensives: enhanced hypotensive effect when diazoxide given with HYDRALAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE

Diclofenac see NSAIDs
Dicyclomine see Antimuscarinics
Didanosine

NOTE Antacids in tablet formulation might affect absorption of other drugs—give at least 2 hours apart

Allopurinol: plasma concentration of didanosine increased by

Allopurinol (risk of toxicity)—avoid concomitant use

Analgesics: plasma concentration of didanosine possibly reduced by METHADONE

Antibacterials: didanosine tablets reduce absorption of CIPROFLOXACIN (give at least 2 hours before or 4 hours after ciprofloxacin); manufacturer of levofloxacin advises give didanosine tablets at least 2 hours before or after LEVOFLOXACIN; manufacturer of moxifloxacin advises give didanosine tablets at least 6 hours before or after MOXIFLOXACIN

Antihistamines: plasma concentration of didanosine possibly reduced by GANCICLOVIR and VALGANCICLOVIR; didanosine tablets reduce absorption of INDINAVIR (give at least 1 hour apart); increased risk of side-effects when didanosine given with RIBAVIRIN—avoid concomitant use; manufacturer of rilpivirine advises give didanosine 2 hours before or 4 hours after RILPIVIRINE; manufacturer of ritonavir advises didanosine and RITONAVIR should be taken 2.5 hours apart; increased risk of side-effects when didanosine given with STAVUDINE; plasma concentration of didanosine increased by TENOFIRVIR (increased risk of toxicity)—avoid concomitant use; plasma concentration of didanosine reduced by TIPRANAVIR—manufacturer of tipranavir advises tipranavir and didanosine capsules should be taken at least 2 hours apart

Cytotoxics: increased risk of toxicity when didanosine given with HYDROXYCARBAMIDE—avoid concomitant use

Orlistat: absorption of didanosine possibly reduced by ORLISTAT

Dienogest see Progestogens
Diethylcarbamazine

» Antacids: excretion of diethylcarbamazine reduced by SODIUM BICARBONATE

Digoxin see Cardiac Glycosides
Dihydrocodeine see Opioid Analgesics
Dihydrotachysterol see Vitamins

Diltiazem see Calcium-channel Blockers
Dimethyl sulfoxide

» Analgesics: avoid concomitant use of dimethyl sulfoxide with SULINDAC

Disoprostone see Prostaglandins
Diphenoxylate see Opioid Analgesics
Diptheria Vaccines see Vaccines
Dipipanone see Opioid Analgesics
Dipyridamole

» Antiarrhythmics: absorption of dipyridamole possibly reduced by ANTAGONISTS

» Anti-arrhythmics: dipyridamole enhances and extends effect of AMIODARONE (important risk of toxicity)—reduce dose of amiodarone, see p. 101

» Antiarrhythmics: antiplatelet action of dipyridamole enhances anticoagulant effect of COUMARINS and PHENINDIONE; dipyridamole enhances anticoagulant effect of HEPARINS

» Clopidogrel: increased risk of bleeding when dipyridamole given with CLOPIDOGREL

» Cytotoxics: dipyridamole possibly reduces effects of FLUDARABINE

Disopyramide

» Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with BUPIVAUCINE, LEVOBUPIVAUCINE, PRILOCaine or ROFIVAUCINE

» Antiarrhythmics: increased myocardial depression when anti-arrhythmics given with other ANTI-ARRHYTHMICS; increased risk of ventricular arrhythmias when disopyramide given with AMIODARONE or DRONEDARONE—avoid concomitant use

» Antiarrhythmics: plasma concentration of disopyramide possibly increased by AZITHROMYCIN (increased risk of toxicity); plasma concentration of disopyramide possibly increased by CLARITHROMYCIN (increased risk of ventricular arrhythmias); plasma concentration of disopyramide disopyramide increased by ERYTHROMYCIN (increased risk of toxicity); increased risk of ventricular arrhythmias when disopyramide given with MOXIFLOXACIN—avoid concomitant use; increased risk of ventricular arrhythmias when disopyramide given with DELAMANID; metabolism of disopyramide accelerated by RIFAMYCINS (reduced plasma concentration); possible increased risk of ventricular arrhythmias when disopyramide given with TELITHROMYCIN

» Antiarrhythmic: disopyramide may enhance or reduce anticoagulant effect of WARFARIN

» Antidepressants: avoidance of disopyramide advised by manufacturer of CITALOPRAM and ESCITALOPRAM (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when disopyramide given with TRICYCLICS

» Antiarrhythmic: disopyramide possibly enhances hypoglycaemic effect of GLICLAZIDE, INSULIN and METFORMIN

» Antiarrhythmics: plasma concentration of disopyramide reduced by FOSPHENYTOIN and PHENOTIN; metabolism of disopyramide accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration)

» Antiarrhythmics: increased risk of ventricular arrhythmias when disopyramide given with KETOCONAZOLE—avoid concomitant use; avoidance of disopyramide advised by manufacturer of ITRACONAZOLE

» Antiarrhythmics: increased risk of ventricular arrhythmias when disopyramide given with MIZOLASTINE—avoid concomitant use

» Antiarrhythmic: avoidance of disopyramide advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE (risk of ventricular arrhythmias); avoidance of disopyramide advised by manufacturer of ARTEMETHER WITH PIPERAQUINE (possible risk of ventricular arrhythmias)

» Antiarrhythmics: increased risk of antimuscarinic side-effects when disopyramide given with ANTIMUSCARINICS; increased risk of ventricular arrhythmias when disopyramide given with TOLERODINE

» Antiarrhythmics: increased risk of ventricular arrhythmias when disopyramide given with AMISULPRIDE, DROPERIDOL, PIMOZIDE or ZUCLOPENTHIXOL—avoid concomitant use; possible increased...
Disopyramide

● Antipsychotics (continued)
  
  risk of ventricular arrhythmias when disopyramide given with
  • HALDOPERIDOL—avoid concomitant use; increased risk of
  ventricular arrhythmias when disopyramide given with
  • PHENOTHIAZINES or • SULPIRIDE
  • Antivirals: plasma concentration of disopyramide possibly
  increased by • RITONAVIR (increased risk of toxicity); increased risk of
  ventricular arrhythmias when disopyramide given with
  • SAQUINAVIR—avoid concomitant use; avoidance of
  disopyramide advised by manufacturer of • TELAPREVIR (risk of
  ventricular arrhythmias)
  • Atomoxetine: increased risk of ventricular arrhythmias
  when disopyramide given with • ATOMOXETINE
  • Beta-blockers: increased myocardial depression when anti-
  arrhythmics given with • BETA-BLOCKERS; increased risk of
  ventricular arrhythmias when disopyramide given with
  • SOTALOL—avoid concomitant use
  • Calcium-channel Blockers: increased risk of myocardial
  depression and astystole when disopyramide given with
  • VERAPAMIL
  • Cytotoxics: possible increased risk of ventricular arrhythmias
  when disopyramide given with • DOXORUBICIN and • CEPHALOSPORINS;
  possible increased risk of ventricular arrhythmias when
  disopyramide given with • VANDENATIN—avoid concomitant use;
  increased risk of ventricular arrhythmias when disopyramide given with •
  ARSENIC TRIOXIDE
  • Diuretics: increased cardiac toxicity with disopyramide if
  hypokalaemia occurs with • ACETAZOLAMIDE, • LOOP DIURETICS
  or • THIAZIDES AND RELATED DIURETICS
  • Fingolimod: possible increased risk of bradycardia when
  disopyramide given with • FINGOLIMOD
  • Ivabradine: increased risk of ventricular arrhythmias when
  disopyramide given with • IVABRADINE
  • Nitrates: disopyramide reduces effects of sublingual tablets of
  NITRATES (failure to dissolve under tongue owing to dry
  mouth)
  • Panobinostat: possible increased risk of ventricular
  arrhythmias when disopyramide given with • PANOBINOSTAT—
  avoid concomitant use
  • Pentamidine isetionate: possible increased risk of ventricular
  arrhythmias when disopyramide given with • PENTAMIDINE
  ISETIONATE
  • Ranolazine: avoidance of disopyramide advised by
  manufacturer of • RANOLAZINE
  • Sildenafil: manufacturer of disopyramide advises avoid
  concomitant use with • SILDENAFIL (risk of ventricular
  arrhythmias)
  • Tadalafil: manufacturer of disopyramide advises avoid
  concomitant use with • TADALAFIL (risk of ventricular
  arrhythmias)
  • Vardenafil: manufacturer of disopyramide advises avoid
  concomitant use with • VARDENAFIL (risk of ventricular
  arrhythmias)

Disulfiram

● Alcohol: disulfiram reaction when disulfiram given with
  • ALCOHOL
  • Aminophylline: disulfiram inhibits metabolism of
  • AMINOPHYLLINE (increased risk of toxicity)
  • Antibacterials: psychotic reaction reported when disulfiram
  given with • METRONIDAZOLE; CNS effects of disulfiram possibly
  increased by • ISONIAZID
  • Anticoagulants: disulfiram enhances anticoagulant effect of
  • COUMARINS
  • Antidepressants: increased disulfiram reaction with alcohol
  reported with concomitant • AMITRIPTYLINE; disulfiram inhibits
  metabolism of • TRICYCLES (increased plasma concentration)
  • Antiepileptics: disulfiram inhibits metabolism of
  • FOSPHENYTOIN and • PHENYTOIN (increased risk of toxicity)
  • Anxiolytics and Hypnotics: disulfiram increases risk of
  • TEMAZEPAM toxicity; disulfiram inhibits metabolism of
  • BENZODIAZEPINES (increased sedative effects)
  • Paraldehyde: risk of toxicity when disulfiram given with
  • PARALDEHYDE
  • Theophylline: disulfiram inhibits metabolism of • THEOPHYLLINE
  (increased risk of toxicity)

Diuretics

NOTE Since systemic absorption may follow topical application
of brinzolamide to the eye, the possibility of interactions
should be borne in mind

NOTE Since systemic absorption may follow topical application
of dorzolamide to the eye, the possibility of interactions
should be borne in mind

● ACE Inhibitors: enhanced hypotensive effect when diuretics
  given with • ACE INHIBITORS; increased risk of severe
  hyperkalaemia when eplerenone and spironolactone given with
  • ACE INHIBITORS—avoid concurrent use or use lowest
  possible doses of both drugs; increased risk of severe
  hyperkalaemia when amiloride, potassium canrenoate or
  triamterene given with • ACE INHIBITORS
  • Adrenergic Neurone Blockers: enhanced hypotensive effect
  when diuretics given with • ADREnergic NeURONE BLOCKERS
  • Alcohol: enhanced hypotensive effect when diuretics given
  with • ALCOHOL
  • Aldesleukin: enhanced hypotensive effect when diuretics given
  with • ALDESLEUKIN
  • Aliksiren: increased risk of hyperkalaemia when aldosterone
  antagonists or potassium-sparing diuretics given with
  • ALSKIREN; plasma concentration of furosemide reduced by
  • ALSKIREN
  • Alfopurinol: increased risk of hypersensitivity when thiazides
  and related diuretics given with • ALLOPURINOL especially in
  renal impairment
  • Alpha-blockers: enhanced hypotensive effect when diuretics
  given with • ALPHA-BLOCKERS, also increased risk of first-dose
  hypotension with post-synaptic alpha-blockers such as
  prazosin
  • Aminophylline: increased risk of hypokalaemia when
  acetazolamide, loop diuretics or thiazide diuretics given with
  • AMINOPHYLLINE
  • Anaesthetics, General: enhanced hypotensive effect when
  diuretics given with • GENERAL ANAESTHETICS
  • Analgesics: possible increased risk of hyperkalaemia when
  aldosterone antagonists or potassium-sparing diuretics given with
  • KSADs; diuretics increase risk of nephrotoxicity of
  • NSAID S, also antagonism of diuretic effect; diuretic effect
  of potassium canrenoate possibly antagonised by • NSAID S;
  furosemide possibly increases the excretion of • ACEMETACIN;
  effects of diuretics antagonised by • INDOMETACIN and
  • KETOROLAC; increased risk of hyperkalaemia when aldosterone
  antagonists or potassium-sparing diuretics given with
  • INDOMETACIN; occasional reports of reduced renal function
  when triamterene given with • INDOMETACIN—avoid
  concomitant use; diuretic effect of spironolactone
  antagonised by • ASPRIN; increased risk of toxicity when
  acetazolamide given with high-dose • ASPRIN; possible
  increased risk of toxicity when loop diuretics given with high-
  • ASPRIN (also possible reduced effect of loop diuretics)
  • Angiotensin-II Receptor Antagonists: enhanced hypotensive
  effect when diuretics given with • ANGIOTENSIN-II RECEPTOR
  ANTAGONISTS; increased risk of severe hyperkalaemia when
  eplerenone and spironolactone given with • ANGIOTENSIN-II
  RECEPTOR ANTAGONISTS—avoid concurrent use or use lowest
  possible doses of both drugs; increased risk of severe
  hyperkalaemia when amiloride, potassium canrenoate or
  triamterene given with • ANGIOTENSIN-II RECEPTOR
  ANTAGONISTS; plasma concentration of furosemide reduced by
  • VALSARTAN
  • Anti-arrhythmics: plasma concentration of eplerenone
  increased by • AMIODARONE (reduce dose of eplerenone); hypokalaemia caused by acetazolamide, loop diuretics or
  thiazides and related diuretics increases cardiac toxicity with
  • AMIODARONE; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac
toxicity with • DISOPYRAMIDE; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with • FLECAINIDE;
hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics antagonises action of
• LIDOCAINE
• Antibacterials: plasma concentration of eplerenone increased by • CLARITHROMYCIN and • TELITHROMYCIN—avoid
Diuretics
- Antibacterials (continued) concomitant use; plasma concentration of eplerenone increased by ERYTHROMYCIN (reduce dose of eplerenone); plasma concentration of eplerenone reduced by RIFAMPICIN, avoid concomitant use; avoidance of diuretics advised by manufacturer of LYMECTYLIN; increased risk of toxicity when loop diuretics given with AMINOGLYCOSIDES, POLYMIXINS or VANCOMYCIN; acetazolamide antagonises effects of METHENAMINE; possible increased risk of hyperkalaemia when spironolactone given with TRIMETHOPRIM; increased risk of hyperkalaemia when eplerenone given with TRIMETHOPRIM.
- Antidepressants: possible increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with ATOMOXETINE; enhanced hypotensive effect when diuretics given with MAOI; plasma concentration of eplerenone reduced by ST JOHN'S WORT—avoid concomitant use; increased risk of postural hypotension when diuretics given with TRICYCLICS.
- Antidiabetics: loop diuretics and thiazides and related diuretics antagonise hypoglycaemic effect of ANTIDIABETICS; avoidance of loop diuretics advised by manufacturer of CANAGLIFLOZIN; diuretic effect of diuretics possibly enhanced by DAPAGLIFLOZIN; diuretic effect of loop diuretics and thiazides and related diuretics possibly enhanced by DAPAGLIFLOZIN.
- Antiparkinsonists: increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with REBOXETINE; enhanced hypotensive effect when diuretics given with MAOI; plasma concentration of eplerenone reduced by CICLOSPORIN—avoid concomitant use; increased risk of hyperkalaemia when acetazolamide increases risk of ventricular arrhythmias with FRANKENSOHN; spironolactone increases plasma concentration of eplerenone given with CICLOSPORIN.
- Anticonvulsants: increased risk of hyperkalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with CORTICOSTEROIDS; increased risk of hyperkalaemia when methotrexate acts synergistically with CORTICOSTEROIDS; increased risk of nephrotoxicity and possibly hypermagnesaemia when thiazides and related diuretics given with CORTICOSTEROIDS; acetazolamide possibly increases plasma concentration of CORTICOSTEROIDS.
- Antihistamines: increased risk of hyperkalaemia when loop diuretics or thiazides and related diuretics given with PLATINUM COMPOUNDS.
- Antihypertensives: loop diuretics and thiazides and related diuretics antagonise hypotensive effect of BETA BLOCKERS; enhanced hypotensive effect when diuretics given with CICLOSPORIN; hypokalaemia caused by diuretics antagonises effect of CICLOSPORIN; increased risk of nephrotoxicity and possibly hypermagnesaemia when thiazides and related diuretics given with CICLOSPORIN; acetazolamide possibly increases plasma concentration of CICLOSPORIN.
- Cytotoxics: enhanced hypotensive effect when diuretics given with METHOTREXATE; hypokalaemia caused by diuretics antagonised by CYTOTOXICS; increased risk of nephrotoxicity and ototoxicity when diuretics given with CYTOTOXICS.
- Diuretics: increased risk of hyperkalaemia when loop diuretics or thiazides and related diuretics given with ACETAZOLAMIDE; reduced diuretic effect of diuretics enhanced hypotensive and hyperglycaemic effects when diuretics given with DASABUVIR, OMBITASVIR or RITONAVIR.
- Hormone Antagonists: increased risk of hyperkalaemia when thiazides and related diuretics given with CORTICOSTEROIDS; acetazolamide increases plasma concentration of DASABUVIR, OMBITASVIR and RITONAVIR, reduce dose of diuretic with CORTICOSTEROIDS; avoidance of spironolactone advised by manufacturer of MITOTANE—antagonism of effect; increased risk of nephrotoxicity and ototoxicity when diuretics given with MITOTANE.
- Lipid-regulating Drugs: absorption of thiazides and related diuretics reduced by COLESTIPOL and COLESTYRAMINE give at least 2 hours apart.
- Lithium: aldosterone antagonists and potassium-sparing diuretics reduce increase of LITHIUM (increased plasma concentration and risk of toxicity); loop diuretics and thiazides and related diuretics reduce increase of LITHIUM (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides; acetazolamide increases the excretion of LITHIUM.
- Methyldopa: enhanced hypotensive effect when diuretics given with METHYLDOPA.
- Moxisylyte: enhanced hypotensive effect when diuretics given with MOXISYLYTE.
- Moxonidine: enhanced hypotensive effect when diuretics given with MOXONIDINE.
- Muscle Relaxants: enhanced hypotensive effect when diuretics given with BACLOFEN or TIZANIDINE.
- Nitrates: enhanced hypotensive effect when diuretics given with NITRATES.
- Oestrogens: diuretic effect of diuretics antagonised by OESTROGENS.
- Potassium Salts: increased risk of hyperkalaemia when aldosterone antagonists or potassium-sparing diuretics given with POTASSIUM SALTS.
- Progestogens: risk of hyperkalaemia when aldosterone antagonists or potassium-sparing diuretics given with DROSPIRENONE (monitor serum potassium during first cycle).
- Prostaglandins: enhanced hypotensive effect when diuretics given with ALPROSTADIL.
- Sacubitril: plasma concentration of furosemide reduced by SACUBITRIL.
- Sympathomimetics, Beta2: increased risk of hyperkalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with high doses of BETA2 SYMPATHOMIMETICS.
Diuretics (continued)

- Tacrolimus: increased risk of hyperkalaemia when aldosterone antagonists or potassium-sparing diuretics given with
  - TACROLIMUS
- Theophylline: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with THEOPHYLLINE
- Vasodilator Antihypertensives: enhanced hypotensive effect when diuretics given with HYDRAZONE, MINOXIDIL or SODIUM NITROPRUSSIDE
- Vitamins: increased risk of hypercalcaemia when thiazides and related diuretics given with ALFACALCICOL, CALCIOTRIOL, COLECALCIFEROL, DIHYDROTACHYSTEROL, ERGOCALCIFEROL, PARICALCITOL or VITAMIN D

Diuretics, Loop | see Diuretics
Diuretics, Potassium-sparing | see Diuretics
Diuretics, Thiazide and related | see Diuretics
Doxatexel

- Antibacterials: plasma concentration of docetaxel possibly increased by
  - CLARITHROMYCIN and
  - TELITHROMYCIN
- Antivirals: reduced plasma concentration of docetaxel when given with
  - VACCAZOLE (consult docetaxel product literature); plasma concentration of docetaxel possibly increased by
  - IRACONAZOLE and
  - VORICONAZOLE
- Antidepressants: manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose
- Antibacterials: plasma concentration of docetaxel possibly increased by
  - PHENYTOIN
  - FOSPHENYTOIN
- Antifungals: in vitro studies suggest a possible interaction between docetaxel and NETUPITAN; plasma concentration of docetaxel increased by
  - SORAFENIB
- Netupitant: plasma concentration of docetaxel increased by NETUPITAN

Dolutesgravir

- Antacids: absorption of dolutesgravir reduced by ALUMINIUM HYDROXIDE and ORAL MAGNESIUM SALTS—manufacturer of dolutesgravir advises give at least 2 hours before or 6 hours after aluminium hydroxide and oral magnesium salts
- Antivirals: plasma concentration of dolutesgravir reduced by
  - RIFAMPICIN (see under Dolutesgravir, p. 592)
- Antidepressants: plasma concentration of dolutesgravir possibly reduced by
  - ST JOHN’S WORT (see under Dolutesgravir, p. 592)
- Antidiabetics: dolutesgravir increases the plasma concentration of METFORMIN—consider reducing dose of metformin
- Antiepileptics: plasma concentration of dolutesgravir reduced by
  - CARBAMAZEPINE (see under Dolutesgravir, p. 592); plasma concentration of dolutesgravir possibly reduced by
  - OXCARBAZEPINE, PHENOBARBITAL, PHENYTOIN and
  - PRIMIDONE (see under Dolutesgravir, p. 592)
- Antivirals: plasma concentration of dolutesgravir reduced by
  - EFAVIRENZ, ETIRAVIRINE and
  - TIPRANAVIR (see under Dolutesgravir, p. 592)
- Calcium Salts: absorption of dolutesgravir reduced by
  - CALCIUM SALTS—manufacturer of dolutesgravir advises give at least 2 hours before or 6 hours after calcium salts
- Iron Salts: absorption of dolutesgravir reduced by
  - ORAL IRON SALTS—manufacturer of dolutesgravir advises give at least 2 hours before or 6 hours after oral iron salts

Domperidone

- Analgesics: effects of domperidone on gastro-intestinal activity antagonised by OPIOID ANALGESICS
- Antibacterials: possible increased risk of ventricular arrhythmias when domperidone given with
  - CLARITHROMYCIN or
  - TELITHROMYCIN
- Antivirals: reduced plasma concentration of domperidone when given with
  - VORICONAZOLE (risk of ventricular arrhythmias; possible increased risk of ventricular arrhythmias when domperidone given with
  - ITROCONAZOLE or
  - CICLOSPORIN
- Antidepressants: possible increased risk of ventricular arrhythmias when domperidone given with
  - ARTEMOMIL WITH PIPAQUAINE
- Antifungals: avoid concomitant use of domperidone with
  - ORAL RIFAMPICIN
- Cytotoxics: possible increased risk of ventricular arrhythmias when domperidone given with
  - DOXORUBICIN
- Diuretics: possible increased risk of ventricular arrhythmias when domperidone given with
  - DOXORUBICIN
- Theophylline: possible increased risk of ventricular arrhythmias when domperidone given with
  - THEOPHYLLINE
- Doxapram given with
  - VORICONAZOLE—avoid concomitant use
  - CICLOSPORIN
  - PHENYTOIN
  - FOSPHENYTOIN
  - PRIMIDONE, RASAGILINE, ROTIGOTINE, SELEGILINE, and TOLCAPONE

Doxazosin see Alpha-blockers

Doxepin see Antidepressants, Tricyclic

Doxycycline see Tetracyclines

Diuretics (continued)

- Tacrolimus: increased risk of hyperkalaemia when aldosterone antagonists or potassium-sparing diuretics given with
  - TACROLIMUS
- Theophylline: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with THEOPHYLLINE
- Vasodilator Antihypertensives: enhanced hypotensive effect when diuretics given with HYDRAZONE, MINOXIDIL or SODIUM NITROPRUSSIDE
- Vitamins: increased risk of hypercalcaemia when thiazides and related diuretics given with ALFACALCICOL, CALCIOTRIOL, COLECALCIFEROL, DIHYDROTACHYSTEROL, ERGOCALCIFEROL, PARICALCITOL or VITAMIN D

Diuretics, Loop | see Diuretics
Diuretics, Potassium-sparing | see Diuretics
Diuretics, Thiazide and related | see Diuretics
Dobutamine see Sympathomimetics

Dolutesgravel

- Antidepressants: possible increased risk of ventricular arrhythmias when domperidone given with
  - DOXAPRAM
  - THEOPHYLLINE
- Cytotoxics: possible increased risk of ventricular arrhythmias when domperidone given with
  - APOMORPHINE
  - VORICONAZOLE

Dopamine see Sympathomimetics

Dopaminergics see Amantadine, Apomorphine, Bromocriptine, Cabergoline, Entacapone, Levodopa, Pergolide, Pramipexole, Quinagolide, Rasagiline, Ropinirole, Rotigotine, Selegiline, and Tolcapone

Dopexamine see Sympathomimetics

Dorzolamidene see Diuretics

Dosulepine see Antidepressants, Tricyclic

Doxapram

- Aminophylline: increased CNS stimulation when doxapram given with
  - AMINOPHYLLINE
    - Anaesthetics, General: increased risk of arrhythmias when doxapram given with
      - VOLATILE LIQUID GENERAL ANAESTHETICS
        - (avoid doxapram for at least 10 minutes after volatile liquid general anaesthetics)
    - Antidepressants: effects of doxapram enhanced by
      - MAOIS
    - Sympathomimetics: increased risk of hypertension when doxapram given with
      - SYMPATHOMIMETICS
    - Theophylline: increased CNS stimulation when doxapram given with
      - THEOPHYLLINE

Doxazosin see Alpha-blockers

Doxepin see Antidepressants, Tricyclic

Doxorubicin

- Antipsychotics: avoid concomitant use of cytoxotics with
  - CLOzapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of doxorubicin reduced by
  - RIFAMPICIN (see under Doxorubicin, p. 592)
- Antidepressants: plasma concentration of doxorubicin possibly increased by
  - ST JOHN’S WORT (see under Doxorubicin, p. 592)
- Antidiabetics: doxorubicin possibly increases the plasma concentration of METFORMIN—consider reducing dose of metformin
- Antiepileptics: plasma concentration of doxorubicin reduced by
  - CARBAMAZEPINE (see under Doxorubicin, p. 592); plasma concentration of doxorubicin possibly reduced by
  - EFFENBARTAL, PHENOBARBITAL, PHENYTOIN and
  - PRIMIDONE (see under Doxorubicin, p. 592)
- Antibacterials: plasma concentration of doxorubicin reduced by
  - EFVIRENZ, ETIVIRINE and
  - TIPRANAVIR (see under Dolutesgravir, p. 592)
- Calcium Salts: absorption of doxorubicin reduced by
  - CALCIUM SALTS—manufacturer of doxorubicin advises give at least 2 hours before or 6 hours after calcium salts
- Iron Salts: absorption of doxorubicin reduced by
  - ORAL IRON SALTS—manufacturer of doxorubicin advises give at least 2 hours before or 6 hours after oral iron salts
- Antituberculous agents: plasma concentration of doxorubicin possibly increased by
  - VORICONAZOLE—avoid concomitant use
- Cardiac Glycosides: doxorubicin possibly reduces absorption of
  - DIGOXIN TABLETS
- Cytotoxics: possible increased risk of cardiotoxicity when doxorubicin given with
  - CICLOSPORIN
- Antivirals: doxorubicin possibly reduces absorption of
  - VACCAZOLE
- Vaccines: risk of generalised infections when cytotoxic antibiotics given with
  - VACCINES—avoid concomitant use
Dronedarone

- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with BUPIVACAINE, LEVOBUPIVACAINE, PRILOCAINE or ROPIVACAINE
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other 
  - Anti-ARRHYTHMICS; increased risk of ventricular arrhythmias when dronedarone given with 
  - AMIODARONE or 
  - DISOPYRAMIDE—avoid concomitant use
- Antibacterials: manufacturer of dronedarone advises avoid concomitant use with 
  - CLRTHROMYCIN (risk of ventricular arrhythmias); plasma concentration of dronedarone increased by 
  - ERYTHROMYCIN (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of dronedarone reduced by 
  - Rifampicin—avoid concomitant use; avoidance of dronedarone advised by manufacturer of 
  - FIDAXOMICIN; increased risk of ventricular arrhythmias when dronedarone given with 
  - Telithromycin—avoid concomitant use
- Anticoagulants: dronedarone possibly enhances anticoagulant effect of 
  - Coumarins and 
  - Phenindione; dronedarone increases plasma concentration of 
  - Dabigatran—avoid concomitant use; dronedarone increases plasma concentration of 
  - Edoxaban (reduce dose of edoxaban—see under Edoxaban, p. 118); avoidance of dronedarone advised by manufacturer of 
  - Rivaroxaban
- Antidepressants: avoidance of dronedarone advised by 
  - Citalopram and 
  - Escitalopram (risk of ventricular arrhythmias); plasma concentration of dronedarone possibly reduced by 
  - St John's Wort—avoid concomitant use; manufacturer of dronedarone advises concomitant use with 
  - Tricyclics (risk of ventricular arrhythmias)
- Antiepileptics: plasma concentration of dronedarone possibly reduced by 
  - Carbamazepine, 
  - Fosphenytoin, 
  - Phenobarbital, 
  - Phenytoin and 
  - Primidone—avoid concomitant use
- Antifungals: plasma concentration of dronedarone increased by 
  - Ketoconazole—avoid concomitant use; manufacturer of dronedarone advises avoid concomitant use with 
  - Itraconazole, 
  - Posaconazole and 
  - Voriconazole
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with 
  - Antipsychotics that prolong the QT interval; manufacturer of dronedarone advises avoid concomitant use with 
  - Phenothiazines (risk of ventricular arrhythmias)
- Antivirals: manufacturer of dronedarone advises avoid concomitant use with 
  - Ritonavir; increased risk of ventricular arrhythmias when dronedarone given with 
  - Saquinavir—avoid concomitant use
- Beta-blockers: increased myocardial depression when anti-arrhythmics given with 
  - Beta-blockers; dronedarone possibly increases plasma concentration of 
  - Metoprolol and 
  - Propranolol; increased risk of ventricular arrhythmias when dronedarone given with 
  - Sotalol—avoid concomitant use
- Calcium-channel Blockers: plasma concentration of dronedarone increased by 
  - Nifedipine; increased risk of bradyarrhythmia and myocardial depression when dronedarone given with 
  - Diltiazem and 
  - Verapamil
- Cardiac Glycosides: dronedarone increases plasma concentration of 
  - Digoxin (halve dose of digoxin)
- Cytotoxics: dronedarone possibly increases the plasma concentration of 
  - Bosutinib; manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; dronedarone possibly increases the plasma concentration of 
  - Ibrutinib—reduce dose of ibrutinib (see under ibrutinib, p. 867)
- Fingolimod: possible increased risk of bradyarrhythmia when dronedarone given with 
  - Fingolimod
- Grapefruit Juice: plasma concentration of dronedarone increased by 
  - Grapefruit Juice—avoid concomitant use
- Lipid-regulating Drugs: dronedarone possibly increases plasma concentration of 
  - Atorvastatin; dronedarone increases plasma concentration of 
  - Rosuvastatin—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when dronedarone given with 
  - Simvastatin; avoidance of 

Droperidol see Antipsychotics

Drospirenone see Progestogens

Dulaglutide see Antidiabetics

Duloxetine

- Analgesics: possible increased serotonergic effects when SSRI-related antidepressants given with 
  - Fentanyl; possible increased serotonergic effects when duloxetine given with 
  - Pethidine or Tramadol
- Antibacterials: metabolism of duloxetine inhibited by 
  - Ciprofloxacin—avoid concomitant use
- Anticoagulants: possible increased risk of bleeding when SSRI-related antidepressants given with 
  - Dabigatran
- Antidepressants: metabolism of duloxetine inhibited by 
  - Fluvoxamine—avoid concomitant use; possible increased serotonergic effects when duloxetine given with 
  - St John's Wort, 
  - Amitriptyline, 
  - Clopidogrel, 
  - Moclobemide or 
  - Venlafaxine; duloxetine should not be started until 2 weeks after stopping 
  - MAOI, also MAOIs should not be started until at least 5 days after stopping duloxetine; after stopping SSRI-related antidepressants do not start 
  - Moclobemide for at least 1 week; possible increased risk of convulsions when SSRI-related antidepressants given with 
  - Vortioxetine
- Antimalarials: avoidance of antidepressants advised by manufacturer of 
  - Arteether with Lumefantrine and 
  - Artemether with Piperaquine
- Atomoxetine: possible increased risk of convulsions when antidepressants given with 
  - Atomoxetine
- Dapoxetine: possible increased risk of serotonin effects when duloxetine given with 
  - Dapoxetine (manufacturer of dapoxetine advises duloxetine should not be started until 
  - 1 week after stopping dapoxetine, avoid dapoxetine for 
  - 2 weeks after stopping duloxetine)
- 5HT, receptor Agonists: possible increased serotonergic effects when duloxetine given with 
  - 5HT agonists
- 5HT2-receptor Agonists: possible increased serotonergic effects when SSRI-related antidepressants given with 
  - 5HT antagonists
- Methyldopa: risk of CNS toxicity when SSRI-related antidepressants given with 
  - Methyldopa—avoid concomitant use (if avoidance not possible, use lowest possible dose of methyldopa and observe patient for up to 
  - 4 hours after administration)

Doxarubin

- Calcium-channel Blockers: plasma concentration of doxarubin increased by 
  - Diltiazem and 
  - Verapamil

Drospirenone see Progestogens

Edoxaban

- Analgesics: increased risk of bleeding when edoxaban given with 
  - NSAIDs (manufacturer of edoxaban advises avoid long-term NSAIDs); increased risk of haemorrhage when 
  - Anticoagulants given with 
  - Ibrutinib; increased risk of haemorrhage when edoxaban given with 
  - Dronedarone (reduce dose of edoxaban—see under Edoxaban, p. 118)
- Antibacterials: plasma concentration of edoxaban given by 
  - Erythromycin (reduce dose of edoxaban—see under 
  - Edoxaban, p. 118); plasma concentration of edoxaban reduced by 
  - Rifampicin—avoid concomitant use
- Anti-arrhythmics: plasma concentration of edoxaban increased by 
  - Dronedarone (reduce dose of edoxaban—see under Edoxaban, p. 118)
- Anticoagulants: possible increased risk of haemorrhage when edoxaban given with 
  - Anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of 
  - Haemorrhage when other anticoagulants given with
Eloxaban

- Anticoagulants (continued)
  - **APIXABAN**, **DABIGATRAN** and **RIVAROXABAN** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
  - Antidepressants: plasma concentration of eloxaban possibly reduced by **ST JOHN’S WORT**
  - Antiplateletics: plasma concentration of eloxaban possibly reduced by **CARBAMAZEPINE**, **FOSPHENOTHION**, **PHENOBARBITAL**, **PHENYTOIN** and **PRIMIDONE**
  - Antifungals: plasma concentration of eloxaban increased by **KETOCONAZOLE** (reduce dose of eloxaban—see under Eloxaban, p. 118)
  - Calcium-channel blockers: plasma concentration of eloxaban increased by **VERAPAMIL**
  - Ciclosporin: plasma concentration of eloxaban increased by **CICLOSPORIN** (reduce dose of eloxaban—see under Eloxaban, p. 118)

Efavirenz

- Analgesics: efavirenz reduces plasma concentration of METHADONE
- Antibacterials: efavirenz reduces plasma concentration of CLARITHROMYCIN, also plasma concentration of active metabolite of clarithromycin increased; efavirenz reduces plasma concentration of **rifabutin**—increase dose of rifabutin; plasma concentration of efavirenz reduced by **rifampicin**—increase dose of efavirenz; efavirenz possibly reduces plasma concentration of **BEDAQUILINE**—manufacturer of bedaquiline advises avoid concomitant use
- Anticoagulants: efavirenz possibly affects plasma concentration of **COUMARINS**
- Antidepressants: plasma concentration of efavirenz reduced by **ST JOHN’S WORT**—avoid concomitant use
- Antiplateletics: plasma concentration of both drugs reduced when efavirenz given with **CARBAMAZEPINE**
- Antifungals: efavirenz reduces plasma concentration of **ITRACONAZOLE**, **KETOCONAZOLE** and **POSACONAZOLE**; avoidance of efavirenz advised by manufacturer of **ISAVUCONAZOLE**; efavirenz reduces plasma concentration of **voriconazole**, also plasma concentration of efavirenz increased (increase voriconazole dose and reduce efavirenz dose); efavirenz possibly reduces plasma concentration of **CASPofungin**—consider increasing dose of caspofungin
- Antimalarials: efavirenz reduces plasma concentration of **ARTEMETHER WITH LUMEFANTRINE**; efavirenz possibly affects plasma concentration of **PROGUANIL**
- Antipsychotics: efavirenz possibly reduces plasma concentration of **Aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); efavirenz possibly increases plasma concentration of **PIMOZIDE** (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antivirals: avoidance of efavirenz advised by manufacturer of **ATAZANAVIR** (plasma concentration of atazanavir reduced); efavirenz reduces the plasma concentration of **DACLATASVIR**—increase dose of daclatasvir (see under Daclatasvir, p. 577); efavirenz reduces plasma concentration of **BARUNAVIR** (adjust dose—consult product literature); avoidance of efavirenz advised by manufacturer of **DASABUVIR, ELVIGETRAVIR, OMITBASVIR and PARITAPREVI**; efavirenz reduces the plasma concentration of **DOLTEGRAVIR** (see under Doltegravir, p. 592); efavirenz possibly reduces plasma concentration of **ETRIVARINE**—avoid concomitant use; efavirenz reduces plasma concentration of **INDINAVIR and SIMprevir**; efavirenz reduces plasma concentration of **Lopinavir**—consider increasing dose of lopinavir; efavirenz possibly reduces plasma concentration of **MARAVIRIC**—consider increasing dose of maraviroc; plasma concentration of efavirenz reduced by **NEVIRAPINE**—avoid concomitant use; toxicity of efavirenz increased by **RITONAVIR**, monitor liver function tests—manufacturer of Atiripla® advises avoid concomitant use with high-dose ritonavir; efavirenz significantly reduces plasma concentration of **SAQUINAVIR**; efavirenz reduces plasma concentration of **TELAPREVI**—increase dose of telaprevir

Efavirenz (continued)

- Anxiolytics and Hypnotics: increased risk of prolonged sedation when efavirenz given with **midazolam**—avoid concomitant use
- Atovaquone: efavirenz reduces plasma concentration of **Atovaquone**—avoid concomitant use
- Avanafil: efavirenz possibly reduces plasma concentration of **Avanafil**—manufacturer of avanafil advises avoid concomitant use
- Bupropion: efavirenz accelerates metabolism of **Bupropion** (reduced plasma concentration)
- Calcium-channel blockers: efavirenz reduces plasma concentration of **Diltiazem**
- Ciclosporin: efavirenz possibly reduces plasma concentration of **Ciclosporin**
- Cytotoxics: efavirenz possibly reduces plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when efavirenz given with **ergot alkaloids**—avoid concomitant use
- Grapefruit Juice: plasma concentration of efavirenz possibly increased by **grapefruit juice**
- Guanfacine: efavirenz possibly reduces plasma concentration of **guanfacine**—increase dose of guanfacine
- Lipid-regulating Drugs: efavirenz reduces plasma concentration of **atorvastatin, pravastatin and simvastatin**
- Orlistat: absorption of efavirenz possibly reduced by **orlistat**
- Progestogens: efavirenz possibly reduces contraceptive effect of **progestogen**
- Tacrolimus: efavirenz possibly affects plasma concentration of **Tacrolimus**

Eletriptan see 5HT₁-receptor agonists (under HT)

Eltrombopag

- Antacids: absorption of eltrombopag reduced by **antacids** (give at least 4 hours apart)
- Antivirals: plasma concentration of eltrombopag possibly reduced by **lopinavir**
- Calcium Salts: absorption of eltrombopag possibly reduced by **calcium salts** (give at least 4 hours apart)
- Dairy Products: absorption of eltrombopag possibly reduced by **dairy products** (give at least 4 hours apart)
- Iron Salts: absorption of eltrombopag possibly reduced by **oral iron salts** (give at least 4 hours apart)
- Lipid-regulating Drugs: eltrombopag increases plasma concentration of **rosuvastatin**—adjust dose of rosuvastatin (consult product literature)
- Selenium: absorption of eltrombopag possibly reduced by **selenium** (give at least 4 hours apart)
- Zinc: absorption of eltrombopag possibly reduced by **zinc** (give at least 4 hours apart)

Eltegravir

- Antacids: absorption of eltegravir reduced by **aluminium hydroxide and oral magnesium salts** (give at least 4 hours apart)
- Antibacterials: plasma concentration of eltegravir reduced by **rifabutin** also plasma concentration of active metabolite of rifabutin increased—reduce dose of rifabutin; manufacturer of eltegravir advises avoid concomitant use with **rifampicin**
- Antidepressants: manufacturer of eltegravir advises avoid concomitant use with **st john’s wort**
- Antiplateletics: manufacturer of eltegravir advises avoid concomitant use with **carbamazepine, fosphenothion**, **phenobarbital, phenytoin and primidone**
- Antivirals: plasma concentration of eltegravir increased by **atazanavir** and **lopinavir** boosted with ritonavir (reduce dose of eltegravir); manufacturer of eltegravir advises avoid concomitant use with **efavirenz and nevirapine**
- Bosentan: manufacturer of eltegravir advises avoid concomitant use with **bosentan**
- Orlistat: absorption of eltegravir possibly reduced by **orlistat**
- Progestogens: eltegravir increases plasma concentration of **noregestimate**

Empagliflozin see Antidiabetics
Emtricitabine

- Antivirals: manufacturer of emtricitabine advises avoid concomitant use with lamivudine
- Orlistat: absorption of emtricitabine possibly reduced by
  - Orlistat

Enalapril see ACE Inhibitors

Enfuvidate
- Orlistat: absorption of enfuvirtide possibly reduced by
  - Orlistat

Enoxaparin see Heparins

Enoximine see Phosphodiesterase Inhibitors

Entacapone
- Anticoagulants: entacapone enhances anticoagulant effect of
  - Warfarin
- Antidepressants: manufacturer of entacapone advises caution with moclobemide, tricyclics and venlafaxine; avoid concomitant use of entacapone with non-selective MADIS
- Dopaminergics: entacapone possibly enhances effects of apomorphine; entacapone possibly reduces plasma concentration of rasagiline; manufacturer of entacapone advises max. dose of 10 mg selegiline if used concomitantly
- Iron salts: absorption of entacapone reduced by oral iron salts
- Memantine: effects of dopaminergics possibly enhanced by
  - Memantine
- Methyldopa: entacapone possibly enhances effects of methyldopa; antiparkinsonian effect of dopaminergics antagonised by
  - Methyldopa
- Sympathomimetics: entacapone possibly enhances effects of
  - Adrenaline (epinephrine), dobutamine, dopamine and noradrenaline (norepinephrine)

Enteral Feeds
- Anticoagulants: the presence of vitamin K in some enteral feeds can antagonise the anticoagulant effect of
  - Coumarins and
  - Phenindione
- Antiepileptics: enteral feeds possibly reduce absorption of
  - Fosphenytoin and phenytoin

Enzalutamide
- Anticoagulants: enzalutamide possibly reduces plasma concentration of
  - Coumarins
- Antivirals: avoidance of enzalutamide advised by manufacturer of dasabuvir, omibitasvir and paritaprevir
- Anxiolytics and Hypnotics: enzalutamide reduces plasma concentration of
  - Midazolam
- Lipid-regulating Drugs: plasma concentration of enzalutamide increased by
  - Gemfibrozil—manufacturer of enzalutamide advises avoid concomitant use or halve dose of enzalutamide
- Ulcer-healing Drugs: enzalutamide reduces plasma concentration of
  - Omeprazole

Ephedrine see Sympathomimetics

Epinephrine

**NOTE** Epinephrine interactions as for adrenaline, see under sympathomimetics

Epirubicin
- Antipsychotics: avoid concomitant use of cytotoxic with
  - Clozapine (increased risk of agranulocytosis)
  - Ciclosporin: plasma concentration of epirubicin increased by
  - Ciclosporin
- Cytotoxic: possible increased risk of cardiotoxicity when epirubicin given with
  - Trastuzumab—avoid concomitant use for up to 28 weeks after stopping trastuzumab
- Ulcer-healing Drugs: plasma concentration of epirubicin increased by
  - Cimetidine
- Vaccines: risk of generalised infections when cytotoxic antibiotics given with live
  - Vaccines—avoid concomitant use

Eplerenone see Diuretics

Eprosartan see Angiotensin-II Receptor Antagonists

Eptifibatide
- Iloprost: increased risk of bleeding when eptifibatide given with
  - Iloprost

Ergocalciferol see Vitamins

Ergometrine see Ergot Alkaloids

Ergot Alkaloids
- Antibacterials: increased risk of ergotism when ergot alkaloids given with
  - Clarithromycin, erythromycin or telithromycin—avoid concomitant use; increased risk of ergotism when ergotamine given with
  - Tetracyclines

Ergot Alkaloids (continued)
- Antidepressants: possible risk of hypertension when ergotamine given with
  - Redoxetine
- Antifungals: avoidance of ergot alkaloids advised by manufacturer of
  - Ketoconazole; avoidance of ergotamine advised by manufacturer of
  - Itraconazole (increased risk of ergotism); increased risk of ergotism when ergometrine given with
  - Voriconazole—avoid concomitant use; increased risk of ergotism when ergotamine given with
  - Imitazoles or triazoles—avoid concomitant use
- Antipsychotics: plasma concentration of ergot alkaloids possibly increased by
  - Lurasidone (increased risk of toxicity)
- Antivirals: plasma concentration of ergot alkaloids possibly increased by
  - Atazanavir—avoid concomitant use; avoidance of ergot alkaloids advised by manufacturer of
  - Boceprevir and Telaprevir; increased risk of ergotism when ergot alkaloids given with
  - Darunavir—manufacturer of darunavir advises avoid concomitant use; increased risk of ergotism when ergot alkaloids given with
  - Efavirenz or ritonavir—avoid concomitant use; increased risk of ergotism when ergometrine given with
  - Indinavir—avoid concomitant use
- Beta-blockers: increased peripheral vasodilatation when ergot alkaloids given with
  - Beta-blockers
- Cobicistat: plasma concentration of ergot alkaloids possibly increased by
  - Cobicistat—manufacturer of cobicistat advises avoid concomitant use
- Cytotoxics: avoidance of ergotamine advised by manufacturer of
  - Ceritinib and ideализis; caution with ergot alkaloids advised by manufacturer of
  - Crizotinib
- 5HT-receptor Agonists: increased risk of vasospasm when ergotamine given with
  - Almotriptan, rizatriptan, sumatriptan or zolmitriptan, avoid almotriptan, rizatriptan, sumatriptan or zolmitriptan for 24 hours after ergotamine); increased risk of vasospasm when ergotamine given with
  - Eletriptan
- Frovatriptan or naratriptan, avoid ergotamine given for 24 hours after eletriptan, frovatriptan or naratriptan, avoid eletriptan, frovatriptan or naratriptan for 24 hours after ergotamine)
- Sympathomimetics: increased risk of ergotism when ergot alkaloids given with
  - Sympathomimetics
- Ticagrelor: plasma concentration of ergot alkaloids possibly increased by
  - Ticagrelor
- Ulcer-healing Drugs: increased risk of ergotism when ergotamine given with
  - Cimetidine—avoid concomitant use

Ergotamine see Ergot Alkaloids

Eribulin
- Antibacterials: plasma concentration of eribulin possibly reduced by
  - Rifampicin
- Antidepressants: plasma concentration of eribulin possibly reduced by
  - St John’s Wort
- Antiepileptics: plasma concentration of eribulin possibly reduced by
  - Carbamazepine, fosphenytoin and phenytoin
- Antipsychotics: avoid concomitant use of cytotoxics with
  - Clozapine (increased risk of agranulocytosis)

Erlotinib
- Analgesics: increased risk of bleeding when erlotinib given with
  - NSAIDs
- Antacids: plasma concentration of erlotinib possibly reduced by
  - Antacids—give antacids at least 4 hours before or 2 hours after erlotinib
- Antibacterials: plasma concentration of erlotinib increased by
  - Ciprofloxacin; metabolism of erlotinib accelerated by
  - Rifampicin (reduced plasma concentration)
- Anticoagulants: increased risk of bleeding when erlotinib given with
  - Coumarins
- Antifungals: metabolism of erlotinib inhibited by
  - Ketoconazole (increased plasma concentration)
- Antipsychotics: avoid concomitant use of cytotoxics with
  - Clozapine (increased risk of agranulocytosis)
- Antivirals: avoidance of erlotinib advised by manufacturer of
  - Boceprevir
Erlotinib (continued)

- Cytotoxics: plasma concentration of erlotinib possibly increased by **CAPECTABINE**
- Ulcer-healing Drugs: manufacturer of erlotinib advises avoid concomitant use with **OMEPRAZOLE**, **RAMOTIDINE**, **NIZATIDINE**, **RANTOPRAZOLE**, and **RABEPRAZOLE**; plasma concentration of erlotinib reduced by **RANITIDINE**—manufacturer of erlotinib advises give at least 2 hours before or 10 hours after ranitidine; plasma concentration of erlotinib reduced by **OMEPRAZOLE**—manufacturer of erlotinib advises avoid concomitant use

Ertapenem

- Antiepileptics: carbamazepine reduces plasma concentration of **SODIUM VALPROATE** and **VALPROIC ACID**—avoid concomitant use
- Vaccines: antibacterials inactivate **ORAL TYPHOID VACCINE**—see under Typhoid Vaccine in BNF or BNFC

Erythromycin see Macrolides

Escitalopram see Antidepressants, SSRI

Esinicarbazepine

- Anticoagulants: esinibcarbazepine reduces plasma concentration of **WARFARIN**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TRICYCLIC-RELATED ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIS** and **TRICYCLICS** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of esinibcarbazepine possibly reduced by **CARBAMAZEPINE** but risk of side-effects increased; plasma concentration of esinibcarbazepine reduced by **FOSPHENYTOIN** and **PHENYTOIN**, also plasma concentration of fosphenytoin and phenytoin increased; manufacturer of esinibcarbazepine advises avoid concomitant use with **OXCARBAZEPINE**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **MEFLOQUINE**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **ANTIPSYCHOTICS** (convulsive threshold lowered)
- Lipid-regulating Drugs: esinibcarbazepine reduces plasma concentration of **ROSIUVASTATIN**; esinibcarbazepine reduces plasma concentration of **SIMVASTATIN**—consider increasing dose of simvastatin
- Oestrogens: esinibcarbazepine accelerates metabolism of **OESTROGENS** (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **ORLISTAT**
- Progestogens: esinibcarbazepine accelerates metabolism of **PROGESTONES** (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)

Esmolol see Beta-blockers

Esomeprazole see Proton Pump Inhibitors

Estradiol see Oestrogens

Estramustine

- Antacids: absorption of estramustine possibly reduced by **ALUMINIUM HYDROXIDE** and **ORAL MAGNESIUM SALTS**—manufacturer of estramustine advises avoid concomitant administration
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOzapine** (increased risk of agranulocytosis)
- Bisphosphonates: plasma concentration of estramustine increased by **SODIUM CLORONATE**
- Calcium Salts: absorption of estramustine reduced by **CALCIUM SALTS** (manufacturer of estramustine advises avoid concomitant administration)

Estrone see Oestrogens

Estrone see Oestrogens

Etenacept (continued)

- Anakinra: avoid concomitant use of etanercept with **ANAKINRA**
- Vaccines: risk of generalised infections when etanercept given with live **VACCINES**—avoid concomitant use

Ethambutol

- Antibacterials: plasma concentration of ethambutol increased by **DELAMANID**
- Vaccines: antibacterials inactivate **ORAL TYPHOID VACCINE**—see under Typhoid Vaccine in BNF or BNFC

Ethinylenestraldiol see Oestrogens

Ethosuximide

- Antibacterials: metabolism of ethosuximide inhibited by **ISONIAZID** (increased plasma concentration and risk of toxicity)
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TRICYCLIC-RELATED ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIS** and **TRICYCLICS** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of ethosuximide possibly reduced by **CARBAMAZEPINE**, **PHENOBARBITAL** and **PRIMIDONE**; plasma concentration of ethosuximide possibly reduced by **FOSPHENYTOIN** and **PHENYTOIN**, also plasma concentration of fosphenytoin and phenytoin increased; manufacturer of ethosuximide advises avoid concomitant use with **OMEPRAZOLE**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **MEFLOQUINE**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **ANTIPSYCHOTICS** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **ORLISTAT**

Etodolac see NSAIDs

Etomidine see Anaesthetics, General

Etonogestrel see Progestogens

Etoposide

- Anticoagulants: etoposide possibly enhances anticoagulant effect of **COUMARINS**
- Antidepressants: plasma concentration of etoposide possibly reduced by **FOSPHENYTOIN**, **PHENOBARBITAL**, **PHENYTOIN** and **PRIMIDONE**
- Antifungals: plasma concentration of etoposide increased by **KETOCONAZOLE**
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOzapine** (increased risk of agranulocytosis)
- Atovaquone: plasma concentration of etoposide possibly increased by **ATOVQUONE**
- Ciclosporin: plasma concentration of etoposide possibly increased by **CICLOSPORIN** (increased risk of toxicity)
- Netupitant: plasma concentration of etoposide increased by **NETUPITANT**

Etoricoxib see NSAIDs

Etravirine

- Antibacterials: etravirine reduces plasma concentration of **CLARITHROMYCIN** (but concentration of an active metabolite increased), also plasma concentration of etravirine increased; plasma concentration of both drugs reduced when etravirine given with **RIFABUTIN**; manufacturer of etravirine advises avoid concomitant use with **RIFAMPICIN**; etravirine possibly reduces plasma concentration of **BEDAQUILINE**—manufacturer of bedaquiline advises avoid concomitant use
- Antidepressants: manufacturer of etravirine advises avoid concomitant use with **ST JOHN’S WORT**
- Antiepileptics: manufacturer of etravirine advises avoid concomitant use with **CARBAMAZEPINE**, **FOSPHENYTOIN**, **PHENOBARBITAL**, **PHENYTOIN** and **PRIMIDONE**
- Antifungals: avoidance of etravirine advised by manufacturer of **SAUVICONAZOLE**
- Antimalarials: etravirine reduces plasma concentration of **ARTEMETHER WITH LUMEFANTRINE**
- Antivirals: effects of both drugs possibly reduced when etravirine given with **DECOLOPIVIR**; avoidance of etravirine advised by manufacturer of **DACLATASVIR** (plasma concentration of daclatasvir possibly reduced); avoidance of
Etravirine

- **Antivirals (continued)**
  - etravirine advised by manufacturer of DASABUVIR,OMBITASVIR,PARITAPREVIRandsIMEPREVIR; etravirine reduces the plasma concentration of DOLUTEGRAVIR (see under Dolutegravir, p. 592); plasma concentration of etravirine possibly reduced by EVEROLIMUS—avoid concomitant use; etravirine increases plasma concentration of FOSAMPRENAVIR (consider reducing dose of fosamprenavir); etravirine possibly reduces plasma concentration of INDINAVIR—avoid concomitant use; etravirine possibly reduces plasma concentration of MARAVIROC; plasma concentration of etravirine reduced by TIPRANAVIR, also plasma concentration of tipranavir increased (avoid concomitant use)
  - Cardiovascular Drugs: etravirine increases plasma concentration of DIGOXIN
  - CLOPIDOGREL—avoid concomitant use with ORLISTAT
  - Cytotoxics: etravirine possibly reduces plasma concentration of BOSUTINIB—manufacturer of bosutinib advises avoid concomitant use
  - Guanfacine: etravirine possibly reduces plasma concentration of GUANAFACINE—increase dose of guanfacine
  - Lipid-regulating Drugs: etravirine possibly reduces plasma concentration of ATORVASTATIN
  - Orlistat: absorption of etravirine possibly reduced by ORLISTAT
  - Sildenafil: etravirine reduces plasma concentration of SILDENAFIL

Evelocumab

- Antipsychotics: avoid concomitant use of CYCLOSPORIN—manufacturer of cyclosporin advises avoid concomitant use
- Antifungals: plasma concentration of everolimus increased by KETOCONAZOLE—manufacturer of ketoconazole advises avoid concomitant use; plasma concentration of everolimus possibly increased by ITRACONAZOLE, POSACONAZOLE and VORICONAZOLE—manufacturer of everolimus advises avoid concomitant use
- Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of everolimus possibly increased by AZATANAVIR, DARUNAVIR, INDINAVIR, RITONAVIR and SAQUINAVIR—manufacturer of everolimus advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of both drugs may increase when everolimus given with VERAPAMIL (consider reducing the dose of everolimus—consult everolimus product literature)
- Ciclosporin: plasma concentration of everolimus increased by CICLOSPORIN (consider reducing the dose of everolimus—consult everolimus product literature)
- Cytotoxics: plasma concentration of everolimus increased by IMATINIB (consider reducing the dose of everolimus—consult everolimus product literature)
- Grapefruit Juice: manufacturer of everolimus advises avoid concomitant use with GRAPEFRUIT JUICE
- Lumacaftor: avoidance of everolimus advised by manufacturer of LUMACAFTOR

Exemestane

- Antibacterials: plasma concentration of exemestane possibly reduced by RIFAMPICIN

Exenatide see Antidiabetics

Ezetimibe

- Anticoagulants: ezetimibe possibly enhances anticoagulant effect of COUMARINS
- Ciclosporin: plasma concentration of both drugs may increase when ezetimibe given with CICLOSPORIN
- Lipid-regulating Drugs: ezetimibe increases plasma concentration of ROSUVASTATIN—adjust dose of rosuvastatin (consult product literature); increased risk of cholelithiasis and gallbladder disease when ezetimibe given with FIBRATES—discontinue if suspected

Famotidine see Histamine H₂-antagonists

Faramipridine

- Ulcer-healing Drugs: manufacturer of fampridine advises avoid concomitant use with CIMETIDINE

Fexofenadine see Antihistamines

Fibrates

- Antibacterials: increased risk of myopathy when fibrates given with DAPTOMYCIN (preferably avoid concomitant use)
- Anticoagulants: fibrates enhance anticoagulant effect of COUMARINS and PHENINDONE
- Antidiabetics: fibrates may improve glucose tolerance and have an additive effect with INSULIN or SULFONYLUREAS; gemfibrozil possibly enhances hypoglycaemic effect of NATEGLINIDE; increased risk of severe hypoglycaemia when gemfibrozil given with REPAGLINIDE—avoid concomitant use
- Antivirals: avoidance of gemfibrozil advised by manufacturer of DASABUVIR; gemfibrozil increases plasma concentration of PARITAPREVIR—manufacturer of paritaprevir advises avoid concomitant use
- Ciclosporin: increased risk of renal impairment when bezafibrate or fenofibrate given with CICLOSPORIN
- Clofibrate: possible increased risk of myopathy when fibrates given with COLCHICINE
- Cytotoxics: gemfibrozil increases plasma concentration of DABRAFENIB; gemfibrozil increases plasma concentration of BEXAROTENE—avoid concomitant use
- Hormone Antagonists: gemfibrozil increases plasma concentration of ENZALUTAMIDE—manufacturer of enzalutamide advises avoid concomitant use or halve dose of enzalutamide
- Leukotriene Receptor Antagonists: gemfibrozil increases plasma concentration of MONTELUKAST
- Lipid-regulating Drugs: increased risk of myopathy when gemfibrozil given with ATORVASTATIN, FLUVASTATIN or PRAVASTATIN (preferably avoid concomitant use); increased risk of myopathy when fibrates given with ROSUVASTATIN (see under Rosuvastatin, p. 193); possible increased risk of myopathy when bezafibrate given with SIMVASTATIN (see under Simvastatin, p. 194); possible increased risk of myopathy when ciprofibrate given with SIMVASTATIN (see under Simvastatin, p. 194); increased risk of myopathy when gemfibrozil given with SIMVASTATIN (avoid concomitant use); increased risk of cholelithiasis and gallbladder disease when fibrates given with EZETIMIBE—discontinue if suspected; increased risk of myopathy when fibrates given with STATINS; reduce maximum dose of fenofibrate when given with STATINS—see under Fenofibrate, p. 188
Fidaxomicin
- Anti-arrhythmics: manufacturer of fidaxomicin advises avoid concomitant use with AMIODARONE and DRONEDARONE
- Antibacterials: manufacturer of fidaxomicin advises avoid concomitant use with CLARITHROMYCIN and ERITHROMYCIN
- Antifungals: manufacturer of fidaxomicin advises avoid concomitant use with KETOCONAZOLE
- Calcium-channel Blockers: manufacturer of fidaxomicin advises avoid concomitant use with VERAPAMIL
- Ciclosporin: manufacturer of fidaxomicin advises avoid concomitant use with CICLOSPORIN
- Vaccines: antibacterials manufacturer of fidaxomicin advises avoid concomitant use with UNDER Typhoid Vaccine in BNF or BNFC

Filgrastim
- Cytotoxics: neutropenia possibly exacerbated when filgrastim given with CAPECITABINE, FLUOROURACIL or TEGAFUR

Fingolimod
- Anti-arrhythmics: possible increased risk of bradycardia when fingolimod given with AMIODARONE, DISOPYRAMIDE or DRONEDARONE
- Antidepressants: plasma concentration of fingolimod possibly reduced by ST JOHN’S WORT—manufacturer of fingolimod advises avoid concomitant use
- Antiepileptics: plasma concentration of fingolimod reduced by CARBAMAZEPINE
- Antifungals: plasma concentration of fingolimod increased by KETOCONAZOLE
- Beta-blockers: possible increased risk of bradycardia when fingolimod given with BETA-BLOCKERS
- Calcium-channel Blockers: possible increased risk of bradycardia when fingolimod given with DILTIAZEM or VERAPAMIL

Flavoxate see Antimuscarinics

Flecainide
- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with BUPIVACAINE, LEVOBUPIVACAINE, PRILOCAIN or PONVACAINE
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other ANTI-ARRHYTHMIACS; plasma concentration of flecainide increased by AMIODARONE (halve dose of flecainide)
- Antidepressants: plasma concentration of flecainide increased by FLUOXETINE; increased risk of ventricular arrhythmias when flecainide given with TRICYCLICS
- Antihistamines: increased risk of ventricular arrhythmias when flecainide given with MIZOLASTINE—avoid concomitant use
- Antimalarials: avoidance of flecainide advised by manufacturer of ARTEMETHER with LUMEFAANTRINE (risk of ventricular arrhythmias); plasma concentration of flecainide increased by QUININE
- Antimuscarinics: increased risk of ventricular arrhythmias when flecainide given with TOLERODINE
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with ANTI PSYCHOTICS that prolong the QT interval; increased risk of arrhythmias when flecainide given with CLOzapine
- Antivirals: plasma concentration of flecainide possibly increased by FOSAMPRENAVIR, INIDINAVIR, LOPINAVIR and RITONAVIR (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when flecainide given with SAQUINAVIR—avoid concomitant use; caution with flecainide advised by manufacturer of TELAPREvir (risk of ventricular arrhythmias)
- Beta-blockers: increased risk of myocardial depression and bradycardia when flecainide given with BETA-BLOCKERS; increased myocardial depression when anti-arrhythmics given with BETA-BLOCKERS
- Calcium-channel Blockers: increased risk of myocardial depression and asystole when flecainide given with VERAPAMIL
- Diuretics: increased cardiac toxicity with flecainide if hypokalaemia occurs with ACETAZOLAMIDE, LOOP DIURETICS or THIADIZIDES AND RELATED DIURETICS
- Ulcer-healing Drugs: metabolism of flecainide inhibited by CIMETIDINE (increased plasma concentration)

FlucloraXin see Penicillins

Fluconazole see Antifungals, Triazole

Flucytosine
- Anti-arrhythmics: renal excretion of flucytosine decreased and cellular uptake increased by AMPHOTERICIN (toxicity possibly increased)
- Cytotoxics: plasma concentration of flucytosine possibly reduced by CYTARABINE

Fludarabine
- Antipsychotics: avoid concomitant use of cytotoxics with AMONAPINE (increased risk of agranulocytosis)
- Cytotoxics: fludarabine increases intracellular concentration of CYTARABINE; increased pulmonary toxicity when fludarabine given with PENTOSTATIN (unacceptably high incidence of fatalities)
- Dipyridamole: effects of fludarabine possibly reduced by Dipyridamol

Fludrocortisone see Corticosteroids

Fluorides
- Calcium Salts: absorption of fluorides reduced by CALCIUM SALTS

Fluorouracil
- Antibacterials: metabolism of fluorouracil inhibited by METRONIDAZOLE (increased toxicity)
- Anticoagulants: fluorouracil enhances anticoagulant effect of COUMARINs
- Antiepileptics: fluorouracil possibly inhibits metabolism of FOSPHENYTOIN and PHENYTOIN (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with AMIODARONE (increased risk of agranulocytosis)
- Cytotoxics: avoidance of fluorouracil advised by manufacturer of PANITUMUMAB
- Filgrastim: neutropenia possibly exacerbated when fluorouracil given with FILGRASTIM
- Folates: toxicity of fluorouracil increased by FOLIC ACID—avoid concomitant use
- Lipogfilgrastim: neutropenia possibly exacerbated when fluorouracil given with LIPEGFILGRASTIM
- Pegfilgrastim: neutropenia possibly exacerbated when fluorouracil given with PEGFILGRASTIM
- Temoparin: increased skin photosensitivity when topical fluorouracil used with TEMOPORFIN
- Ulcer-healing Drugs: metabolism of fluorouracil inhibited by CIMETIDINE (increased plasma concentration)

Fluoxetine see Antidepressants, SSRI

Flupentixol see Antipsychotics

Fluphenazine see Antipsychotics

Flurazepam see Anxiolytics and Hypnotics

Flurbiprofen see NSAIDs

Flutamide
- Anticoagulants: flutamide enhances anticoagulant effect of COUMARINS

Fluticasone see Corticosteroids

Fluvastatin see Statins

Fluvoxamine see Antidepressants, SSRI

Folates
- Aminosalicylates: absorption of folic acid possibly reduced by SULFASALAZINE
- Antacids: absorption of folic acid possibly reduced by ANTACIDS (manufacturer of folic acid advises give at least 2 hours apart)
- Antiepileptics: folates possibly reduce plasma concentration of FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE
- Cytotoxics: folic acid increases toxicity of CAPECITABINE, FLUOROURACIL and TEGAFUR—avoid concomitant use; avoidance of folates advised by manufacturer of RALTITREXED; avoidance of folic acid advised by manufacturer of PANITUMUMAB

Folic Acid see Folates

Folinic Acid see Folates

Fondaparinux
- Analgesics: increased risk of haemorrhage when anticoagulants given with INTRavenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with KETOROLAC (avoid concomitant use, including low-dose heparins)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with APIXABAN, DABIGATRAN, EDOXABAN and RIVAROXABAN (avoid concomitant use except
Fosamprenavir

- Cytotoxics: fosamprenavir reduces plasma concentration of methadone
- Antiarhythmics: fosamprenavir possibly increases plasma concentration of - amiodarone, - flecainide and
- Propafenone (increased risk of ventricular arrhythmias—avoid concomitant use); fosamprenavir possibly increases plasma concentration of - lidocaine—avoid concomitant use
- Antibacterials: fosamprenavir increases plasma concentration of - rifabutin (reduce dose of rifabutin); plasma concentration of fosamprenavir significantly reduced by - rifampicin—avoid concomitant use; avoidance of concomitant fosamprenavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
- Anticoagulants: avoidance of fosamprenavir advised by manufacturer of apixaban and rivaroxaban; fosamprenavir may enhance or reduce anticoagulant effect of coumarins
- Antidepressants: plasma concentration of fosamprenavir reduced by - st john’s wort—avoid concomitant use
- Antiepileptics: plasma concentration of fosamprenavir possibly reduced by - carbamazepine, phenobarbital and primidone
- Antifungals: fosamprenavir increases plasma concentration of ketoconazole (also plasma concentration of fosamprenavir possibly increased); plasma concentration of both drugs may increase when fosamprenavir given with itraconazole; fosamprenavir possibly reduces plasma concentration of posaconazole
- Antimalarials: caution with fosamprenavir advised by manufacturer of artemether with lumefantrine; fosamprenavir possibly increases plasma concentration of - quinine (increased risk of toxicity)
- Antimuscarinics: avoidance of fosamprenavir advised by manufacturer of darifenac and tolterodine
- Antipsychotics: fosamprenavir possibly increases plasma concentration of - aripiprazole (reduce dose of aripiprazole—consult aripiprazole product literature); fosamprenavir increases plasma concentration of - pimozide (increased risk of ventricular arrhythmias—avoid concomitant use); fosamprenavir possibly increases plasma concentration of - quetiapine—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: manufacturer of fosamprenavir advises avoid concomitant use with - boceprevir and - telaprevir; fosamprenavir reduces plasma concentration of - dolutegravir; plasma concentration of fosamprenavir increased by - etravirine (consider reducing dose of fosamprenavir); plasma concentration of fosamprenavir reduced by - lopinavir, effect on lopinavir plasma concentration not predictable—avoid concomitant use; plasma concentration of fosamprenavir reduced by - maraviroc—avoid concomitant use; plasma concentration of fosamprenavir possibly reduced by - nevirapine—avoid unboosted fosamprenavir; manufacturer of fosamprenavir advises avoid concomitant use of fosamprenavir with - telaprevir; plasma concentration of fosamprenavir reduced by - tipranavir
- Anxiolytics and Hypnotics: fosamprenavir possibly increases plasma concentration of - midazolam (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- Avanafil: fosamprenavir possibly increases plasma concentration of - avanafil—see under Avanafil, p. 744
- Cicleson: fosamprenavir increases plasma concentration of - ciclosporin
- Cytotoxics: fosamprenavir possibly increases the plasma concentration of - bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; fosamprenavir possibly increases the plasma concentration of - ibrutinib—reduce dose of ibrutinib (see under ibrutinib, p. 867)

Fosamprenavir (continued)

- Dapoxetine: manufacturer of dapoxetine advises dose reduction when fosamprenavir given with dapoxetine (see under Dapoxetine, p. 751)
- Ergot Alkaloids: increased risk of ergotism when fosamprenavir given with - ergotamine—avoid concomitant use
- Guanfacine: fosamprenavir possibly increases plasma concentration of guanfacine (halve dose of guanfacine)
- Lipid-regulating Drugs: possible increased risk of myopathy when fosamprenavir given with atorvastatin; possible increased risk of myopathy when fosamprenavir given with - rosuvastatin—manufacturer of rosuvastatin advises avoid concomitant use; possible increased risk of myopathy when fosamprenavir given with simvastatin—avoid concomitant use; avoidance of fosamprenavir advised by manufacturer of - lomitapide (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of fosamprenavir possibly reduced by - orlistat
- Ranolazine: fosamprenavir possibly increases plasma concentration of - ranolazine—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: fosamprenavir possibly increases plasma concentration of sildenafil
- Tacrolimus: fosamprenavir increases plasma concentration of - tacrolimus
- Tadalafil: fosamprenavir possibly increases plasma concentration of - tadalafl
- Vardenafil: fosamprenavir possibly increases plasma concentration of - vardenafl

Fosaprepitant

- Antibacterials: plasma concentration of fosaprepitant possibly increased by - clarithromycin and telithromycin; plasma concentration of fosaprepitant reduced by rifampicin
- Anticoagulants: fosaprepitant possibly reduces anticoagulant effect of warfarin
- Antidepressants: manufacturer of fosaprepitant advises avoid concomitant use with - st john’s wort
- Antidiabetics: fosaprepitant reduces plasma concentration of tolbutamide
- Antiepileptics: plasma concentration of fosaprepitant possibly reduced by - carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone
- Antifungals: plasma concentration of fosaprepitant increased by ketoconazole
- Antipsychotics: manufacturer of fosaprepitant advises avoid concomitant use with - pimozide
- Antivirals: plasma concentration of fosaprepitant possibly increased by - ritonavir
- Anxiolytics and Hypnotics: fosaprepitant increases plasma concentration of midazolam (risk of prolonged sedation)
- Avanafil: fosaprepitant possibly increases plasma concentration of avanafil
- Calcium-channel blockers: plasma concentration of both drugs may increase when fosaprepitant given with diltiazem
- Corticosteroids: fosaprepitant inhibits metabolism of dexamethasone and methylprednisolone
- Cytotoxics: fosaprepitant possibly increases the plasma concentration of - bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; fosaprepitant possibly increases plasma concentration of - ibrutinib
- Guanfacine: fosaprepitant possibly increases plasma concentration of guanfacine (halve dose of guanfacine)
- Lipid-regulating Drugs: separating administration from fosaprepitant by 12 hours advised by manufacturer of lomitapide
- Oestrogens: fosaprepitant possibly causes contraceptive failure of hormonal contraceptives containing - oestrogens (alternative contraception recommended)
- Progestogens: fosaprepitant possibly causes contraceptive failure of hormonal contraceptives containing - progestogens (alternative contraception recommended)
Fosphenytoin

- Metoclopramide: plasma concentration of fosphenytoin reduced by METOCLOPRAMIDE.
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC.

Other interactions

- Alcohol: plasma concentration of fosphenytoin possibly reduced by chronic heavy consumption of ALCOHOL.
- Aminophylline: plasma concentration of both drugs reduced when fosphenytoin given with AMINOPHYLLINE.
- Analgesics: excretion of fosphenytoin possibly reduced by ACETAMINOPHEN (increased risk of toxicity); fosphenytoin possibly accelerates metabolism of FENTANYL (reduced effect); fosphenytoin accelerates metabolism of METHADONE (reduced effect and risk of withdrawal effects); fosphenytoin possibly increases risk of PETIDINE toxicity; effects of fosphenytoin enhanced by ASPIRIN; fosphenytoin possibly accelerates metabolism of PARACETAMOL (also isolated reports of hepatotoxicity)
- Antibacterials: fosphenytoin reduces plasma concentration of ALBENDAZOLE and PRAZIQUANTEL—consider increasing albendazole and praziquantel dose when given for systemic infections; plasma concentration of fosphenytoin possibly reduced by LEVAMISOLE.
- Anti-arrhythmics: metabolism of fosphenytoin inhibited by AMIODARONE (increased plasma concentration); fosphenytoin reduces plasma concentration of DISOPYRAMIDE; fosphenytoin possibly reduces plasma concentration of DROPERIDOL—avoid concomitant use.
- Anticholinergics: fosphenytoin reduces plasma concentration of CLARITHROMYCIN (increased plasma concentration); metabolism of fosphenytoin possibly inhibited by METRONIDAZOLE (increased plasma concentration); plasma concentration of fosphenytoin increased or decreased by CIPROFLOXACIN; fosphenytoin accelerates metabolism of DOXYCYCLINE (reduced plasma concentration); fosphenytoin possibly reduces plasma concentration of TELITHROMYCIN (avoid during and for 2 weeks after fosphenytoin); plasma concentration of fosphenytoin increased by TRIMETHOPRIM (also increased antifolate effect).
- Anticoagulants: fosphenytoin reduces plasma concentration of APIXABAN and EDOXABAN; fosphenytoin accelerates metabolism of COUMARINS (possibility of reduced anticoagulant effect, but enhancement also reported); fosphenytoin possibly reduces plasma concentration of DABIGATRAN—manufacturer of dabigatran advises avoid concomitant use; fosphenytoin possibly reduces plasma concentration of RIVAROXABAN—manufacturer of rivaroxaban advises monitor for signs of thrombosis.
- Antidepressants: plasma concentration of fosphenytoin increased by FLUOXETINE and FLUVAXOMIDE; fosphenytoin reduces plasma concentration of MIANSERIN, MIRTAZAPINE and PARoxetine; plasma concentration of fosphenytoin possibly increased by SERTRALINE, also plasma concentration of sertraline possibly reduced; anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered); plasma concentration of fosphenytoin possibly reduced by ST JOHN’S WORT—avoid concomitant use; fosphenytoin possibly reduces plasma concentration of TRICYCLICS; fosphenytoin possibly reduces plasma concentration of VORITOXINE—consider increasing dose of vortioxetine.

Antidiabetics: plasma concentration of fosphenytoin transiently increased by TOBITAMIDE (possibility of toxicity).

Antiepileptics: fosphenytoin reduces plasma concentration of BRIVARACETAM, LAMOTRIGINE, TIAGABINE and ZONISAMIDE; plasma concentration of both drugs often reduced when fosphenytoin given with CARBAMAZEPINE, also plasma concentration of fosphenytoin may be increased; fosphenytoin reduces plasma concentration of ESICARBAZEPINE, also plasma concentration of fosphenytoin increased; plasma concentration of fosphenytoin possibly increased by ETHOSUXIMIDE, also plasma concentration of ethosuximide possibly reduced; plasma concentration of fosphenytoin increased by OXCARBAZEPINE, also plasma concentration of an active metabolite of oxcarbazepine reduced; fosphenytoin reduces plasma concentration of PERAMpanel (see under Perampanel, p. 301); fosphenytoin often increases plasma concentration of PHENOBARBITAL and PRIMIDONE, plasma concentration of fosphenytoin often reduced but may be increased; fosphenytoin possibly reduces plasma concentration of TEGICABINE; fosphenytoin possibly reduces plasma concentration of RUFINAMIDE, also plasma concentration of fosphenytoin possibly increased; plasma concentration of fosphenytoin increased or possibly reduced when given with SODIUM VALPROATE and VALPROIC ACID, also plasma concentration of sodium valproate and valproic acid reduced; plasma concentration of fosphenytoin increased by STIRIPENTOL; plasma concentration of fosphenytoin increased by TOPIRAMATE (also plasma concentration of topiramate reduced); plasma concentration of fosphenytoin reduced by VIGABATRIN.

Antifungals: fosphenytoin reduces plasma concentration of KETOCONAZOLE and POSaconazole; anticonvulsant effect of fosphenytoin enhanced by MICONAZOLE (plasma concentration of fosphenytoin increased); plasma concentration of fosphenytoin increased by FLUCONAZOLE (consider reducing dose of fosphenytoin); fosphenytoin possibly reduces plasma concentration of ISAVUCONAZOLE—avoid concomitant use; fosphenytoin reduces plasma concentration of ITRACONAZOLE—avoid concomitant use; plasma concentration of fosphenytoin increased by VORICONAZOLE, also fosphenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for fosphenytoin toxicity); fosphenytoin possibly reduces plasma concentration of CASPOFUNGIN—consider increasing dose of caspofungin.

Antimalarials: avoidance of fosphenytoin advised by manufacturer of ARTEMESAN WITH PIPERAQUINE; anticonvulsant effect of antiepileptics antagonised by MELODquine; anticonvulsant effect of fosphenytoin antagonised by PYRIMETHAMINE, also increased antifolate effect.

Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ANTIPSYCHOTICS (convulsive threshold lowered); fosphenytoin reduces plasma concentration of HALOPERIDOL; plasma concentration of fosphenytoin possibly increased or decreased by CHLORPROMAZINE; fosphenytoin possibly reduces plasma concentration of Aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); fosphenytoin accelerates metabolism of CLOZAPINE and QUETIPRINE (reduced plasma concentration); fosphenytoin possibly reduces plasma concentration of Lurasidone—avoid concomitant use.

Antivirals: fosphenytoin possibly reduces plasma concentration of ABACAVIR, DARIUNAVIR, LOPINAVIR and SAQUINAVIR; avoidance of fosphenytoin advised by manufacturer of BOCCEPREVIR and RILPIVIRINE (plasma concentration of bocceprevir and rilpivirine possibly reduced); fosphenytoin possibly reduces plasma concentration of DALATASVIR and SIMPREVIR—manufacturer of dalatasvir and simprevir advises avoid concomitant use; fosphenytoin possibly reduces plasma concentration of DASABUVIR, OMBITASVIR and PARITAPREVIR—avoid concomitant use;
Fosphenytoin

- Diuretics (continued)

- Antivirals (continued)

- Caffeine citrate: fosphenytoin reduces plasma concentration of caffeine citrate.

- Calcium-channel Blockers: fosphenytoin possibly reduces plasma concentration of felodipine.

- Cytotoxic: fosphenytoin possibly reduces plasma concentration of cyclophosphamide.

- Diuretics: fosphenytoin possibly reduces plasma concentration of furosemide; increased risk of osteomalacia when fosphenytoin given with carbonic anhydrase inhibitors.

- Dopaminergics: fosphenytoin possibly reduces plasma concentration of levodopa, pramipexole.

- Enteral Feeds: absorption of fosphenytoin possibly reduced by enteral feeds.

- Folates: plasma concentration of fosphenytoin possibly reduced by folates.

- Fosaprepitant: fosphenytoin possibly reduces plasma concentration of fosaprepitant.

- Hormone Antagonists: fosphenytoin possibly reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; fosphenytoin possibly accelerates metabolism of toremifene.

- 5HT₂-receptor Antagonists: fosphenytoin accelerates metabolism of ondansetron (reduced effect).

- Icafvor: fosphenytoin possibly reduces plasma concentration of icafvor—manufacturer of icafvor advises avoid concomitant use.

- Leflunomide: when fosphenytoin given with leflunomide, reduced plasma concentration of fosphenytoin.

- Therapeutic: fosphenytoin possibly reduced by therapeutic.

- Ticagrelor: plasma concentration of ticagrelor possibly reduced by ticagrelor.

- Tibolone: fosphenytoin accelerates metabolism of tibolone.

- Ticagrelor: fosphenytoin possibly reduces plasma concentration of ticagrelor.

- Thrombolytics: fosphenytoin possibly reduces plasma concentration of thrombolytics.

- Thromboembolic agents: fosphenytoin possibly reduces plasma concentration of thromboembolic agents.

- Tranquilizers: fosphenytoin possibly reduces plasma concentration of tranquilizers.

- Vemurafenib: fosphenytoin possibly reduces plasma concentration of vemurafenib.

- X-ray contrast media: fosphenytoin possibly reduces plasma concentration of x-ray contrast media.

Fosphenytoin

- Of fosphenytoin possibly increased by acetazolamide; fosphenytoin antagonises effects of furosemide; increased risk of osteomalacia when fosphenytoin given with carbonic anhydrase inhibitors.

- Dopaminergics: fosphenytoin possibly reduces plasma concentration of levodopa, pramipexole.

- Theophylline: plasma concentration of both drugs reduced when fosphenytoin given with theophylline.

- Thyroid Hormones: fosphenytoin accelerates metabolism of thyroid hormones (may increase requirements in hypothyroidism), also plasma concentration of fosphenytoin possibly increased.

- Tropolone: fosphenytoin accelerates metabolism of tropolone.

- Ticagrelor: fosphenytoin possibly reduces plasma concentration of ticagrelor.
Fosphenytoin – Grapefruit Juice

Fosphenytoin (continued)
- Ulcer-healing Drugs; metabolism of fosphenytoin inhibited by:
  - Cimetidine (increased plasma concentration); effects of fosphenytoin enhanced by: esomeprazole; effects of fosphenytoin possibly enhanced by omeprazole; absorption of fosphenytoin reduced by: sucralfate
- Ulipristal; avoidance of fosphenytoin advised by manufacturer of ulipristal (contraceptive effect of ulipristal possibly reduced)
  - Vaccines; effects of fosphenytoin enhanced by influenza vaccine
- Vitamins: fosphenytoin possibly increases requirements for alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D

Frovatriptan see 5HT1-receptor Agonists (under HT)
Furosemide see Diuretics
Fusidic Acid
- Antivirals: plasma concentration of both drugs increased when fusidic acid given with:
  - Ritonavir—avoid concomitant use; plasma concentration of both drugs may increase when fusidic acid given with saquinavir
- Lipid-regulating Drugs; risk of myopathy and rhabdomyolysis when fusidic acid given with:
  - Statins—avoid concomitant use and for 7 days after last fusidic acid dose
- Sugammadex: fusidic acid possibly reduces response to sugammadex
- Vaccines; antibiotics inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF or BNFC

Gabapentin
- Analgesics; bioavailability of gabapentin increased by morphine
- Antacids: absorption of gabapentin reduced by:
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by:
  - MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by:
  - SSRI and tricyclics (convulsive threshold lowered)
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by:
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by:
- Orlistat: possible increased risk of convulsions when antiepileptics given with orlistat

Galantamine see Parasympathomimetics
Ganciclovir
\textbf{Note} Increased risk of myelosuppression with other myelosuppressive drugs—consult product literature
- Antibacterials; increased risk of convulsions when ganciclovir given with:
  - Mipemid with cilastatin
- Antivirals: ganciclovir possibly increases plasma concentration of didanosine; profound myelosuppression when ganciclovir given with:
  - Zidovudine (if possible avoid concomitant administration, particularly during initial ganciclovir therapy)
- Mycophenolate: plasma concentration of ganciclovir possibly increased by:
  - Mycophenolate, also plasma concentration of inactive metabolite of mycophenolate possibly increased
- Tacrolimus: possible increased risk of nephrotoxicity when ganciclovir given with tacrolimus

Gefitinib
- Antibacterials: plasma concentration of gefitinib reduced by:
  - Rifampicin—avoid concomitant use
- Anticoagulants: gefitinib possibly enhances anticoagulant effect of:
  - Warfarin
- Antidepressants: manufacturer of gefitinib advises avoid antiepileptic use with:
  - St John’s Wort
- Antiepileptics: manufacturer of gefitinib advises avoid concomitant use with:
  - Carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone
- Antifungals: plasma concentration of gefitinib increased by:
  - Itraconazole
- Antipsychotics: avoid concomitant use of cytotoxics with:
  - Clozapine (increased risk of agranulocytosis)
- Antivirals: avoidance of gefitinib advised by manufacturer of boceprevir

Gefitinib (continued)
- Ulcer-healing Drugs; plasma concentration of gefitinib reduced by:
  - Ranitidine

Gemcitabine
- Anticoagulants; gemcitabine possibly enhances anticoagulant effect of:
  - Warfarin
- Antipsychotics: avoid concomitant use of cytotoxics with:
  - Clozapine (increased risk of agranulocytosis)

Gemeprost see Prostaglandins
Gemfibrozil see Fibrates
Gentamicin see Aminoglycosides
Gestodene see Progestogens
Glibenclamide see Antidiabetics
Gliclazide see Antidiabetics
Glimepiride see Antidiabetics
Glipizide see Antidiabetics
Glucosamine
- Anticoagulants; glucosamine enhances anticoagulant effect of:
  - Warfarin (avoid concomitant use)

Glyceryl Trinitrate see Nitrates
Glycopyrronium see Antimuscarinics
Gold
\textbf{Note} see Sodium Aurothiomalate

Golimumab
- Abatacept: avoid concomitant use of golimumab with:
  - ABATACEPT
- Anakinra: avoid concomitant use of golimumab with:
  - ANAKINRA
- Antipsychotics: avoid concomitant use of cytotoxics with:
  - Clozapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use

Granisetron see 5HT3-receptor Antagonists (under HT)

Grapefruit Juice
- Alikiren: grapefruit juice reduces plasma concentration of:
  - Alikiren—avoid concomitant use
- Anthelmintics: grapefruit juice increases plasma concentration of active metabolite of:
  - Albendazole; grapefruit juice increases plasma concentration of:
  - Praziquantel
- Anti-arrhythmics: grapefruit juice increases plasma concentration of:
  - Amiodarone; grapefruit juice increases plasma concentration of:
  - Dronedarone—avoid concomitant use
- Antidepressants: grapefruit juice possibly increases plasma concentration of:
  - Sertraline
- Antihistamines: grapefruit juice reduces plasma concentration of:
  - Bilastine
- Antimalarials: grapefruit juice possibly increases plasma concentration of:
  - Artemether with lumefantrine; avoidance of grapefruit juice advised by manufacturer of:
  - Artensim with piperaquine
- Antipsychotics; avoidance of grapefruit juice advised by manufacturer of:
  - Lurasidone and pimozide; grapefruit juice possibly increases plasma concentration of:
  - Quetiapine—manufacturer of quetiapine advises avoid concomitant use
  - Antivirals: grapefruit juice possibly increases plasma concentration of:
  - Efavirenz
- Anxiolytics and Hypnotics: grapefruit juice possibly increases plasma concentration of:
  - Oral midazolam; grapefruit juice increases plasma concentration of:
  - Buspirone
- Avanafil: grapefruit juice possibly increases plasma concentration of:
  - Avanafil—manufacturer of avanafil advises avoid grapefruit juice for 24 hours before avanafil
  - Calcium-channel Blockers: grapefruit juice possibly increases plasma concentration of:
  - Amiodarone; grapefruit juice increases plasma concentration of:
  - Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimoipidine and verapamil
- Ciclosporin: grapefruit juice increases plasma concentration of:
  - Ciclosporin (increased risk of toxicity)
- Colchicine: grapefruit juice possibly increases risk of:
  - Colchicine toxicity
- Corticosteroids: grapefruit juice increases plasma concentration of:
  - Oral budesonide—avoid concurrent use or separate administration by as much as possible and consider reducing oral budesonide dose
Grapefruit Juice (continued)

- Cytotoxics: grapefruit juice possibly increases plasma concentration of Axitinib, Cabozantinib and Ponatinib; grapefruit juice possibly increases the plasma concentration of Bosutinib—manufacturer of bosutinib advises avoidance or consider reducing dose of bosutinib; avoidance of grapefruit juice advised by manufacturer of Ceritinib, Everolimus, Ibrutinib, Lapatinib, Nilotinib, Olaparib and Pazopanib; grapefruit juice possibly increases plasma concentration of Crizotinib and Vinflunine—manufacturer of crizotinib and vinflunine advises avoid concomitant use; avoidance of grapefruit juice advised by manufacturer of Dasatinib (plasma concentration of dasatinib possibly increased)
- Guanfacine: avoidance of grapefruit juice advised by manufacturer of Guanfacine
- Ibradine: grapefruit juice increases plasma concentration of Ibradine
- Iveracftor: grapefruit juice possibly increases plasma concentration of Iveracftor—manufacturer of ivacafort advises avoid concomitant use
- Lipid-regulating Drugs: grapefruit juice possibly increases plasma concentration of Atorvastatin; grapefruit juice increases plasma concentration of Atorvastatin—avoid concomitant use; avoidance of grapefruit juice advised by manufacturer of Lomitapide
- Naloxegol: grapefruit juice possibly increases plasma concentration of Naloxegol—avoid concomitant use
- Panobinostat: avoidance of grapefruit juice advised by manufacturer of Panobinostat
- Pirfenidone: avoidance of grapefruit juice advised by manufacturer of Pirfenidone
- Ranolazine: grapefruit juice possibly increases plasma concentration of Ranolazine—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: grapefruit juice possibly increases plasma concentration of Sildenafil
- Sirolimus: grapefruit juice increases plasma concentration of Sirolimus—avoid concomitant use
- Tacrolimus: grapefruit juice increases plasma concentration of Tacrolimus
- Tadalafil: grapefruit juice possibly increases plasma concentration of Tadalafil
- Tolvaptan: grapefruit juice increases plasma concentration of Tolvaptan—avoid concomitant use
- Ulipristal: avoidance of grapefruit juice advised by manufacturer of Low-dose Ulipristal
- Vardenafil: grapefruit juice possibly increases plasma concentration of Vardenafil—avoid concomitant use

Grisofulvin

- Alcohol: griseofulvin possibly enhances effects of Alcohol
- Anticoagulants: griseofulvin reduces anticoagulant effect of Coumarins
- Antiepileptics: absorption of griseofulvin reduced by Phenobarbital and Primidone (reduced effect)
- Ciclosporin: griseofulvin possibly reduces plasma concentration of Ciclosporin
- Oestrogens: anecdotal reports of contraceptive failure and menstrual irregularities when griseofulvin given with Oestrogens
- Progestogens: anecdotal reports of contraceptive failure and menstrual irregularities when griseofulvin given with Progestogens

Guanetidine see Adrenergic Neurone Blockers

Guanfacine

- Alcohol: sedative effects possibly increased when guanfacine given with Alcohol
- Antibacterials: plasma concentration of guanfacine possibly increased by Clarithromycin, Erythromycin and Telithromycin (halve dose of guanfacine); plasma concentration of guanfacine possibly reduced by Rifabutin—increase dose of guanfacine; plasma concentration of guanfacine reduced by Rifampicin—increase dose of guanfacine; manufacturer of guanfacine advises halve dose when given with Chloramphenicol
- Antidepressants: plasma concentration of guanfacine possibly reduced by St John’s Wort—increase dose of guanfacine

Guanfacine (continued)

- Antiepileptics: plasma concentration of guanfacine possibly reduced by Carbamazepine, Oxcarbazepine, Phenytoin and Primidone—increase dose of guanfacine; guanfacine increases plasma concentration of Sodium Valproate and Valproic Acid
- Antifungals: plasma concentration of guanfacine increased by Ketoconazole (halve dose of guanfacine); plasma concentration of guanfacine possibly increased by Fluconazole, Itraconazole and Posaconazole (halve dose of guanfacine)
- Antipsychotics: sedative effects possibly increased when guanfacine given with Antipsychotics
- Antivirals: plasma concentration of guanfacine possibly increased by Azithromycin, Becepruvir, Fosamprenavir, Indinavir, Ritonavir, Saquinavir and Telaprevir (halve dose of guanfacine); plasma concentration of guanfacine possibly reduced by Efavirenz, Etravirine and Nevirapine—increases dose of guanfacine
- Anxiolytics and Hypnotics: sedative effects possibly increased when guanfacine given with Anxiolytics and Hypnotics
- Aprepitant: plasma concentration of guanfacine possibly increased by Aprepitant (halve dose of guanfacine)
- Bosentan: plasma concentration of guanfacine possibly reduced by Bosentan—increases dose of guanfacine
- Calcium-channel Blockers: plasma concentration of guanfacine possibly increased by Dilatazem and Verapamil (halve dose of guanfacine)
- Cytotoxics: plasma concentration of guanfacine possibly increased by Crizotinib and Imatinib (halve dose of guanfacine)
- Fosaprepitant: plasma concentration of guanfacine possibly increased by Fosaprepitant (halve dose of guanfacine)
- Grapefruit Juice: manufacturer of guanfacine advises avoid concomitant use with Grapefruit Juice
- Modafinil: plasma concentration of guanfacine possibly reduced by Modafinil—increases dose of guanfacine

Haemophilus Vaccine see Vaccines

Haloperidol see Antipsychotics

Heparin see Heparins

Heparins

- ACE Inhibitors: increased risk of hyperkalaemia when heparins given with ACE inhibitors
- Aliskiren: increased risk of hyperkalaemia when heparins given with Aliskiren
- Analgesics: possible increased risk of bleeding when heparins given with NSAIDs; increased risk of haemorrhage when anticoagulants given with Intravenous Diclofenac (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with Ketorolac (avoid concomitant use, including low-dose heparins); anticoagulant effect of heparins enhanced by Aspirin
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when heparins given with Angiotensin-II Receptor Antagonists
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with Arixiban, Darbigantran, Edoxaban and Rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Clodigrel: increased risk of bleeding when heparins given with Clopidogrel
- Dipyriramole: anticoagulant effect of heparins enhanced by Dipyriramole
- Iloprost: anticoagulant effect of heparins possibly enhanced by Iloprost
- Nitrates: anticoagulant effect of heparins reduced by infusion of Glyceryl Trinitrate

Hepatitis Vaccines see Vaccines

Histamine

- Antidepressants: manufacturer of histamine advises avoid concomitant use with MAOIs; effects of histamine theoretically antagonised by Tricyclics—manufacturer of histamine advises avoid concomitant use
Histamine — Histamine H2-antagonists

Histamine H2-antagonists
- Antivirals (continued)
  - ATAZANAVIR (adjust doses of both drugs—consult atazanavir product literature); famotidine reduces plasma concentration of LEDIPASVIR; famotidine increases plasma concentration of Raltegravir; avoidance of histamine H2-antagonists for 12 hours before or 4 hours after RILPIVIRINE advised by manufacturer of rilpivirine—consult product literature; cimetidine possibly increases plasma concentration of SAQUINAVIR
- Anxiolytics and Hypnotics: cimetidine inhibits metabolism of BENZODIAZEPINES, CLOMETHIAZOLE and ZALEPLON (increased plasma concentration); cimetidine increases plasma concentration of MELATONIN
- Azathioprine: manufacturer of azathioprine advises possible increased risk of myelosuppression when cimetidine given with AZATHIOPRINE
- Beta-blockers: cimetidine increases plasma concentration of LABELTALOL, METOPROLOL and PROPRANOL; cimetidine possibly increases plasma concentration of oral TIMOLOL
- Caffeine citrate: cimetidine increases plasma concentration of CAFFEINE CITRATE
- Calcium—Channel Blockers: cimetidine possibly inhibits metabolism of CALCIUM—CHANNEL BLOCKERS (increased plasma concentration); cimetidine increases plasma concentration of ISRADINE (halve dose of isradipine)
- Ciclosporin: cimetidine possibly increases plasma concentration of CYCLOSPORIN
- Clopidogrel: cimetidine possibly reduces antplatelet effect of CLOPIDOGREL
- Cytotoxics: cimetidine possibly enhances myelosuppressive effects of CARMUSTINE and COMUSTINE; cimetidine reduces plasma concentration of DOXORUBICIN; cimetidine increases plasma concentration of EPIRUBICIN; cimetidine inhibits metabolism of CAPECITABINE, FLUOROURACIL and TEGAFUR (increased plasma concentration); avoidance of histamine H2-antagonists advised by manufacturer of DASATINIB—consider using an antacid as an alternative; famotidine reduces plasma concentration of DASATINIB—consider using an antacid as an alternative; avoidance of cimetidine, famotidine and nizatidine advised by manufacturer of ERLOTINI; ranitidine reduces plasma concentration of ERLOTINIB—manufacturer of erlotinib advises give at least 2 hours before or 10 hours after ranitidine; ranitidine reduces plasma concentration of GEFITINIB; histamine H2-antagonists possibly reduce absorption of LAPATINIB; histamine H2-antagonists possibly reduce absorption of PAZOPANIB—manufacturer of pazopanib advises give at least 2 hours before or 10 hours after histamine H2-antagonists
- Dopaminergics: cimetidine reduces excretion of PRAMIPEXOLE (increased plasma concentration)
- Ergot Alkaloids: increased risk of ergotism when cimetidine given with ergotamine—avoid concomitant use
- Fampridine: avoidance of cimetidine advised by manufacturer of FAMPRIDINE
- Histamine: histamine H2—antagonists theoretically antagonise effects of HISTAMINE—manufacturer of histamine advises avoid concomitant use
- Hormone Antagonists: absorption of cimetidine possibly delayed by OCTREOTIDE
- S5H receptor Agonists: cimetidine inhibits metabolism of ZOLMITRIPTAN (reduce dose of zolmitriptan)
- Lipid—Regulating Drugs: separating administration from cimetidine and ranitidine by 12 hours advised by manufacturer of LOMTAPID
- Roflumilast: cimetidine inhibits the metabolism of ROFLUMILAST
- Sildenafil: cimetidine increases plasma concentration of SILDENAFIL—consider reducing dose of sildenafil for erectile dysfunction
- Symptomiotics: cimetidine possibly inhibits metabolism of DOBUTAMINE
- Theophylline: cimetidine inhibits metabolism of THEOPHYLLINE (increased plasma concentration)
- Thyroid Hormones: cimetidine reduces absorption of LEVOThYRoxINE
Harmotropine see Antimuscarinics
Hormone Antagonists see Abiraterone, Bicalutamide, Danazol, Dutasteride, Enzalutamide, Exemestane, Flutamide, Lanreotide, Octreotide, Pasireotide, Tamoxifen, and Toremifene

5HT3-receptor Agonists

Antidepressants: increased risk of CNS toxicity when SHT1 agonists given with • CITALOPRAM (manufacturer of citalopram advises avoid concomitant use; increased risk of CNS toxicity when sumatriptan given with • CITALOPRAM, • ESICITALOPRAM, • LUMOZIRAXINE, • PAROXETINE; metabolism of frovatriptan inhibited by FLUVAXOMINE; metabolism of zolmitriptan possibly inhibited by FLUVAXOMINE (reduce dose of zolmitriptan); CNS toxicity reported when sumatriptan given with SERTRALINE; possible increased serotoninergic effects when SHT1 agonists given with • DULOXETINE, • VENLAFAXINE or VORTEXETINE; risk of CNS toxicity when rizatRIPTAN or sumatriptan given with • MAOIS (avoid rizatRIPTAN or sumatriptan for 2 weeks after MAOIs); risk of CNS toxicity when zolmitriptan given with • MAOIS or • MOCLOBEMIDE (reduce dose of zolmitriptan); risk of CNS toxicity when rizatRIPTAN or sumatriptan given with • MOCLOBEMIDE (avoid rizatRIPTAN or sumatriptan for 2 weeks after moclobemide); possible increased serotoninergic effects when naratriptAN given with • SSRI S; increased serotoninergic effects when SHT1 agonists given with • ST JOHN’S WORT—avoid concomitant use

Antifungals: plasma concentration of eletriptan increased by • ITRACONAZOLE and • KETOCONAZOLE (risk of toxicity)—avoid concomitant use; plasma concentration of almotriptAN increased by KETOCONAZOLE (increased risk of toxicity)

Antivirals: plasma concentration of eletriptan increased by • INDAVIR and • RITONAVIR (risk of toxicity)—avoid concomitant use

Beta-blockers: plasma concentration of rizatRIPTAN increased by PROPRANOLOL (manufacturer of rizatRIPTAN advises halve dose and avoid within 2 hours of propranolol)

Dopamine: possible increased risk of serotoninergic effects when SHT1 agonists given with • DAPOXETINE (manufacturer of dapoxetine advises SHT1 agonists should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SHT1 agonists)

Dopaminergics: avoidance of SHT1 agonists advised by manufacturer of SELEGILINE

Ergot Alkaloids: increased risk of vasospasm when eletriptAN, frovatriptAN or naratriptAN given with • ERGOTAMINE (avoid ergotamine for 24 hours after eletriptAN, frovatriptAN or naratriptAN, avoid eletriptAN, frovatriptAN or naratriptAN for 24 hours after ergotamine); increased risk of vasospasm when almotriptAN, rizatRIPTAN, sumatriptAN or zolmitriptAN given with • ERGOTAMINE (avoid ergotamine for 6 hours after almotriptAN, rizatRIPTAN, sumatriptAN or zolmitriptAN, avoid almotriptAN, rizatRIPTAN, sumatriptAN or zolmitriptAN for 24 hours after ergotamine)

Lithium: possible risk of toxicity when sumatriptAN given with LITHIUM

Ulcer-healing Drugs: metabolism of zolmitriptAN inhibited by CIMETIDINE (reduce dose of zolmitriptAN)

Harmotropine see Antimuscarinics
Hormone Antagonists see Abiraterone, Bicalutamide, Danazol, Dutasteride, Enzalutamide, Exemestane, Flutamide, Lanreotide, Octreotide, Pasireotide, Tamoxifen, and Toremifene

5HT3-receptor Antagonists

Analgesics: ondansetron possibly antagonises effects of TRAMADOL

Antibacterials: metabolism of ondansetron accelerated by • RIFAMPICIN (reduced effect)

Antidepressants: possible increased serotoninergic effects when SHT1 antagonists given with • SSRI-RELATED ANTIDEPRESSANTS or SSRI S

Antiepileptics: metabolism of ondansetron accelerated by • CARBAMAZEPINE, • FOSPHENYTINU and • PHENYTINU (reduced effect)

Cytotoxics: increased risk of ventricular arrhythmias when ondansetron given with • VANDETANIN—avoid concomitant use

Dopaminergics: possible increased hypertensive effect when ondansetron given with • APOMORPHINE—avoid concomitant use

SHT3-receptor Antagonists (continued)

Panobinostat: possible increased risk of ventricular arrhythmias when granisetron and ondansetron given with • PANOBINOSTAT

Hydroxychloroquine see Vaccines
Hydralazine see Vasodilator Antihypertensives
Hydrochlothiazide see Diuretics
Hydrocortison see Corticosteroids
Hydroflumethiazide see Diuretics
Hydromorphone see Opioid Analgesics
Hydrotalcit see Antacids
Hydroxocobalamin

Antibacterial: response to hydroxocobalaminst reduced by CHLORAMPHENICOL

Hydroxyuric Acid

Antipsychotics: avoid concomitant use of cytoxotics with • CLOZAPINE (increased risk of agranulocytosis)

Antivirals: increased risk of toxicity when hydroxyuric acid given with • DIDANOSINE and • STAVUDINE—avoid concomitant use

Vaccines: risk of generalised infections when hydroxyuric acid given with live • VACCINES—avoid concomitant use

Hydroxychloroquine

Adsorbents: absorption of hydroxychloroquine reduced by • KAOLIN • Agalsidase Alfa and Beta: hydroxychloroquine possibly inhibits effects of AGALSIDASE ALFA AND BETA (manufacturers of agalsidase alfa and beta advise avoid concomitant use) • Antacids: absorption of hydroxychloroquine reduced by • ANTACIDS • Anti-arrhythmics: increased risk of ventricular arrhythmias when hydroxychloroquine given with • AMIODARONE—avoid concomitant use • Antimalarials: avoidance of antimalarials advised by manufacturer of • ARTEMETHER WITH LUMEFANTRINE; increased risk of convulsions when hydroxychloroquine given with • MELOQUINE • Antipsychotics: increased risk of ventricular arrhythmias when hydroxychloroquine given with • DROPERIDOL—avoid concomitant use • Cardiac Glycosides: hydroxychloroquine possibly increases plasma concentration of • DIGOXIN • Ciclosporin: hydroxychloroquine increases plasma concentration of • CICLOSPORIN (increased risk of toxicity) • Cytotoxics: possible increased risk of ventricular arrhythmias when hydroxychloroquine given with • BOSUTINIB • Histamine: avoidance of antimalarials advised by manufacturer of • HISTAMINE • Lanthanum: absorption of hydroxychloroquine possibly reduced by • LANTHANUM (give at least 2 hours apart) • Laronidase: hydroxychloroquine possibly inhibits effects of • LARONIDASE (manufacturer of laronidase advises avoid concomitant use) • Parasympathomimetics: hydroxychloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of • NEOSTIGMINE and • PYRIDOSTIGMINE • Penicillamine: increased risk of haematological toxicity when antimalarials given with • PENICILLAMINE—manufacturer of penicillamine advises avoid concomitant use • Ulcer-healing Drugs: metabolism of hydroxychloroquine inhibited by • CIMETIDINE (increased plasma concentration)

Vaccines; antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Hydroxyurea see Antimalarial Agents
Hydantoin Acid see Bisphosphonates
Ibrutinib

Antirrhinum: plasma concentration of ibrutinib possibly increased by • AMIODARONE and • DROPERIDOL—reduce dose of ibrutinib (see under ibrutinib, p. 867)

Antibacterials: plasma concentration of ibrutinib possibly increased by • CIPROFLOXACIN, • CLARITHROMYCIN,
Idelalisib

- Antipsychotics (continued) of idelalisib avoids concomitant use with PIMOZIDE and QUETIAPINE
- Anti-infectives; manufacturer of idelalisib advises avoid concomitant use with oral MIDAZOLAM
- Ergot Alkaloids: manufacturer of idelalisib advises avoid concomitant use with ERGOTAMINE
- Lipid-regulating Drugs: manufacturer of idelalisib avoids concomitant use with SIMVASTATIN
- Sildenafil: manufacturer of idelalisib avoids concomitant use with sildenafil for pulmonary arterial hypertension
- Sympathomimetics, Beta2; manufacturer of idelalisib avoids concomitant use with SALMETEROL

Ibosfamide

- Anticoagulants: ibosfamide possibly enhances anticoagulant effect of COUMARINS
- Antifungals: metabolism of ibosfamide inhibited by ketoconazole
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Antidepressants: ibosfamide possibly enhances anticoagulant effect of clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: plasma concentration of ibosfamide possibly increased by FOSAMPRENIVAR and SQUINAPIN—reduce dose of ibosfamide (see under Ibrutinib, p. 867)
- Aprepitant: plasma concentration of ibosfamide possibly increased by APREPITANT—reduce dose of ibosfamide (see under Ibrutinib, p. 867)
- Calcium-channel Blockers: plasma concentration of ibosfamide possibly increased by DILTIAZEM and VERAPAMIL—reduce dose of ibosfamide (see under Ibrutinib, p. 867)
- Cardiac Glycosides: manufacturer of ibosfamide advises give DIGOXIN at least 6 hours before or after ibosfamide
- Ciclosporin: manufacturer of imatinib advises avoid concomitant use with tacrolimus (increased risk of agranulocytosis)
- Cytotoxics: plasma concentration of imatinib increased by imatinib—reduce dose of imatinib (see under Ibrutinib, p. 867)
- Fosaprepitant: plasma concentration of ibosfamide possibly increased by FOSAMPRENIVAR
- Illoprost

- Analgesics: increased risk of bleeding when illoprost given with NSAIDS of ASPIRIN
- Anticoagulants: illoprost possibly enhances anticoagulant effect of COUMARINS and HEPARINS; increased risk of bleeding when illoprost given with phenindione
- Clopidogrel: increased risk of bleeding when illoprost given with clopidogrel
- Ephedrines: increased risk of bleeding when illoprost given with ephedrine
- Tirosiban: increased risk of bleeding when illoprost given with tirosiban

Imatinib

- Anticoagulants: manufacturer of imatinib advises caution with warfarin (possibility of enhanced warfarin effect)
- Anti-infectives; plasma concentration of imatinib reduced by ST JOHN’S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of imatinib reduced by COUMARINS and HEPARINS
- Antituberculosis: manufacturer of imatinib advises replacement of warfarin with a heparin (possibility of enhanced warfarin effect)
- Antidepressants: plasma concentration of imatinib possibly increased by imatinib increases plasma concentration of imatinib possibly increased by COUMARINS and HEPARINS
- Anti-infectives; manufacturer of imatinib advises concomitant use with ritonavir—avoid concomitant use
- Antineoplastic Agents: plasma concentration of imatinib possibly increased by PARACETAMOL
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Antidepressants: plasma concentration of imatinib increased by imatinib possibly increases plasma concentration of imatinib possibly increased by GEMCITABINE and IMATINIB—reduce dose of imatinib (see under Ibrutinib, p. 867)
- Antiepileptics: plasma concentration of imatinib possibly increased by CLOZAPINE and IMATINIB—reduce dose of imatinib (see under Ibrutinib, p. 867)
- Grapefruit Juice: manufacturer of ibosfamide advises avoid concomitant use with GRAPEFRUIT JUICE
- Vitamins: manufacturer of ibosfamide advises avoid concomitant use with VITAMIN E

Ibuprofen see NSAIDs

Idarubicin

- Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
- Ciclosporin: plasma concentration of idarubicin increased by CYCLOSPORIN
- Cytotoxics: possible increased risk of cardiotoxicity when idarubicin given with TRASTUZUMAB—avoid concomitant use for up to 28 weeks after stopping trastuzumab
- Vaccines: risk of generalised infections when cytotoxic antibiotics given with live VACCINES—avoid concomitant use

Idevralisib

- Alpha-blockers: manufacturer of idelalisib advises avoid concomitant use with alfuzosin
- Anti-arhythmic drugs: manufacturer of idelalisib advises avoid concomitant use with amiodarone
- Antibacterials: plasma concentration of idelalisib reduced by rifampicin (avoid concomitant use)
- Antidepressants; plasma concentration of idelalisib possibly reduced by ST JOHN’S WORT—manufacturer of idelalisib advises avoid concomitant use
- Antiepileptics: plasma concentration of idelalisib possibly reduced by CARBAMAZEPINE, FOSPHENTOIN and PHENYTOIN—manufacturer of idelalisib advises avoid concomitant use
- Antifungals: plasma concentration of idelalisib increased by ketoconazole
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis); manufacturer
Imipenem with Cilastatin

- Antiepileptics: carbamepenes reduce plasma concentration of • SODIUM VALPROATE and • VALPROIC ACID—avoid concomitant use
- Antivirals: increased risk of convulsions when imipenem with cilastatin given with • GANCICLOVIR or • VALGANICLOVIR
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Imipramine see Antidepressants, Tricyclic

Immunoglobulins
- Vaccines: anti-d immunoglobulins and normal immunoglobulin might impair immune response to • BCG VACCINE—give BCG vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to • MMR VACCINE—give MMR vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to live • INFLUENZA VACCINE—give live influenza vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to oral • POLIOMYELITIS VACCINE—give oral poliomyelitis vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to oral • ROTA VIRUS VACCINE—give live oral rotavirus vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to oral • SMALLPOX VACCINE—give smallpox vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to • VARICELLA-ZOSTER VACCINE—give live varicella-zoster vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; anti-d immunoglobulins and normal immunoglobulin might impair immune response to • YELLOW FEVER VACCINE—give live yellow fever vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin

Indacaterol see Sympathomimetics, Beta2

Indapamide see Diuretics

Indinavir
- Aldesleukin: plasma concentration of indinavir possibly increased by • ALDESLEUKIN
- Anti-arrhythmics: indinavir possibly increases plasma concentration of • AMIODARONE—avoid concomitant use; indinavir possibly increases plasma concentration of • FLECAINIDE (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antibacterials: indinavir increases plasma concentration of • RIFABUTIN, also plasma concentration of indinavir decreased (reduce dose of rifabutin and increase dose of indinavir); metabolism of indinavir accelerated by • RIFAMPICIN (reduced plasma concentration—avoid concomitant use); avoidance of concomitant indinavir in severe renal and hepatic impairment advised by manufacturer of • TELITHROMYCIN
- Anticoagulants: avoidance of indinavir advised by manufacturer of • APIXABAN and • RIVAROXABAN
- Antidepressants: plasma concentration of indinavir reduced by • ST JOHN’S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of indinavir possibly reduced by • CARBAMAZEPINE, • PHOSPHENTOIN and • PHENYTOIN, also plasma concentration of carbamazepine, fosphenytoin and phenytoin possibly increased; plasma concentration of indinavir possibly reduced by • PHENOBARBITAL and • PRIMIDONE
- Antifungals: plasma concentration of indinavir increased by • ITRACONAZOLE and • KETOCONAZOLE (consider reducing dose

Indinavir
- Antifungals (continued) of indinavir); plasma concentration of indinavir reduced by • ISAVUCONAZOLE
- Antimalarials: caution with indinavir advised by manufacturer of • ARTESATE WITH LUMEFANTRINE; indinavir possibly increases plasma concentration of • QUININE (increased risk of toxicity)
- Antimycobacterials: avoidance of indinavir advised by manufacturer of • DARIFENACIN and • TOLERTODINE; manufacturer of fesoterodine advises dose reduction when indinavir given with • FESOTERODINE—consult fesoterodine product literature
- Antipsychotics: indinavir possibly increases plasma concentration of • ARIPIPRAZOLE (reduce dose of aripiprazole product literature); indinavir possibly increases plasma concentration of • LURASIDONE—avoid concomitant use; indinavir possibly increases plasma concentration of • QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: avoid concomitant use of indinavir with • ATAZANAVIR; plasma concentration of indinavir possibly reduced when indinavir given with • DARUNAVIR; absorption of indinavir reduced by • DIDANOSINE tablets (give at least 1 hour apart); plasma concentration of indinavir reduced by • EFAVIRENZ and • NEVIRAPINE; plasma concentration of indinavir possibly reduced by • ETRAVIRINE—avoid concomitant use; indinavir increases plasma concentration of • MARAVIROC (consider reducing dose of maraviroc); avoidance of indinavir advised by manufacturer of • PARTAPREVIR; plasma concentration of indinavir increased by • RITONAVIR; indinavir increases plasma concentration of • POZANAVIR
- Anxiolytics and Hypnotics: increased risk of prolonged sedation when indinavir given with • ALPRAZOLAM—avoid concomitant use; indinavir possibly increases plasma concentration of • MIDAZOLAM (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- Atovalaxone: plasma concentration of indinavir possibly reduced by • ATOVAXONE
- Avana: indinavir possibly increases plasma concentration of • AVANAFIL—manufacturer of avanafil advises avoid concomitant use
- Bosentan: plasma concentration of indinavir possibly reduced by • BOSENTAN
- Ciclosporin: indinavir increases plasma concentration of • CICLOSPORIN
- Colchicine: indinavir possibly increases risk of • COLCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: plasma concentration of indinavir possibly reduced by • DEXAMETHASONE
- Cytotoxics: indinavir possibly increases plasma concentration of • AXITINIB (reduce dose of axitinib—consult axitinib product literature); indinavir possibly increases the plasma concentration of • BOSUTINIB and • CABAZITAXEL—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; indinavir possibly increases plasma concentration of • CRIZOTINIB and • EVEROLIMUS—manufacturer of crizotinib and everolimus advises avoid concomitant use; indinavir possibly increases the plasma concentration of • INIBITINIB—reduce dose of inibitinib (see under Inibitinib, p. 867); indinavir possibly increases plasma concentration of • PAZOPANIB (reduce dose of pazopanib); indinavir possibly increases plasma concentration of • PONITINIB—consider reducing initial dose of ponatinib (see under Ponatinib, p. 873); manufacturer of ruxolitinib advises dose reduction when indinavir given with • RUOXITINIB—consult ruxolitinib product literature; indinavir possibly increases plasma concentration of • DEXRoxelaxone—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose
- Ergot Alkaloids: increased risk of ergotism when indinavir given with • ERGOMETRINE or • ERGOTAMINE—avoid concomitant use
- Guanfacine: indinavir possibly increases plasma concentration of • GUANFACINE (halve dose of guanfacine)
Indinavir  
- 5HT1-receptor Agonists: indinavir increases plasma concentration of \textit{Eledriptan} (risk of toxicity)—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when indinavir given with \textit{Atrvostatin}; possible increased risk of myopathy when indinavir given with \textit{Rosuvastatin}—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when indinavir given with
- \textit{Simvastatin} (avoid concomitant use); avoidance of indinavir advised by manufacturer of \textit{Lomitapide} (plasma concentration of lomitapide possibly increased)
- \textit{Naloxegol}: indinavir possibly increases plasma concentration of \textit{Naloxegol}—avoid concomitant use
- \textit{Orlistat}: absorption of indinavir possibly reduced by \textit{Orlistat}
- \textit{Ranolazime}: indinavir possibly increases plasma concentration of \textit{Ranolazime}—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: indinavir increases plasma concentration of \textit{Sildenafil}—reduce initial dose of sildenafil
- Tadalafil: indinavir possibly increases plasma concentration of \textit{Tadalafil}
- Vardenafil: indinavir increases plasma concentration of \textit{Vardenafil}—avoid concomitant use

Indomethacin see NSAIDs
Indoramin see \textit{Alpha-blockers}

Infliximab
- \textit{Abatacept}: avoid concomitant use of infliximab with \textit{Abatacept}
- \textit{Anakina}: avoid concomitant use of infliximab with \textit{Anakinra}
- \textit{Antipsychotics}: avoid concomitant use of cytoxics with \textit{Clozapine} (increased risk of agranulocytosis)
- \textit{Vaccines}: risk of generalised infections when monoclonal antibodies given with live \textit{Vaccines}—avoid concomitant use

Influenza Vaccine see \textit{Vaccines}
Insulin see \textit{Antidiabetics}
Interferon Alpha see \textit{Interferons}
Interferon Gamma see \textit{Interferons}

- Aminophylline: interferon alfa and peginterferon alfa inhibit metabolism of \textit{Aminophylline} (consider reducing dose of aminophylline)
- \textit{Antivirals}: caution with peginterferon alfa advised by manufacturer of \textit{Adefovir}; increased risk of peripheral neuropathy when interferon alfa and peginterferon alfa given with \textit{Telbivudine}
- \textit{Theophylline}: interferon alfa and peginterferon alfa inhibit metabolism of \textit{Theophylline} (consider reducing dose of theophylline)
- \textit{Vaccines}: manufacturer of interferon gamma advises avoid concomitant use with \textit{Vaccines}

Ipriflavone
- \textit{Antipsychotics}: avoid concomitant use of cytoxics with \textit{Clozapine} (increased risk of agranulocytosis)
- \textit{Cytotoxic}: manufacturer of ipilimumab advises avoid concomitant use with \textit{Vemurafenib}
- \textit{Vaccines}: risk of generalised infections when monoclonal antibodies given with live \textit{Vaccines}—avoid concomitant use

Ipratropium
- Antipsychotics: avoid concomitant use of cytoxics with \textit{Clozapine} (increased risk of agranulocytosis)
- \textit{Antivirals}: metabolism of irinotecan possibly inhibited by \textit{Atazanavir} (increased risk of toxicity)

Irinotecan  
- Cytotoxics: avoidance of irinotecan advised by manufacturer of \textit{Panitumumab}; plasma concentration of active metabolite of irinotecan increased by \textit{Lapatinib}—consider reducing dose of irinotecan; plasma concentration of irinotecan increased by \textit{Regorafenib}; plasma concentration of irinotecan possibly increased by \textit{Sorafenib}

Iron Salts
- \textit{Antacids}: absorption of oral iron salts reduced by \textit{Oral Magnesium Salts} (as magnesium trisilicate)
- \textit{Antibacterials}: oral iron salts reduce absorption of \textit{Ciprofloxacin} (give at least 2 hours before or 4 hours after ciprofloxacin); oral iron salts reduce absorption of \textit{Levofloxacin, Norfloxacin} and \textit{Ofloxacin} (give at least 2 hours apart); oral iron salts reduce absorption of \textit{MoXifloxacin} (give at least 6 hours apart); effects of iron salts possibly inhibited by \textit{Chloramphenicol}; oral iron salts reduce absorption of tetracyclines, also absorption of oral iron salts reduced by \textit{Tetracyclines} (give at least 2 to 3 hours apart)
- \textit{Antivirals}: oral iron salts reduce absorption of \textit{Dolutegravir}—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after oral iron salts
- \textit{Bisphosphonates}: oral iron salts reduce absorption of \textit{Bisphosphonates}

- Calcium Salts: absorption of oral iron salts reduced by \textit{Calcium Salts}
- \textit{Dopaminergics}: oral iron salts possibly reduce absorption of \textit{Co-BeNeldopa, Co-Careldopa} and \textit{Levodopa}; oral iron salts reduce absorption of \textit{Entacapone}
- Eltrombopag: oral iron salts possibly reduce absorption of \textit{Eltrombopag} (give at least 4 hours apart)
- \textit{Methyldopa}: oral iron salts antagonise hypotensive effect of \textit{Methyldopa}
- \textit{Mycofenolate}: oral iron salts reduce absorption of \textit{Mycofenolate}
- \textit{Penicillamine}: oral iron salts reduce absorption of \textit{Penicillamine}
- \textit{Thyroid Hormones}: oral iron salts reduce absorption of \textit{Liothyronine, Levothyroxine} (give at least 2 hours apart)
- \textit{Trientine}: absorption of oral iron salts reduced by \textit{Trientine}
- \textit{Zinc}: oral iron salts reduce absorption of \textit{Zinc}, also absorption of oral iron salts reduced by zinc

Isavuconazole see Antifungals, Imidazole
Isocarboxazid see MAOIs
Isosflurane see Anaesthetics, General
Isomethptene see \textit{Symptomimetics}
Isoniazid
- Aminophylline: isoniazid possibly increases plasma concentration of \textit{Aminophylline}
- \textit{Anaesthetics, General}: increased risk of hepatotoxicity when isoniazid given with \textit{Isosflurane}
- \textit{Analgesics}: avoidance of isoniazid advised by manufacturer of \textit{Pethidine}

Iron Salts
- \textit{Antacids}: absorption of oral iron salts reduced by \textit{Oral Magnesium Salts} (as magnesium trisilicate)
- \textit{Antibacterials}: oral iron salts reduce absorption of \textit{Ciprofloxacin} (give at least 2 hours before or 4 hours after ciprofloxacin); oral iron salts reduce absorption of \textit{Levofloxacin, Norfloxacin} and \textit{Ofloxacin} (give at least 2 hours apart); oral iron salts reduce absorption of \textit{MoXifloxacin} (give at least 6 hours apart); effects of iron salts possibly inhibited by \textit{Chloramphenicol}; oral iron salts reduce absorption of tetracyclines, also absorption of oral iron salts reduced by \textit{Tetracyclines} (give at least 2 to 3 hours apart)
- \textit{Antivirals}: oral iron salts reduce absorption of \textit{Dolutegravir}—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after oral iron salts
- \textit{Bisphosphonates}: oral iron salts reduce absorption of \textit{Bisphosphonates}

- Calcium Salts: absorption of oral iron salts reduced by \textit{Calcium Salts}
- \textit{Dopaminergics}: oral iron salts possibly reduce absorption of \textit{Co-BeNeldopa, Co-Careldopa} and \textit{Levodopa}; oral iron salts reduce absorption of \textit{Entacapone}
- Eltrombopag: oral iron salts possibly reduce absorption of \textit{Eltrombopag} (give at least 4 hours apart)
- \textit{Methyldopa}: oral iron salts antagonise hypotensive effect of \textit{Methyldopa}
- \textit{Mycofenolate}: oral iron salts reduce absorption of \textit{Mycofenolate}
- \textit{Penicillamine}: oral iron salts reduce absorption of \textit{Penicillamine}
- \textit{Thyroid Hormones}: oral iron salts reduce absorption of \textit{Liothyronine, Levothyroxine} (give at least 2 hours apart)
- \textit{Trientine}: absorption of oral iron salts reduced by \textit{Trientine}
- \textit{Zinc}: oral iron salts reduce absorption of \textit{Zinc}, also absorption of oral iron salts reduced by zinc

Isavuconazole see Antifungals, Imidazole
Isocarboxazid see MAOIs
Isosflurane see Anaesthetics, General
Isomethptene see \textit{Symptomimetics}
Isoniazid
- Aminophylline: isoniazid possibly increases plasma concentration of \textit{Aminophylline}
- \textit{Anaesthetics, General}: increased risk of hepatotoxicity when isoniazid given with \textit{Isosflurane}
- \textit{Analgesics}: avoidance of isoniazid advised by manufacturer of \textit{Pethidine}

Antacids: absorption of isoniazid reduced by \textit{Antacids}
- \textit{Antibacterials}: increased risk of hepatotoxicity when isoniazid given with \textit{Rifampicin}; increased risk of CNS toxicity when isoniazid given with \textit{Cycloserine}
- \textit{Antiepileptics}: isoniazid increases plasma concentration of \textit{Carbamazepine} (also possibly increased isoniazid hepatotoxicity); isoniazid inhibits metabolism of \textit{Ethosuximide} (increased plasma concentration and risk of toxicity); isoniazid possibly inhibits metabolism of \textit{Fosphenytoin} and \textit{Phenytoin} (increased risk of toxicity)
- \textit{Antifungals}: isoniazid possibly reduces plasma concentration of \textit{Ketoconazole}
- \textit{Anxiolytics and Hypnotics}: isoniazid inhibits the metabolism of \textit{Diazepam}
- \textit{Corticosteroids}: plasma concentration of isoniazid possibly reduced by \textit{Corticosteroids}
- \textit{Disulfiram}: isoniazid possibly increases CNS effects of \textit{Disulfiram}
- \textit{Dopaminergics}: isoniazid possibly reduces effects of \textit{Co-BeNeldopa, Co-Careldopa} and \textit{Levodopa}
- \textit{Lipid-regulating Drugs}: separating administration from isoniazid by 12 hours advised by manufacturer of \textit{Lomitapide}
Isoniazid — Lamotrigine

Isoniazid (continued)

- Theophylline: isoniazid possibly increases plasma concentration of theophylline.
- Vaccines: antibacterials inactivate oral typhoid vaccine — see under Typhoid Vaccine in BNF or BNFC.

Itraconazole see Antifungals, Triazole

- Anti-arrrhythmics: increased risk of ventricular arrhythmias when ivabradine given with amiodarone or disopyramide.
- Antibacterials: plasma concentration of ivabradine possibly increased by clarithromycin and telithromycin — avoid concomitant use; increased risk of ventricular arrhythmias when ivabradine given with erthyromycin — avoid concomitant use.
- Antidepressants: plasma concentration of ivabradine reduced by St John’s Wort — avoid concomitant use.
- Antifungals: plasma concentration of ivabradine increased by ketoconazole — avoid concomitant use.
- Antivirals: plasma concentration of ivabradine possibly increased by ritonavir — avoid concomitant use.
- Beta-blockers: increased risk of ventricular arrhythmias when ivabradine given with sotalol.
- Calcium-channel Blockers: plasma concentration of ivabradine increased by diltiazem and verapamil — avoid concomitant use.
- Grapefruit Juice: plasma concentration of ivabradine increased by grapefruit juice.
- Pentamidine isetionate: increased risk of ventricular arrhythmias when ivabradine given with pentamidine isetionate.

Ivacaftor (continued)

- Grapefruit Juice: plasma concentration of ivacaftor possibly increased by grapefruit juice — manufacturer of ivacaftor advises avoid concomitant use.
- Lipid-regulating Drugs: separating administration from ivacaftor by 12 hours advised by manufacturer of lovatatin.
- Ivermectin
- Anthelmints: plasma concentration of ivermectin possibly increased by levamisole.
- Anticoagulants: ivermectin possibly enhances anticoagulant effect of coumarins.

Japanese Encephalitis Vaccine see Vaccines

- Kaolin
- Analgesics: kaolin possibly reduces absorption of aspirin.
- Antibacterials: kaolin possibly reduces absorption of tetracyclines.
- Antimalarials: kaolin reduces absorption of chloroquine and hydroxychloroquine.
- Antipsychotics: kaolin possibly reduces absorption of phenothiazines.

Ketamine see Anaesthetics, General

Ketoconazole see Antifungals, Imidazole

Ketoprofen see NSAIDs

Ketorolac see NSAIDs

Ketotifen see Antihistamines

Labeletal see Beta-blockers

Lacidipine see Calcium-channel Blockers

Lacosamide
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered).
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by Mefloquine.
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered).
- Oralstat: possible increased risk of convulsions when antiepileptics given with orlistat.

Lactulose
- Anticoagulants: lactulose possibly enhances anticoagulant effect of coumarins.

Lamivudine
- Antibacterials: plasma concentration of lamivudine increased by trimethoprim (as co-trimoxazole) — avoid concomitant use of high-dose co-trimoxazole.
- Antivirals: avoidance of lamivudine advised by manufacturer of emtricitabine.
- Cytoxics: manufacturer of lamivudine advises avoid concomitant use with cladribine.
- Oralstat: absorption of lamivudine possibly reduced by orlistat.

Lamotrigine
- Antidepressants: plasma concentration of lamotrigine reduced by rifampicin.
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered).
- Antiepileptics: plasma concentration of lamotrigine often reduced by carbamazepine, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); plasma concentration of lamotrigine reduced by fosphenytoin, phenobarbital, phenytoin and primidone; plasma concentration of lamotrigine increased by sodium valproate and valproic acid (increased risk of toxicity — reduce lamotrigine dose).
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by Mefloquine.
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered).
- Antivirals: plasma concentration of lamotrigine possibly reduced by ritonavir.

Ivermectin
- Anthelmints: plasma concentration of ivermectin possibly increased by levamisole.
- Anticoagulants: ivermectin possibly enhances anticoagulant effect of coumarins.
**Lamotrigine** (continued)
- Oestrogens: plasma concentration of lamotrigine reduced by **OESTROGENS**—consider increasing dose of lamotrigine
- Orlistat: possible increased risk of convulsions when antipsychotics given with **ORLISTAT**
- Progestogens: plasma concentration of lamotrigine possibly increased by **DESOGESTREL**

**Lanreotide**
- Antidiabetics: lanreotide possibly reduces requirements for **ANTI DIABETICS**
- Ciclosporin: lanreotide reduces plasma concentration of **CICLOSPORIN**

**Lansoprazole** see Proton Pump Inhibitors

**Lanthanum**
- Antibacterials: lanthanum possibly reduces absorption of **ANTIBACTERIALS**
- Antacids: (give at least 2 hours before or 4 hours after lanthanum)
- Antifungals: lanthanum possibly reduces absorption of **ANTIFUNGALS** and **HYDROxychlOROQUINE** (give at least 2 hours apart)
- Antimalarials: lanthanum possibly reduces absorption of **ANTIMALARIALS**
- Thyroid Hormones: lanthanum reduces absorption of **LEVOTHYROXINE** (give at least 2 hours apart)

**Lapatinib**
- Antibacterials: manufacturer of lapatinib advises avoid concomitant use with **RIFABUTIN, RIFAMPICIN** and **PHENYTOIN**
- Antidepressants: manufacturer of lapatinib advises avoid concomitant use with **ST JOHN’S WORT**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOzapine** (increased risk of agranulocytosis); manufacturer of lapatinib advises avoid concomitant use with **PIMOZIDE**
- Antivirals: avoidance of lapatinib advised by manufacturer of **BOCeprevir**; manufacturer of lapatinib advises avoid concomitant use with **RITONAVIR** and **SAQUINAVIR**
- Cytotoxics: lapatinib increases plasma concentration of **AZAteparAZOLE**—increased risk of neutropenia when lapatinib given with **DOCETAXEL;** increased risk of neutropenia when lapatinib given with **PLACITAXEL;** lapatinib increases plasma concentration of active metabolite of **IRINOTECAN**—consider reducing dose of irinotecan
- Calcium-channel Blockers: absorption of lapatinib possibly reduced by **HISTamine H2-ANTAGONISTS** and **PROTON PUMP INHIBITORS**

**Laronidase**
- Antihistamines: increased risk of agranulocytosis; manufacturer of laronidase advises avoid concomitant use
- Heparin: manufacturer of laronidase advises avoid concomitant use

**Ledipasvir** (continued)
- Antivirals: plasma concentration of both drugs increased when ledipasvir given with **SIMEPREVIR**—manufacturer of ledipasvir advises avoid concomitant use
- Calcium Salts: manufacturer of ledipasvir advises separating administration from **CALCIUM SALTS** by 4 hours
- Lipid-regulating Drugs: possible increased risk of myopathy when ledipasvir given with **ATORVASTATIN, FLUVASTATIN** and **SIMVASTATIN**—manufacturer of ledipasvir advises consider reducing dose of atorvastatin, fluvastatin and simvastatin; manufacturer of ledipasvir advises avoid concomitant use with **ROsvASTATIN**
- Ulcer-healing Drugs: plasma concentration of ledipasvir reduced by **FAMOTIDINE** and **OMEPRAZOLE**; manufacturer of ledipasvir advises do not take **PROTON PUMP INHIBITORS** before ledipasvir

**Leflunomide**

**Lipid-regulating Drugs**
- **Antibacterials**: plasma concentration of both drugs increased when ledipasvir given with **SIMEPREVIR**—manufacturer of ledipasvir advises avoid concomitant use
- Anticoagulants: leflunomide possibly enhances anticoagulant effect of **WARFARIN**
- Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of **TOLButAMIDE**
- Antiepileptics: leflunomide possibly increases plasma concentration of **FOSPHENyTOIN and PHENyTOIN**
- Cytotoxics: risk of toxicity when leflunomide given with **METHotreXATE**
- Lipid-regulating Drugs: the effect of leflunomide is significantly decreased by **COLESTRAMINE** (enhanced elimination)—avoid unless drug elimination desired
- Vaccines: risk of generalised infections when leflunomide given with live **VACCINES**—avoid concomitant use

**Lenalidomide**
- Antibacterials: plasma concentration of lenalidomide possibly increased by **CLARITHRomyCIN** (increased risk of toxicity)
- Antifungals: plasma concentration of lenalidomide possibly increased by **itraCOnazole** and **KETOCONAZOLE** (increased risk of toxicity)
- Calcium-channel Blockers: plasma concentration of lenalidomide possibly increased by **VERAPAMIL** (increased risk of toxicity)
- Cardiovascular: lenalidomide possibly increases plasma concentration of **DIGoxin**
- Ciclosporin: plasma concentration of lenalidomide possibly increased by **CICLOSPORIN** (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOzapine** (increased risk of agranulocytosis)

**Lercanidipine** see Calcium-channel Blockers

**Leukotriene Receptor Analogists**
- Aminophylline: zafirlukast possibly increases plasma concentration of **AMINOPHYLLINE**, also plasma concentration of zafirlukast reduced
- Analgesics: plasma concentration of zafirlukast increased by **ASPIRIN**
- Antibacterials: plasma concentration of zafirlukast reduced by **ERYthROMYCIN**
- Anticoagulants: zafirlukast enhances anticoagulant effect of **WARFARIN**
- Antiepileptics: plasma concentration of montelukast reduced by **PHENOBARBITAL** and **PRIMIDONE**
- Antifungals: plasma concentration of zafirlukast increased by **FLUCONAZOLE**
- Lipid-regulating Drugs: plasma concentration of montelukast increased by **GEMFIBROZIL**
- Theophylline: zafirlukast possibly increases plasma concentration of **THEOPHYLLINE**, also plasma concentration of zafirlukast reduced

**Levamisole**
- Alcohol: possibility of disulfiram-like reaction when levamisole given with **ALCOHOL**
- Anthelmintics: plasma concentration of both drugs possibly reduced when levamisole given with **ALBENDAZOLE**; levamisole possibly increases plasma concentration of **IVERmECTIN**
Levamisole (continued)

- Anticoagulants: levamisole possibly enhances anticoagulant effect of warfarin
- Antiepileptics: levamisole possibly increases plasma concentration of fosphenytoin and phenytoin

Levetiracetam

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRI and tricyclics (convulsive threshold lowered)
- Antiepileptics: levetiracetam possibly increases risk of carbamazepine toxicity
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by mefloquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered)
- Antituberculars: levamisole possibly increases plasma concentration of
- Orlistat: possible increased risk of convulsions when antiepileptics given with orlistat

Levobunolol

- Anti-arrhythmics: reduced plasma concentration of lidocaine possibly increased by antiepileptics given with
- Antihistamines, beta-blockers: possible increased risk of side-effects when levodopa given with

Levodopa (continued)

- ACE inhibitors: enhanced hypotensive effect when levodopa given with ACE inhibitors
- Adrenergic Neurone Blockers: enhanced hypotensive effect when levodopa given with adrenergic neurone blockers
- Alpha-blockers: enhanced hypotensive effect when levodopa given with alpha-blockers
- Anaesthetics, General: increased risk of arrhythmias when levodopa given with volatile liquid general anaesthetics
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when levodopa given with angiotensin-II receptor antagonists
- ANTIHISTAMINES: effects of levodopa possibly reduced by isoniazid
- Antidepressants: risk of hypertensive crisis when levodopa given with MAOIs, avoid levodopa for at least 2 weeks after stopping MAOIs; increased risk of side-effects when levodopa given with moclobemide
- Antiepileptics: effects of levodopa possibly reduced by fosphenytoin and phenytoin
- Antimuscarinics: absorption of levodopa possibly reduced by antimuscarinics
- Antipsychotics: effects of levodopa antagonised by antipsychotics; avoidance of levodopa advised by manufacturer of amisulpride (antagonism of effect)
- Anxiolytics and Hypnotics: effects of levodopa possibly antagonised by benzodiazepines
- Beta-blockers: enhanced hypotensive effect when levodopa given with beta-blockers
- Bupropion: increased risk of side-effects when levodopa given with bupropion
- Calcium-channel Blockers: enhanced hypotensive effect when levodopa given with calcium-channel blockers
- Clonidine: enhanced hypotensive effect when levodopa given with clonidine
- Diazoxide: enhanced hypotensive effect when levodopa given with diazoxide
- Diuretics: enhanced hypotensive effect when levodopa given with diuretics
- Dopaminergics: enhanced effects and increased toxicity of levodopa when given with selegiline (reduce dose of levodopa)
- Iron Salts: absorption of levodopa possibly reduced by oral iron salts
- Memantine: effects of dopaminergics possibly enhanced by memantine

Levodopa (continued)

- Methyldopa: enhanced hypotensive effect when levodopa given with methyldopa; antiparkinsonian effect of dopaminergics antagonised by methyldopa
- Moxonidine: enhanced hypotensive effect when levodopa given with moxonidine
- Muscle Relaxants: possible agitation, confusion and hallucinations when levodopa given with baclofen
- Nitrates: enhanced hypotensive effect when levodopa given with nitrates
- Vasodilator Anti-hypertensives: enhanced hypotensive effect when levodopa given with hydralazine, minoxidil or sodium nitroprusside

Levofloxacin see Quinolones

Levofolic Acid see Folicates

Levozepromazine see Antipsychotics

Levonorgestrel see Progestogens

Levosimendan

- Nitrates: possible severe postural hypotension when levosimendan given with isosorbide mononitrate

Levotyroxine see Thyroid Hormones

Lidocaine

- ACE Inhibitors
- Adrenergic Neurone Blockers
- Alpha-blockers
- Anaesthetics, General
- Angiotensin-II Receptor Antagonists
- Antiarrhythmics that prolong the QT interval
- Antidepressants
- Antipsychotics that prolong the QT interval
- Antivirals: plasma concentration of lidocaine possibly increased by atazanavir and lopinavir; plasma concentration of lidothane possibly increased by darunavir and fosamprenavir—avoid concomitant use; increased risk of ventricular arrhythmias when lidocaine given with saquinavir—avoid concomitant use; caution with intravenous lidocaine advised by manufacturer of telaprevir
- Beta blockers: increased myocardial depression when anti-arrhythmics given with beta-blockers; possible increased risk of lidothane toxicity when given with nalidixic acid; increased risk of lidothane toxicity when given with propafenone
- Diuretics: action of lidothane antagonised by hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics
- Muscle Relaxants: neuromuscular blockade enhanced and prolonged when lidothane given with suxamethonium
- Ulcer-healing Drugs: plasma concentration of lidothane increased by cimetidine (increased risk of toxicity)

Linagliptin see Antidiabetics

Linezolid see MAOIs

Liothyronine see Thyroid Hormones

Lipefoglifastim

- Cytotoxics: neutropenia possibly exacerbated when lipoglifastim given with capецептин, флуроруракил or tegafur

Lipid-regulating Drugs see Colesevelam, Colestipol, Colestyremin, Ezetimibe, Fibrate, Lomitapide, Nicotinic Acid, and Statins

Liraglutide see Antidiabetics

Lisdexametanfate see Sympathomimetics

Lisinopril see ACE Inhibitors

Lithium

- ACE inhibitors: excretion of lithium reduced by ACE inhibitors (increased plasma concentration)
- Aminophylline: excretion of lithium increased by aminophylline (reduced plasma concentration)
- Analgesics: excretion of lithium reduced by NSAIDs (increased risk of toxicity); excretion of lithium reduced by ketorolac (increased risk of toxicity)—avoid concomitant use
- Angiotensin-II Receptor Antagonists: excretion of lithium reduced by angiotensin-II receptor antagonists (increased plasma concentration)
Lithium (continued)

- Antacids: excretion of lithium increased by sodium bicarbonate (reduced plasma concentration)
- Anti-arrhythmics: avoidance of lithium advised by manufacturer of amiodarone (risk of ventricular arrhythmias)
- Antibacterials: increased risk of lithium toxicity when given with metronidazole
- Antidepressants: possible increased serotoninergic effects when lithium given with venlafaxine; increased risk of CNS effects when lithium given with SSRIs (lithium toxicity reported); risk of toxicity when lithium given with tricyclics
- Antiepileptics: neurotoxicity may occur when lithium given with carbamazepine, fosphenytoin or phenytoin without increased plasma concentration of lithium; plasma concentration of lithium possibly affected by topiramate
- Antipsychotics: increased risk of extrapyramidal side-effects and possibly neurotoxicity when lithium given with clozapine, flupentixol, haloperidol, phenothiazines, risperidone or zuclopenthixol; possible risk of toxicity when lithium given with quetiapine; increased risk of extrapyramidal side-effects when lithium given with sulpiride
- Anxiolytics and Hypnotics: increased risk of neurotoxicity when lithium given with clonazepam
- Calcium-channel Blockers: neurotoxicity may occur when lithium given with Diltiazem or Verapamil; without increased plasma concentration of lithium
- Cytotoxics: increased risk of ventricular arrhythmias when lithium given with arsenic trioxide
- Dopamine: possible increased risk of serotoninergic effects when lithium given with dapoxetine (manufacturer of dapoxetine advises lithium should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping lithium)
- Diuretics: excretion of lithium increased by acetazolamide; excretion of lithium reduced by aldosterone antagonists and potassium-sparing diuretics (increased plasma concentration and risk of toxicity); excretion of lithium reduced by loop diuretics and thiazides and related diuretics (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides
- 5HT1-receptor Agonists: possible risk of toxicity when lithium given with sumatriptan
- Methyl/dopa: neurotoxicity may occur when lithium given with methyl/dopa without increased plasma concentration of lithium
- Muscle Relaxants: lithium enhances effects of muscle relaxants; hyperkinesis caused by lithium possibly aggravated by baclofen
- Parasympathomimetics: lithium antagonises effects of neostigmine
- Theophylline: excretion of lithium increased by theophylline (reduced plasma concentration)
- Lixisenatide see Antidiabetics
- Loperamime see Antidiarrheics, Tricyclic
- Lofexidine
- Alcohol: increased sedative effect when lofexidine given with alcohol
- Anxiolytics and Hypnotics: increased sedative effect when lofexidine given with anxiolytics and hypnotics

Lomitapide (continued)

- Anticoagulants: lomitapide possibly enhances anticoagulant effect of warfarin
- Antidepressants: manufacturer of lomitapide advises separating administration from fluoxetine and fluvoxamine by 12 hours
- Antidiabetics: manufacturer of lomitapide advises separating administration from linagliptin by 12 hours
- Antifungals: plasma concentration of lomitapide increased by ketoconazole—avoid concomitant use; manufacturer of lomitapide advises avoid concomitant use with triazoles (plasma concentration of lomitapide possibly increased)
- Antivirals: manufacturer of lomitapide advises avoid concomitant use with dapavinavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, telaprevir and tipranavir (plasma concentration of lomitapide possibly increased)
- Anxiolytics and Hypnotics: manufacturer of lomitapide advises separating administration from alprazolam by 12 hours
- Calcium-channel Blockers: manufacturer of lomitapide advises avoiding concomitant use with amlopidine and lacidipine by 12 hours; manufacturer of lomitapide advises avoid concomitant use with diltiazem and verapamil (plasma concentration of lomitapide possibly increased)
- Ciclosporin: manufacturer of lomitapide advises separating administration from ciclosporin by 12 hours
- Clofazimine: manufacturer of lomitapide advises separating administration from ciclosporin by 12 hours
- Cytotoxics: manufacturer of lomitapide advises separating administration from lapatinib, nilotinib and pazopanib by 12 hours
- Fosaprepitant: manufacturer of lomitapide advises separating administration from fosaprepitant by 12 hours
- Grapefruit Juice: manufacturer of lomitapide advises avoid concomitant use with grapefruit juice
- Hormone Antagonists: manufacturer of lomitapide advises separating administration from aminoglutethimide, bicalutamide and ketoconazole by 12 hours; increased risk of ventricular arrhythmias
- Lipid-regulating Drugs: lomitapide increases plasma concentration of atorvastatin—manufacturer of lomitapide advises reduce dose of atorvastatin by half or separate administration by 12 hours; lomitapide increases plasma concentration of simvastatin (see under Simvastatin, p. 194); absorption of lomitapide possibly reduced by bile acid sequestrants (give at least 4 hours apart)
- Oestrogens: manufacturer of lomitapide advises separating administration from oestrogens by 12 hours
- Ranolazine: manufacturer of lomitapide advises separating administration from ranolazine by 12 hours
- Tacrolimus: manufacturer of lomitapide advises separating administration from tacrolimus by 12 hours
- Tiaclopidine: manufacturer of lomitapide advises separating administration from ticlopidine by 12 hours
- Ulcer-healing Drugs: manufacturer of lomitapide advises separating administration from cimetidine and ranitidine by 12 hours

Lomustine

- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Ulcer-healing Drugs: myelosuppressive effects of lomustine possibly enhanced by cimetidine

Loperamide

- Desmopressin: loperamide increases plasma concentration of oral desmopressin

Lopinavir

Note in combination with ritonavir as Kaletra® (ritonavir is noted to inhibit lopinavir metabolism and increase plasma-lopinavir concentration)—see also Ritonavir
- Anti-arrhythmics: lopinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias—avoid concomitant use); lopinavir possibly increases plasma concentration of lidocaine
Lopinavir — Macrolides

Lopinavir (continued)

- Antibacterials: plasma concentration of lopinavir reduced by
  - **RIFAMPICIN**—avoid concomitant use; lopinavir increases plasma concentration of **DELAMANID**; avoidance of concomitant lopinavir in severe renal and hepatic impairment advised by manufacturer of **SIMEPATIDE**
  - **TELITHROMYCIN**
- Anticoagulants: avoidance of lopinavir advised by manufacturer of **APIXABAN**; manufacturers advise avoid concomitant use of lopinavir with **RIVAROXABAN**
- Antidepressants: plasma concentration of lopinavir reduced by
  - **ST JOHN’S WORT**—avoid concomitant use
- Antiepileptics: plasma concentration of lopinavir possibly reduced by **CARBAMAZEPINE, FOSPHENYTIOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE**
- Antifungals: lopinavir increases plasma concentration of **ISAVICONAZOLE** (also plasma concentration of lopinavir reduced)
- Antihistamines: lopinavir possibly increases plasma concentration of **CHLORPHENAMINE**
- Antimalarials: caution with lopinavir advised by manufacturer of **ARTEMETHER WITH LUMEFANTRINE**
- Antimuscarinics: avoidance of lopinavir advised by manufacturer of **DARIFENACIN and TOLTERODINE**
- Antipsychotics: lopinavir possibly increases plasma concentration of **ARIPIPRAZOLE** (reduce dose of aripiprazole—consult aripiprazole product literature); lopinavir possibly increases plasma concentration of **QUETIAPINE**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: manufacturers advise avoid concomitant use of lopinavir with **BOCDEPREVIR** and **TELAPREVIR**; lopinavir reduces plasma concentration of **DARUNAVIR**—avoid concomitant use; plasma concentration of lopinavir reduced by **EFAVIRENZ**—consider increasing dose of lopinavir; lopinavir boosted with ritonavir increases plasma concentration of **ELVITEGRAVIR** (reduce dose of elvitegravir); lopinavir reduces plasma concentration of **FOSAMPRENAVIR**, effect on lopinavir plasma concentration not predictable—avoid concomitant use; lopinavir increases plasma concentration of **MARAVIROC** (consider reducing dose of maraviroc); plasma concentration of lopinavir possibly reduced by **NEVIRAPINE**—consider increasing dose of lopinavir; lopinavir increases plasma concentration of **PARITAPREVIR**—manufacturer of paritaprevir advises avoid concomitant use; increased risk of ventricular arrhythmias when lopinavir given with **SAQUINAVIR**—avoid concomitant use; lopinavir increases plasma concentration of **TENOFIVIR**; plasma concentration of lopinavir reduced by **TIPRANAVIR**
  - Bosentan: lopinavir increases plasma concentration of **BOSENTAN** (consider reducing dose of bosentan)
  - Corticosteroids: plasma concentration of lopinavir possibly reduced by **DEKAMETHASONE**
- Cytoxotics: manufacturer of ruxolitinib advises dose reduction when lopinavir given with **RUXOLITINIB**—consult ruxolitinib product literature
- Eltrombopag: lopinavir possibly reduces plasma concentration of **ELTROMBOPAG**
- Lipid-regulating Drugs: possible increased risk of myopathy when lopinavir given with **ATORVASTATIN**; lopinavir increases plasma concentration of **ROSUVASTATIN**—adjust dose of rosuvastatin (consult product literature); possible increased risk of myopathy when lopinavir given with **SIMVASTATIN**—avoid concomitant use; avoidance of lopinavir advised by manufacturer of **LOMITAPIDE** (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of lopinavir possibly reduced by **ORLISTAT**
- Ranolazine: lopinavir possibly increases plasma concentration of **RANOLAZINE**—manufacturer of ranolazine advises avoid concomitant use
- Sirolimus: lopinavir possibly increases plasma concentration of **SIROLIMUS**
- Sympathomimetics, Beta₂: manufacturer of lopinavir advises avoid concomitant use with **SALMETEROL**
- Loprazolam see Anxiolytics and Hypnotics
- Loradatine see Antihistamines
- Lorazepam see Anxiolytics and Hypnotics
- Lormetazepam see Anxiolytics and Hypnotics
- Losartan see Angiotensin-II Receptor Antagonists
- Lumacaftor
  - Antibacterials: lumacaftor possibly reduces plasma concentration of **CLARITHROMYCIN** and **TELITHROMYCIN**—reduce dose of lumacaftor with ivacox (see under Lumacaftor with Ivacoxar in BNF or BNFC); lumacaftor possibly reduces plasma concentration of **RIFABUTIN**—avoid concomitant use
  - Antidepressants: manufacturer of lumacaftor advises avoid concomitant use with **ST JOHN’S WORT**
- Antiepileptics: lumacaftor possibly reduces plasma concentration of **CARBAMAZEPINE, FOSPHENYTIOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE**—manufacturer of lumacaftor advises avoid concomitant use
- Antifungals: lumacaftor possibly reduces plasma concentration of **KETOCONAZOLE, POSACONAZOLE** and **VORICONAZOLE**—reduce dose of lumacaftor with ivacoxar (see under Lumacaftor with Ivacoxar in BNF or BNFC); lumacaftor reduces plasma concentration of **ITRAZOPAN**—reduce dose of lumacaftor with Ivacoxar (see under Lumacaftor with Ivacoxar in BNF or BNFC)
- Anxiolytics and Hypnotics: lumacaftor possibly reduces plasma concentration of **MIDAZOLAM**—manufacturer of lumacaftor advises avoid concomitant use
- Ciclosporin: manufacturer of lumacaftor advises avoid concomitant use with **CICLOSPORIN**
- Cytoxotics: manufacturer of lopinavir advises avoid concomitant use with **EVEROLIMUS**
- Oestrogens: lumacaftor possibly causes contraceptive failure of hormonal contraceptives containing **ETHINYLESTRADIOL** (alternative contraception recommended)
- Progestogens: lumacaftor possibly causes contraceptive failure of hormonal contraceptives containing **PROGESTOGENS** (alternative contraception recommended)
- Sirolimus: manufacturer of lumacaftor advises avoid concomitant use with **SIROLIMUS**
- Tacrolimus: manufacturer of lumacaftor advises avoid concomitant use with **TACROLIMUS**
- Lupasidentone see Antipsychotics
- Lymecycline see Tetracyclines
- Macitentan
  - Antibacterials: plasma concentration of macitentan reduced by **RIFAMPICIN**—avoid concomitant use
  - Antidepressants: manufacturer of macitentan advises avoid concomitant use with **ST JOHN’S WORT**
  - Antiepileptics: manufacturer of macitentan advises avoid concomitant use with **CARBAMAZEPINE, FOSPHENYTIOIN and PHENOBARBITAL**
  - Antifungals: plasma concentration of macitentan increased by **KETOCONAZOLE**

Macrogols

Note Some manufacturers suggest taking other oral medication 1 hour before or 1 hour after macrogols to reduce possible interference with absorption

Macrolides

Note See also Telithromycin

Note Interactions do not apply to small amounts of erythromycin used topically

- Aminophylline: clarithromycin possibly increases plasma concentration of **AMINOPHYLLINE**; erythromycin increases plasma concentration of **AMINOPHYLLINE** (also aminophylline may reduce absorption of oral erythromycin)
- Analgesics: erythromycin increases plasma concentration of **ALFENTANIL**; clarithromycin possibly increases plasma concentration of **FENTANYL**
- Antacids: absorption of azithromycin reduced by **ANTACIDS** (give at least 2 hours before or 1 hour after antacids)
- Anti-arrhythmics: increased risk of ventricular arrhythmias when parenteral erythromycin given with **AMIODARONE**—avoid concomitant use; clarithromycin possibly increases plasma concentration of **DISOPYRAMIDE** (increased risk of ventricular arrhythmias); azithromycin possibly increases plasma concentration of **DISOPYRAMIDE** (increased risk of toxicity); erythromycin increases plasma concentration of **DISOPYRAMIDE** (increased risk of toxicity); avoidance of
Macrolides

- Antipsychotics (continued)
  clarithromycin advised by manufacturer of ▶ DRONEDARONE (risk of ventricular arrhythmias); erythromycin increases plasma concentration of ▶ DRONEDARONE (increased risk of ventricular arrhythmias—avoid concomitant use)
- Anticholinergics: increased risk of ventricular arrhythmias when parenteral erythromycin given with ▶ MOXIFLOXACIN—avoid concomitant use; increased risk of side-effects including neutropenia when azithromycin given with ▶ RIFABUTIN; clarithromycin increases plasma concentration of ▶ RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); erythromycin possibly increases plasma concentration of ▶ RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); clarithromycin and erythromycin possibly increase plasma concentration of ▶ BEDAQUILINE—avoid concomitant use if clarithromycin and erythromycin given for more than 14 days; possible increased risk of ventricular arrhythmias when clarithromycin and erythromycin given with ▶ DELAMANID; avoidance of clarithromycin and erythromycin advised by manufacturer of FIDAXOMICIN; plasma concentration of clarithromycin reduced by ▶ RIFAMYCINS
- Anticoagulants: avoidance of clarithromycin advised by manufacturer of parenteral erythromycin; clarithromycin possibly enhances anticoagulant effect of ▶ CUMARINS; clarithromycin and erythromycin enhance anticoagulant effect of ▶ CUMARINS; possible increased risk of bleeding when clarithromycin given with ▶ DABIGATRAN; erythromycin increases plasma concentration of ▶ EDOXABAN (reduce dose of edoxaban—see under Edoxaban, p. 118)
- Antidepressants: avoidance of macrolides advised by manufacturer of ▶ REBOXETINE; avoidance of intravenous erythromycin advised by manufacturer of ▶ CITALOPRAM and ▶ ESCITALOPRAM (risk of ventricular arrhythmias); avoidance of erythromycin advised by manufacturer of ▶ VENLAFAXINE (risk of ventricular arrhythmias); clarithromycin possibly increases plasma concentration of ▶ TRAZODONE
- Anti-diabetics: clarithromycin enhances effects of ▶ REPAGLINIDE
- Antiepileptics: erythromycin increases plasma concentration of ▶ CARBAMAZEPINE; clarithromycin increases plasma concentration of ▶ CARBAMAZEPINE (consider reducing dose of carbamazeptine); clarithromycin inhibits metabolism of ▶ FOSPHENOTYDIN and ▶ PHENOTYDIN (increased plasma concentration); erythromycin possibly inhibits metabolism of ▶ SODIUM VALPROATE and ▶ VALPROIC ACID (increased plasma concentration)
- Antifungals: avoidance of concomitant clarithromycin in severe renal impairment advised by manufacturer of ▶ KETOCONAZOLE; avoidance of erythromycin advised by manufacturer of ▶ FLUCONAZOLE; clarithromycin increases plasma concentration of ▶ ITRACONAZOLE
- Antihistamines: manufacturer of loratadine advises erythromycin possibly increases plasma concentration of ▶ LORATADINE; macrolides possibly inhibit metabolism of ▶ MIZOLASTINE (avoid concomitant use); erythromycin inhibits metabolism of ▶ MIZOLASTINE—avoid concomitant use
- Antimalarials: avoidance of macrolides advised by manufacturer of ▶ ARTENIOLIM WITH PIPERPAQUINE (possible risk of ventricular arrhythmias)
- Antimuscarnics: erythromycin possibly increases plasma concentration of ▶ DARIFENACIN; manufacturer of fosoterodine advises dose reduction when clarithromycin given with ▶ FOSOTERODINE—consult fosoterodine product literature; avoidance of clarithromycin and erythromycin advised by manufacturer of ▶ TOLTERODINE
- Antipsychotics: avoidance of macrolides advised by manufacturer of ▶ DROPERIDOL (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when parenteral erythromycin given with ▶ ZUCLOPENTHIXOL—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ▶ AMISULPRIDE—avoid concomitant use; erythromycin possibly increases plasma concentration of ▶ CLOZAPINE (possible increased risk of convulsions); clarithromycin possibly increases plasma concentration of ▶ LURASIDONE—avoid concomitant use;

Macrolides

- Antipsychotics (continued)
  clarithromycin possibly increases the plasma concentration of ▶ LURASIDONE (see under Lurasidone, p. 573); possible increased risk of ventricular arrhythmias when erythromycin given with ▶ ZIPROZIDE—avoid concomitant use; increased risk of ventricular arrhythmias when clarithromycin given with ▶ ZIPROZIDE—avoid concomitant use; erythromycin increases plasma concentration of ▶ QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use; clarithromycin possibly increases plasma concentration of ▶ QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias when parenteral erythromycin given with ▶ SULPIRIDE
- Antivirals: plasma concentration of both drugs increased when clarithromycin given with ▶ ATAZANAVIR; clarithromycin possibly increases the plasma concentration of ▶ DACLATASVIR—reduce dose of daclatasvir (see under Daclatasvir, p. 577); avoidance of clarithromycin advised by manufacturer of ▶ DASABUVIR and ▶ PARITAPREVIR; plasma concentration of clarithromycin reduced by ▶ Efavirenz, also plasma concentration of active metabolite of clarithromycin increased; plasma concentration of clarithromycin reduced by ▶ Efavirenz and ▶ NEVIRAPINE (but concentration of an active metabolite increased), also plasma concentration of etravirine and nevirapine increased; clarithromycin possibly increases plasma concentration of ▶ MARAVIROC (consider reducing dose of maraviroc); avoidance of clarithromycin and erythromycin advised by manufacturer of ▶ RILPIVIRINE (plasma concentration of rilpivirine possibly increased); plasma concentration of azithromycin and erythromycin possibly increased by ▶ RITONAVIR; plasma concentration of clarithromycin increased by ▶ RITONAVIR (reduce dose of clarithromycin in renal impairment); plasma concentration of both drugs possibly increased when clarithromycin given with ▶ SAQUINAVIR and ▶ TELAPREVI (increased risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when erythromycin given with ▶ SAQUINAVIR—avoid concomitant use; clarithromycin possibly increases plasma concentration of ▶ SIMPREVIR—manufacturer of simprevir advises avoid concomitant use; plasma concentration of both drugs increased when erythromycin given with ▶ SIMPREVIR—manufacturer of simprevir advises avoid concomitant use; plasma concentration of both drugs possibly increased when erythromycin given with ▶ TELAPREVI (increased risk of ventricular arrhythmias); plasma concentration of clarithromycin increased by ▶ TIPRANAVIR (reduce dose of clarithromycin in renal impairment), also clarithromycin increases plasma concentration of tipranavir; clarithromycin tablets reduce absorption of ▶ ZIDOVUDINE (give at least 2 hours apart)
- Anxiolytics and Hypnotics: clarithromycin and erythromycin inhibit metabolism of ▶ MIDAZOLAM (increased plasma concentration with increased sedation); erythromycin increases plasma concentration of ▶ BUSPIRONE (reduce dose of buspironone); erythromycin inhibits the metabolism of ▶ ZOPICLONE
  ▶ Aprepitant: clarithromycin possibly increases plasma concentration of ▶ APREPIANT
- Atomoxetine: increased risk of ventricular arrhythmias when parenteral erythromycin given with ▶ ATOMOXETINE
- Avanafil: clarithromycin possibly increases plasma concentration of ▶ AVANAFIL—manufacturer of avanafil advises avoid concomitant use; erythromycin increases plasma concentration of ▶ AVANAFIL—see under Avanafil, p. 744
- Calcium-channel blockers: clarithromycin and erythromycin possibly inhibit metabolism of ▶ CALCIUM-CHANNEL BLOCKERS (increased risk of side-effects); avoidance of erythromycin advised by manufacturer of ▶ LERCANIDIPINE
- Cardiac Glycosides: macrolides increase plasma concentration of ▶ DIGOXIN (increased risk of toxicity)
- Ciclosporin: macrolides possibly inhibit metabolism of ▶ CICLOSPORIN (increased plasma concentration); azithromycin increases plasma concentration of ▶ CICLOSPORIN; clarithromycin and erythromycin inhibit metabolism of ▶ CICLOSPORIN (increased plasma concentration)
**Macrolides**

- Gliostazol: clarithromycin possibly increases plasma concentration of **CILOSTAZOL** (see under Cilostazol, p. 221); erythromycin increases plasma concentration of **CILOSTAZOL** (see under Cilostazol, p. 221)
- Clopidogrel: erythromycin possibly reduces antiplatelet effect of **CLOPIDOGREL**
- Colchicine: azithromycin, clarithromycin and erythromycin possibly increase risk of **COLCHICINE** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: erythromycin possibly inhibits metabolism of **CORTICOSTEROIDS**; erythromycin inhibits the metabolism of **METHYLPRERIDNOSLONE**; clarithromycin possibly increases plasma concentration of **METHYLPRERIDNOSLONE**
- Cytotoxic: erythromycin possibly increases the plasma concentration of **AFATINIB**—manufacturer of afatinib advises separating administration of erthyromycin by 6 to 12 hours; clarithromycin and erythromycin possibly increase plasma concentration of **AXITINIB** (reduce dose of axitinib—consult axitinib product literature); clarithromycin and erythromycin possibly increase the plasma concentration of **BOSUTINIB**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; clarithromycin and erythromycin possibly increase plasma concentration of **CABOZANTINIB**; possible increased risk of ventricular arrhythmias when clarithromycin given with **CERITINIB**; clarithromycin possibly increases plasma concentration of **CRIZOTINIB** and **EVEROLIMUS**—manufacturer of crizotinib and everolimus advises avoid concomitant use; avoidance of clarithromycin and erythromycin advised by manufacturer of **DASATINIB** (plasma concentration of dasatinib possibly increased); erythromycin increases plasma concentration of **EVEROLIMUS** (consider reducing the dose of everolimus—consult everolimus product literature); clarithromycin and erythromycin possibly increase the plasma concentration of **IBRUTINIB**—reduce dose of ibrutinib (see under ibrutinib, p. 867); avoidance of clarithromycin advised by manufacturer of **NILITINIB**; clarithromycin possibly increases plasma concentration of **PAZOPANIB** (reduce dose of pazopanib); clarithromycin possibly increases plasma concentration of **PONATINIB**—consider reducing initial dose of ponatinib (see under Ponatinib, p. 875); manufacturer of ruxolitinib advises dose reduction when clarithromycin given with **RUXOLITINIB**—consult ruxolitinib product literature; possible increased risk of ventricular arrhythmias when parenteral erythromycin given with **VANDENATIB**—avoid concomitant use; clarithromycin possibly increases the plasma concentration of **CABAZITAXEL**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; clarithromycin possibly increases plasma concentration of **DOCETAXEL**—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose; increased risk of ventricular arrhythmias when erythromycin given with **ARESINIC TRIOXIDE**; clarithromycin and erythromycin possibly increase plasma concentration of **OLAPARIB** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881); erythromycin increases toxicity of **VINBLASTINE**—avoid concomitant use; possible increased risk of neutropenia when clarithromycin given with **VINORELBINE**
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when clarithromycin and erythromycin given with **DAPOXETINE** (see under Dapoxetine, p. 751)
- Diuretics: clarithromycin increases plasma concentration of **EPLERENONE**—avoid concomitant use; erythromycin increases plasma concentration of **EPLERENONE** (reduce dose of eplerenone)
- Domeridone: possible increased risk of ventricular arrhythmias when clarithromycin given with **DOMPERIDONE**—avoid concomitant use; erythromycin increases plasma concentration of **DOMPERIDONE** (increased risk of ventricular arrhythmias—avoid concomitant use)
- Dopaminergics: macrolides possibly increase plasma concentration of **BROMOCRIPTINE** and **CABERGOLINE** (increased risk of toxicity); erythromycin increases plasma concentration of **BROMOCRIPTINE** and **CABERGOLINE** (increased risk of toxicity)
- Dose of bosutinib; clarithromycin and erythromycin possibly increase the plasma concentration of **GUANAFACINE** (halve dose of guanfacine)
- 5HT2-receptor Agonists: clarithromycin and erythromycin increase plasma concentration of **ELIPTRIPTAN** (risk of toxicity)—avoid concomitant use
- Ivabradine: clarithromycin possibly increases plasma concentration of **IVABRADINE**—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with **IVABRADINE**—avoid concomitant use
- Ivacaftor: clarithromycin possibly increases plasma concentration of **IVACAFTOR**—reduce dose of ivacaftor (see under Ivacaftor in BNF or BNFC, and Lumacaftor with Ivacaftor in BNF or BNFC); erythromycin possibly increases plasma concentration of **IVACAFTOR**—reduce dose of ivacaftor (see under Ivacaftor, p. 275)
- Lenalidomide: clarithromycin possibly increases plasma concentration of **LENALIDOMIDE** (increased risk of toxicity)
- Leukotriene Receptor Antagonists: erythromycin reduces plasma concentration of **ZAFIRILUKAST**
- Lipid-regulating Drugs: possible increased risk of myopathy when azithromycin or erythromycin given with **ATORVASTATIN**; clarithromycin increases plasma concentration of **ATORVASTATIN** and **PRAVASTATIN**; erythromycin increases plasma concentration of **PRAVASTATIN**; erythromycin reduces plasma concentration of **ROSUVASTATIN**; possible increased risk of myopathy when azithromycin given with **SIMVASTATIN**; increased risk of myopathy when clarithromycin or erythromycin given with **SIMVASTATIN** (avoid concomitant use); separating administration from azithromycin by 12 hours advised by manufacturer of **LOMITAPIDIE**; avoidance of clarithromycin and erythromycin advised by manufacturer of **LOMITAPIDIE** (plasma concentration of lomitapide possibly increased)
- Lumacaftor: plasma concentration of clarithromycin possibly reduced by **LUMACAFTOR**—reduce dose of lumacaftor with ivacaftor (see under Lumacaftor with Ivacaftor in BNF or BNFC)
- Mirabegron: when given with clarithromycin avoid or reduce dose of **MIRABEGRON** in hepatic or renal impairment—see Mirabegron, p. 715
- Naloxegol: clarithromycin possibly increases plasma concentration of **NALOXEGOL**—avoid concomitant use
- Netupitant: plasma concentration of erythromycin increased by **NETUPITANT**
- Oestrogens: erythromycin increases plasma concentration of **ESTRADIOL**
- Panobinostat: increased risk of ventricular arrhythmias when clarithromycin given with **PANOBINOSTAT**—avoid concomitant use
- Parasympathomimetics: erythromycin increases plasma concentration of **GALANTAMINE**
- Pentamidine Isetionate: increased risk of ventricular arrhythmias when parenteral erythromycin given with **PENTAMIDINE ISETIONATE**
- Progestogens: erythromycin increases plasma concentration of **DIENOGEST**
- Ranolazine: clarithromycin possibly increases plasma concentration of **RANOLAZINE**—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: clarithromycin increases the plasma concentration of **SILDENAFIL**—consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension; erythromycin increases plasma concentration of **SILDENAFIL**—reduce initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to twice daily for pulmonary hypertension
- Sirolimus: clarithromycin increases plasma concentration of **SIROLIMUS**—avoid concomitant use; plasma concentration of
Macrolides

- Sirolimus (continued)
  - both drugs increased when erythromycin given with
    - sIROLimus
  - Tacrolimus: clarithromycin and erythromycin increase plasma concentration of tacrolimus
  - Tadalafil: clarithromycin and erythromycin possibly increase plasma concentration of tadalafil

- Theophylline: clarithromycin possibly increases plasma concentration of theophylline; erythromycin increases plasma concentration of theophylline (also theophylline may reduce absorption of oral erythromycin)
  - Ticagrelor: clarithromycin possibly increases plasma concentration of ticagrelor — manufacturer of ticagrelor advises avoid concomitant use; erythromycin possibly increases plasma concentration of ticagrelor

- Ucer-healing Drugs: plasma concentration of erthyromycin increased by cimetidine (increased risk of toxicity, including deafness); plasma concentration of both drugs increased when clarithromycin given with omeprazole

- Ulipristal: avoidance of clarithromycin advised by manufacturer of low-dose ulipristal; erythromycin increases plasma concentration of low-dose ulipristal — manufacturer of low-dose ulipristal advises avoid concomitant use

- Vaccines; antibacterials inactivate oral typhoid vaccine — see under typhoid vaccine in BNF or BNFC

- Vardenafil: clarithromycin possibly increases plasma concentration of vardenafil (consider reducing initial dose of vardenafil); erythromycin increases plasma concentration of vardenafil (reduce dose of vardenafil)

Magnesium (parenteral)

- Calcium-channel Blockers: profound hypotension reported with concomitant use of parenteral magnesium and nifedipine in pre-eclampsia

- Muscle Relaxants: parenteral magnesium enhances effects of non-depolarising muscle relaxants and suxamethonium

Magnesium Salts (oral)

- see Antacids

Mannitol

- Antibacterials: avoidance of mannitol advised by manufacturer of tobramycin

- Ciclosporin: possible increased risk of nephrotoxicity when mannitol given with ciclosporin

MAOIs

NOTE For interactions of reversible MAO-A inhibitors (RIMAs) see moclobemide, and for interactions of MAO-B inhibitors see rasagiline and selegiline

NOTE Tedizolid is a reversible, non-selective MAO inhibitor and an antibacterial

NOTE Linezolid is a reversible, non-selective MAO inhibitor and an antibacterial

- ACE Inhibitors: MAOIs possibly enhance hypotensive effect of ACE inhibitors

- Adrenergic Neurone Blockers: enhanced hypotensive effect when MAOIs given with adrenergic neurone blockers

- Alcohol: MAOIs interact with tyramine found in some beverages containing alcohol and some dealkoholised beverages (hypertensive crisis) — if no tyramine, enhanced hypotensive effect

- Alpha-2-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of apraclonidine and brimonidine

- Alpha-blockers: avoidance of MAOIs advised by manufacturer of indoramin; enhanced hypotensive effect when MAOIs given with alpha-blockers

- Analgesics: possible increased serotonergic effects when MAOIs given with fentanyl; CNS excitation or depression (hypertension or hypotension) when MAOIs given with paroxetine — avoid concomitant use and for 2 weeks after stopping MAOIs; possible increased serotonergic effects and increased risk of convulsions when MAOIs given with tramadol — some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs

- Angiotensin-II Receptor Antagonists: MAOIs possibly enhance hypotensive effect of angiotensin-II receptor antagonists

- Antibacterials: plasma concentration of linezolid reduced by therapeutic failure of linezolid

- Antidepressants: increased risk of hypertension and CNS excitation when MAOIs given with reboxetine (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs); after stopping MAOIs do not start citalopram, escitalopram, fluvoxamine, paroxetine or sertraline for 2 weeks, also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine, paroxetine or sertraline; after stopping MAOIs do not start duloxetine for 2 weeks, also MAOIs should not be started until at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with venlafaxine (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); increased risk of hypertension and CNS excitation when MAOIs given with other MAOIs (avoid for at least previous 5 days before stopping MAOIs and then start at a reduced dose); after stopping MAOIs do not start moclobemide for at least 1 week; MAOIs increase CNS effects of SSRIS (risk of serious toxicity); after stopping MAOIs do not start mirtazapine for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping mirtazapine; after stopping MAOIs do not start tricyclic-related antidepressants for 2 weeks, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; increased risk of hypertension and CNS excitation when MAOIs given with tricyclics, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine); avoidance of linezolid advised by manufacturer of vortioxetine; increased risk of hypertension and CNS excitation when MAOIs given with vortioxetine (vortioxetine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 2 weeks after stopping vortioxetine)

- Antidiabetics: MAOIs possibly enhance hypoglycaemiac effect of antidiabetics; MAOIs enhance hypoglycaemic effect of insulin, metformin and sulfonylureas

- Antiepileptics: MAOIs possibly antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); avoidance for 2 weeks after stopping MAOIs advised by manufacturer of carbamazepine, also antagonism of anticonvulsant effect

- Antihistamines: avoidance of MAOIs advised by manufacturer of hydroxyzine; avoidance of promethazine for 2 weeks after stopping MAOIs advised by manufacturer of promethazine; increased antimuscarinic and sedative effects when MAOIs given with antihistamines

- Antimalarials: avoidance of antidepressants advised by manufacturer of artepime with lumefantrine and artemether with lumefantrine

- ArtemiNol with piperaquene

- Antimuscarinics: increased risk of antimuscarinic side-effects when MAOIs given with antimuscarinics

- Antipsychotics: CNS effects of MAOIs possibly increased by clozapine

- Anxiolytics and Hypnotics: manufacturer of tranylcypromine advises avoid buspirone for 14 days after stopping tranylcypromine; avoidance of MAOIs advised by manufacturer of buspirone

- Atomoxetine: after stopping MAOIs do not start atomoxetine for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; possible increased risk of convulsions when antidepressants given with atomoxetine

- Beta-blockers: enhanced hypotensive effect when MAOIs given with beta-blockers

- Buspirone: avoidance of buspirone for 2 weeks after stopping MAOIs advised by manufacturer of buspirone

- Bupropion: avoidance of bupropion for 2 weeks after stopping MAOIs advised by manufacturer of bupropion

- Bupropion: avoidance of bupropion for 2 weeks after stopping MAOIs advised by manufacturer of bupropion
MAOIs (continued)
- Calcium-channel Blockers: enhanced hypotensive effect when MAOIs given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when MAOIs given with CLONIDINE
- Dapoxetine: increased risk of serotoninergic effects when MAOIs given with DAPOXETINE (MAOIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping MAOIs)
- Diazoxide: enhanced hypotensive effect when MAOIs given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when MAOIs given with DIURETICS
- Dopaminergics: risk of hypertensive crisis when MAOIs given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA, avoid co-beneldopa, co-careldopa or levdopa for at least 2 weeks after stopping MAOIs; avoid concomitant use of non-selective MAOIs with ENTACAPONE; risk of hypertensive crisis when MAOIs given with RASAGILINE, avoid MAOIs for at least 2 weeks after stopping rasagiline; enhanced hypotensive effect when MAOIs given with SELEGINILE — manufacturer of selegiline advises avoid concomitant use; avoid concomitant use of MAOIs with TOLCAPONE
- Doxapram: MAOIs enhance effects of DOXAPRAM
- Histamine: avoidance of MAOIs advised by manufacturer of HISTAMINE
- SHT-receptor Agonists: risk of CNS toxicity when MAOIs given with RIZATRIPTAN or SUMATRIPTAN (avoid rizatRIPTAN or sumatriptan for 2 weeks after MAOIs); risk of CNS toxicity when MAOIs given with ZOMITRIPTAN (reduce dose of zolmitriptan)
- Methyldopa: avoidance of MAOIs advised by manufacturer of METHYLDOPA
- Moxonidine: enhanced hypotensive effect when MAOIs given with MOXONIDINE
- Muscle Relaxants: phenelzine enhances effects of SUXAMETHONIUM
- Nicorandil: enhanced hypotensive effect when MAOIs given with NICORANDIL
- Nitrates: enhanced hypotensive effect when MAOIs given with NITRATES
- Pholcodine: avoidance of pholcodine for 2 weeks after stopping MAOIs advised by manufacturer of PHOLCODINE
- Sympathomimetics: risk of hypertensive crisis when MAOIs given with ADRENALINE (EPINEPHRINE), DOBUTAMINE, DOPAMINE, NORADRENALINE (NOREPINEPHRINE) or XYLEMETHAZOLINE; risk of hypertensive crisis when MAOIs given with DEXAMFETAMINE, EPHEDRINE, ISOMETHEPHENE, LISDEXAMFETAMINE, METARAMINOL, METHYLPHENIDATE, PHENYLEPHRINE or PSEUDEPHEDRINE, avoid dexamfetamine, ephedrine, isomethephene, lisdexamfetamine, metaraminol, methylphenidate, phenylephrine or pseudoephedrine for at least 2 weeks after stopping MAOIs; avoidance of MAOIs advised by manufacturer of MIOODRINE; risk of hypertensive crisis when MAOIs given with OXYMETHAZOLINE, some manufacturers advise avoid oxymetazoline for at least 2 weeks after stopping MAOIs
- Tetrabenazine: risk of CNS toxicity when MAOIs given with TETRABENAZINE (avoid tetrabenazine for 2 weeks after MAOIs) Vaccines: antibacterials including linezolid and tedizolid inactivate ORAL TYPHOID VACCINE — see under Typhoid Vaccine in BNF or BNFC
- Vasodilator Antihypertensives: enhanced hypotensive effect when MAOIs given with HYDRAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE

MAOIs, reversible see Moclobemide

Maraviroc (continued)
- Antifungals: plasma concentration of maraviroc increased by KETOCONAZOLE (consider reducing dose of maraviroc)
- Antivirals: plasma concentration of maraviroc increased by ATVAZANAVIR, BOCEPREVIR, DARUNAVIR, INDINAVIR, LOPINAVIR, SAQUINAVIR and TELAPREVIR (consider reducing dose of maraviroc); plasma concentration of maraviroc possibly reduced by EFAVIRENZ — consider increasing dose of maraviroc; plasma concentration of maraviroc possibly reduced by ETROVIRINE; maraviroc reduces plasma concentration of FOSAMPRENAVIR — avoid concomitant use; plasma concentration of maraviroc increased by COBICISTAT (reduce dose of maraviroc)
- Orlistat: absorption of maraviroc possibly reduced by ORLSTAT

Mebendazole
- Ulcer-healing Drugs: metabolism of mebendazole possibly inhibited by CIMETIDINE (increased plasma concentration)

Medroxyprogesterone see Progestogens

Mefenamic Acid see NSAIDs

Mefloquine
- Anti-arrhythmics: increased risk of ventricular arrhythmias when mefloquine given with AMIODARONE — avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when mefloquine given with MOXIFLOXACIN — avoid concomitant use; plasma concentration of mefloquine reduced by RIFAMPICIN — avoid concomitant use
- Antidepressants: possible increased risk of convulsions when mefloquine given with VORTICOTINE
- Antiepileptics: mefloquine antagonises anticonvulsant effect of ANTIEPILEPTICS
- Antifungals: plasma concentration of mefloquine increased by KETOCONAZOLE
- Antimalarials: avoidance of antimalarials advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; increased risk of convulsions when mefloquine given with CHLOROQUINE or HYDROXYCHLOROQUINE; increased risk of convulsions when mefloquine given with QUININE (but should not prevent the use of intravenous quinine in severe cases)
- Antipsychotics: possible increased risk of ventricular arrhythmias when mefloquine given with HALOPERIDOL — avoid concomitant use; avoidance of mefloquine advised by manufacturer of AMISULPRIDE; increased risk of ventricular arrhythmias when mefloquine given with PIMOZIDE — avoid concomitant use; manufacturer of risperidone advises possible risk of ventricular arrhythmias when mefloquine given with RISPERIDONE
- Antivirals: mefloquine possibly reduces plasma concentration of RITONAVIR
- Atomoxetine: increased risk of ventricular arrhythmias when mefloquine given with ATOMOXETINE
- Beta-blockers: increased risk of bradycardia when mefloquine given with BETA-BLOCKERS
- Calcium-channel Blockers: possible increased risk of bradycardia when mefloquine given with CALCIUM-CHANNEL BLOCKERS
- Cardiac Glycosides: possible increased risk of bradycardia when mefloquine given with DIGOXIN
- Cytotoxics: possible increased risk of bradycardia when mefloquine given with CRIZOTINIB
- Histamine: avoidance of antimalarials advised by manufacturer of HISTAMINE
- Ibavradine: increased risk of ventricular arrhythmias when mefloquine given with IBRAVADINE
- Penicillamine: increased risk of haematological toxicity when antimalarials given with PENICILLAMINE — manufacturer of penicillamine advises avoid concomitant use
- Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE — see under Typhoid Vaccine in BNF or BNFC

Megestrol see Progestogens

Melatonin see Anxiolytics and Hypnotics

Meloxicam see NSAIDs
Methenamine
- Antibacterials: increased risk of methenamine toxicity when given with **NALIDIXIC ACID**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOZAPINE** (increased risk of agranulocytosis)
- Cardiac Glycosides: methenamine possibly reduces absorption of **DIGOXIN** tablets
- Ciclosporin: increased risk of nephrotoxicity when methenalan given with **CICLOSPORIN**

Memantine
- Anaesthetics, General: increased risk of CNS toxicity when memantine given with **AMANTADINE**
- Analgesics: increased risk of CNS toxicity when memantine given with **DEXTROMETHORPHAN**
- Anticoagulants: memantine possibly enhances anticoagulant effect of **WARFARIN**
- Antimuscarinics: memantine possibly enhances effects of **ANTIMUSCARINICS**
- Antipsychotics: dopamine possibly reduces effects of **DOPAMINERGICS** and **SELEGILINE**
- Muscle Relaxants: memantine possibly modifies effects of **BACLOFEN** and **DANTROLENE**

Meningococcal Vaccines see Vaccines

Mepacrine
- Antimalarials: mepacrine increases plasma concentration of **PRIMAQUINE** (increased risk of toxicity)
- **Meprobamate** see Anxiolytics and Hypnotics
- **Meptazinol** see Opioid Analgesics

Merpenturine
- Allopurinol: enhanced effects and increased toxicity of merpenturine when given with **ALLOPURINOL** (reduce dose of merpenturine to one quarter of usual dose)
- Antibacterials: increased risk of haematological toxicity when merpenturine given with **SULFAMETHOXAZOLE** (as co- trimoxazole); increased risk of haematological toxicity when merpenturine given with **TRIMETHOPRIM** (also with co- trimoxazole)
- Anticoagulants: merpenturine possibly reduces anticoagulant effect of **COUMARINS**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOZAPINE** (increased risk of agranulocytosis)
- **Dairy Products**: plasma concentration of merpenturine possibly reduced by **Dairy Products**—manufacturer of merpenturine advises avoid concomitant use after dairy products
- **Febuxostat**: avoidance of merpenturine advised by manufacturer of **FEBUXOSTAT**

Meroopen
- Antiepileptics: carbapenems reduce plasma concentration of **SODIUM VALPROATE** and **VALPROIC ACID**—avoid concomitant use
- Vaccines: antibacterials inactive **ORAL TYPHOID VACCINE**—see under Typhoid Vaccine in BNF or BNFC

Mestranol see Oestrogens

Metaraminol see Sympathomimetics

Metformin see Antidiabetics

Methadone see Opioid Analgesics

Methenamine
- Antacids: avoid concomitant use of methenamine with **ANTACIDS**
- Antibacterials: increased risk of crystalluria when methenamine given with **SULFONAMIDES**
- Diuretics: effects of methenamine antagonised by **ACEINHIBITORS**
- Potassium Salts: avoid concomitant use of methenamine with **POTASSIUM CITRATE**
- Sodium Citrate: avoid concomitant use of methenamine with **SODIUM CITRATE**
- Vaccines: antibacterials inactive **ORAL TYPHOID VACCINE**—see under Typhoid Vaccine in BNF or BNFC

Methocarbamol see Muscle Relaxants

Methotrexate
- Aminophylline: methotrexate possibly increases plasma concentration of **AMINOPHYLLINE**
- Anaesthetics, General: antifolate effect of methotrexate increased by **NITROUS OXIDE**—avoid concomitant use
- Analgesics: excretion of methotrexate possibly reduced by **NSAIDS** (increased risk of toxicity); excretion of methotrexate reduced by **ASPIRIN**, **DICLOFENAC**, **IBUPROFEN**
- Antimicrobials: methotrexate possibly reduced by **INDOMETACIN**, **KETOPROFEN**, **MELOXICAM** and **NALIDIXIC ACID** (increased risk of toxicity)
- Antibacterials: absorption of methotrexate possibly reduced by **NEOMYCIN**; excretion of methotrexate possibly reduced by **CIPROFLOXACIN** (increased risk of toxicity); increased risk of severe bone marrow depression (fatalities reported) and other haematological toxicities when methotrexate given with **SULFAMETHOXAZOLE** (as co-trimoxazole); increased risk of methotrexate toxicity when given with **DOXYCYCLINE**, **SULFONAMIDES** or **TETRACYCLINE**; excretion of methotrexate reduced by **PENICILLINS** (increased risk of toxicity); increased risk of severe bone marrow depression (fatalities reported) and other haematological toxicities when methotrexate given with **TRIMETHOPRIM** (also with co-trimoxazole)
- Antiepileptics: antifolate effect of methotrexate increased by **FOSPHENYTOIN** and **PHENYTOIN**; plasma concentration of methotrexate possibly increased by **LEVETIRACETAM**
- Antimalarials: antifolate effect of methotrexate increased by **PYRIMETHAMINE**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOZAPINE** (increased risk of agranulocytosis)
- Cardiac Glycosides: methotrexate possibly reduces absorption of **DIGOXIN** tablets
- Ciclosporin: risk of toxicity when methotrexate given with **CICLOSPORIN**
- Corticosteroids: possible increased risk of hepatotoxicity when **high-dose** methotrexate given with **BEMETASONE**
- Cytotoxics: increased pulmonary toxicity when methotrexate given with **CISPLATIN**
- Diuretics: excretion of methotrexate increased by alkaline urine due to **ACETAZOLAMIDE**
- Leflunomide: risk of toxicity when methotrexate given with **LEFLUNOMIDE**
- Retinoids: plasma concentration of methotrexate increased by **ACITRETIN** (also increased risk of hepatotoxicity)—avoid concomitant use
- Theophylline: methotrexate possibly increases plasma concentration of **THEOPHyllINE**
- Ulcer-healing Drugs: excretion of methotrexate possibly reduced by **PROTON PUMP INHIBITORS** (increased risk of toxicity)

Methyldopa
- ACE Inhibitors: enhanced hypotensive effect when methyldopa given with **ACE INHIBITORS**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when methyldopa given with **ADRENERGIC NEURONE BLOCKERS**
- Alcohol: enhanced hypotensive effect when methyldopa given with **ALCOHOL**
- Aldesleukin: enhanced hypotensive effect when methyldopa given with **ALDESLEUKIN**
- Alpha-blockers: enhanced hypotensive effect when methyldopa given with **ALPHA-BLOCKERS**
- Anaesthetics, General: enhanced hypotensive effect when methyldopa given with **GENERAL ANAESTHETICS**
- Analgesics: hypotensive effect of methyldopa antagonised by **NSAIDS**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when methyldopa given with **ANGIOTENSIN-II RECEPTOR ANTAGONISTS**
- Antidepressants: manufacturer of methyldopa advises avoid concomitant use with **MAOIS**
- Antipsychotics: enhanced hypotensive effect when methyldopa given with **ANTIPSYCHOTICS** (also increased risk of extrapyramidal effects)
- Anxiolytics and Hypnotics: enhanced hypotensive effect when methyldopa given with **ANXIOLYTICS AND HYPNOTICS**
- Beta-blockers: enhanced hypotensive effect when methyldopa given with **BETA-BLOCKERS**
Methyldopa (continued)
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when methyldopa given with CLONIDINE
- Corticosteroids: hypotensive effect of methyldopa antagonised by CORTICOSTEROIDS
- Diazoxide: enhanced hypotensive effect when methyldopa given with DIAZoxide
- Diuretics: enhanced hypotensive effect when methyldopa given with DIURETICS
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics; increased risk of extrapyramidal side-effects when methyldopa given with AMANTADINE; enhanced hypotensive effect when methyldopa given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA; effects of methyldopa possibly enhanced by ENTACAPONE
- Iron Salts: hypotensive effect of methyldopa antagonised by oral IRON SALTS
  - Lithium: neurotoxicity may occur when methyldopa given with LITHIUM without increased plasma concentration of lithium with MOXISYLVE, MOXONIDINE
  - Moxonidine: enhanced hypotensive effect when methyldopa given with MOXONIDINE
  - Muscle Relaxants: enhanced hypotensive effect when methyldopa given with BACLOFEN or TIZANIDINE
  - Nitrates: enhanced hypotensive effect when methyldopa given with NITRATES
  - Oestrogens: hypotensive effect of methyldopa antagonised by OESTROGENS
  - Prostaglandins: enhanced hypotensive effect when methyldopa given with ALPROSTADIL
  - Sympathomimetics, Beta-2: acute hypotension reported when methyldopa given with infusion of SALBUTAMOL
  - Vasodilator Antihypertensives: enhanced hypotensive effect when methyldopa given with HYDRALAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE
- Methylphenidate see Sympathomimetics
- Methyleneprisalolone see Corticosteroids
- Methyldopa
- Antidepressants: risk of CNS toxicity when methyldophium given with SSRI-RELATED ANTIDEPRESSANTS, SSRI-RELATED ANTIDEPRESSANTS and CLOMIPRAMINE—avoid concomitant use (if avoidance not possible, use lowest possible dose of methyldophium and observe patient for up to 4 hours after administration); possible risk of CNS toxicity when methyldophium given with MIRTAPATINE—avoid concomitant use (if avoidance not possible, use lowest possible dose of methyldophium and observe patient for up to 4 hours after administration)
- Anxiolytics and Hypnotics: possible risk of CNS toxicity when methyldophium given with BUSPIRONE—avoid concomitant use (if avoidance not possible, use lowest possible dose of methyldophium and observe patient for up to 4 hours after administration)
- Bupropion: possible risk of CNS toxicity when methyldophium given with BUPROPION—avoid concomitant use (if avoidance not possible, use lowest possible dose of methyldophium and observe patient for up to 4 hours after administration)
- Metoclopramide
- Alcohol: metoclopramide possibly increases absorption of ALCOHOL
- Anaesthetics, General: metoclopramide enhances effects of THIOPENTAL
- Analgesics: metoclopramide increases rate of absorption of ASPIRIN (enhanced effect); effects of metoclopramide on gastro-intestinal activity antagonised by OPIOID ANALGESICS; metoclopramide increases rate of absorption of PARACETAMOL
- Antibacterials: metoclopramide reduces plasma concentration of FOSFOMYCIN
- Antidepressants: CNS toxicity reported when metoclopramide given with SSRIS
- Antimuscarinics: effects of metoclopramide on gastro-intestinal activity antagonised by ANTIMUSCARINICS

Methyldopa — Minoxidil

Metoclopramide
- Antipsychotics: increased risk of extrapyramidal side-effects when metoclopramide given with ANTIPSYCHOTICS
- Atovaquone: metoclopramide reduces plasma concentration of ATOVAQUONE—avoid concomitant use
- Cilostazol: metoclopramide increases plasma concentration of CICLOSPORIN
- Dopaminergics: metoclopramide antagonises hypoprolactinaemic effects of BROMOCRIPTINE and CABERGOLINE; metoclopramide antagonises antiparkinsonian effect of PERGOLIDE; avoidance of metoclopramide advised by manufacturer of ROPINIROLE and ROTIGOTINE (antagonism of effect)
- Muscle Relaxants: metoclopramide enhances effects of SUXAMETHONIUM
- Tetrabenazine: increased risk of extrapyramidal side-effects when metoclopramide given with TETRABENAZINE

Metolazo see Diuretics

Metoprolol see Beta-blockers

Methyldopa — Minoxidil

Metronidazole
- Cytotoxics: metronidazole increases plasma concentration of CICLOSPORIN
- Lithium: increased risk of lithium toxicity
- Mycophenolate: metronidazole possibly reduces bioavailability of MYCOPHENOLATE
- Ulcer-healing Drugs: metabolism of metronidazole inhibited by CIMETIDINE (increased plasma concentration)
- Vaccines: antibacterials inactive ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Mianserin see Antidepressants, Tricyclic (related)

Micafungin
- Antifungals: micafungin possibly increases plasma concentration of AMPHOTERICIN; micafungin increases plasma concentration of ITRACONAZOLE (consider reducing dose of itraconazole)
- Calcium-channel Blockers: micafungin increases plasma concentration of NIFEDIPINE
- Cilostazol: micafungin possibly increases plasma concentration of CICLOSPORINE
- Sirolimus: micafungin increases plasma concentration of SIROLIMUS

Miconazole see Antifungals. Imidazole

Midazolam see Antiepileptics: benzodiazepines

Midodrine see Sympathomimetics

Mifamurtide
- Antibacterials: mifamurtide possibly reduces bioavailability of MICAFUNGIN
- Cyclosporin: mifamurtide possibly reduces bioavailability of MYCOPHENOLATE
- Vaccines: antibacterials inactive ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Mifamurtide — Minoxidil

Mifepristone
- Corticosteroids: mifepristone may reduce effect of corticosteroids (including inhaled corticosteroids) for 3–4 days

Milrinone see Phosphodiesterase Inhibitors

Minocycline see Tetracyclines

Minoxidil see Vasodilator Antihypertensives
Mirabegron

- Antimicrobials: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with clarithromycin — see Mirabegron, p. 715
- Antifungals: avoid or reduce dose of mirabegron in hepatic or renal impairment when given withitraconazole and ketoconazole — see Mirabegron, p. 715
- Antivirals: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with ritonavir — see Mirabegron, p. 715
- Beta-blockers: mirabegron increases plasma concentration of metoprolol
- Cardiac Glycosides: mirabegron increases plasma concentration of digoxin — reduce initial dose of digoxin

Miratapine

- Alcohol: increased sedative effect when mirtapapine given with alcohol
- Analgesics: possible increased sedative effects when mirtapapine given with tramadol
- Anticoagulants: mirtapapine enhances anticoagulant effect of warfarin

Moxisylyte

- Antidepressants: possible increased serotonergic effects when mirtapapine given with atomoxetine
- Antimalarials: increased plasma concentration of mirtapapine given with carbamazepine, fosphenytoin and phenytoin
- Antifungals: plasma concentration of mirtapapine increased by ketoconazole
- Antimalarial: avoidance of antidepressants advised by manufacturer of artemether with lumefantrine and artemether with piperaquine
- Anxiety and Hypnotics: increased sedative effect when mirtapapine given with anxiolytics and hypnotics
- Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine
- Clonidine: mirtapapine possibly antagonises hypothensive effect of clonidine
- Methylthioninium: possible risk of CNS toxicity when mirtapapine given with methylthioninium — avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
- Ulcer-healing Drugs: plasma concentration of mirtapapine increased by cimetidine

Missoprostol

- Antacids: absorption of missoprostol possibly reduced by antacids

Mitomycin

- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when cytoxic antibiotics given with live vaccines — avoid concomitant use

Mitotane

- Anticoagulants: mitotane possibly reduces anticoagulant effect of coumarins
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Antivirals: avoidance of mitotane advised by manufacturer of dasabuvir, ombitasvir and paritaprevir
- Diuretics: manufacturer of mitotane advises avoid concomitant use of spironolactone (agonist of action of spironolactone)

Moxifloxacin

- Antidepressants: possible increased serotonergic effects when mirtapapine given with clozapine (increased risk of agranulocytosis)
- Ciclosporin: excretion of moxifloxacin reduced by ciclosporin (increased plasma concentration)
- Vaccines: risk of generalised infections when cytoxic antibiotics given with live vaccines — avoid concomitant use

Mivacurium

- Antihistamines

MMR Vaccine

- Vaccines

Moxisylyte

- ACE Inhibitors: enhanced hypotensive effect when moxisylyte given with ACE inhibitors
- Alpha-blockers: possible severe postural hypotension when moxisylyte given with alpha-blockers
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxisylyte given with angiotensin-II receptor antagonists
- Beta-blockers: possible severe postural hypotension when moxisylyte given with beta-blockers
Moxisylyte — Muscle Relaxants

**Muscle Relaxants**

- ACE Inhibitors: enhanced hypotensive effect when baclofen or tizanidine given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when baclofen or tizanidine given with ADRENERGIC NEURONE BLOCKERS
  - Alcohol: increased sedative effect when baclofen, methycarbalol or tizanidine given with ALCOHOL
  - Alpha-blockers: enhanced hypotensive effect when baclofen or tizanidine given with ALPHA-BLOCKERS
    - Anaesthetics, General: effects of atracurium enhanced by KETAMINE; increased risk of myocardial depression and bradycardia when suxamethonium given with PROPOL; effects of non-depolarising muscle relaxants and suxamethonium enhanced by VOLATILE LIQUID GENERAL ANAESTHETICS
    - Analgesics: excretion of baclofen possibly reduced by NSAIDS (increased risk of toxicity); excretion of baclofen reduced by IBUPROFEN (increased risk of toxicity); increased sedative effect when baclofen given with FENTANYL or MORPHINE
    - Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when baclofen or tizanidine given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
      - Anti-arrhythmics: neuromuscular blockade enhanced and prolonged when suxamethonium given with LIDOCAINE
        - Antibacterials: effects of non-depolarising muscle relaxants and suxamethonium enhanced by PIPERACILLIN; plasma concentration of tizanidine increased by CIPROFLOXACIN (increased risk of toxicity)—avoid concomitant use; plasma concentration of tizanidine possibly increased by NORFLOXACIN (increased risk of toxicity); plasma concentration of tizanidine possibly reduced by BIFAMPICIN; effects of non-depolarising muscle relaxants and suxamethonium enhanced by AMINOGYCOSIDES; effects of non-depolarising muscle relaxants and suxamethonium enhanced by CLINDAMYCIN; effects of non-depolarising muscle relaxants and suxamethonium enhanced by POLYMIXINS; effects of suxamethonium enhanced by VANCOMYCIN
      - Antidepressants: plasma concentration of tizanidine increased by FLUOXAMINE (increased risk of toxicity)—avoid concomitant use; effects of suxamethonium enhanced by PHENELZINE; muscle relaxant effect of baclofen enhanced by TRICYCLICS
        - Antiepileptics: muscle relaxant effect of non-depolarising muscle relaxants antagonised by CARBAMAZEPINE (accelerated recovery from neuromuscular blockade); effects of non-depolarising muscle relaxants reduced by long-term use of FOSPHENYTOIN and PHENYTOIN (but effects of non-depolarising muscle relaxants might be increased by acute use of fosphenytoin and phenytoin)
        - Antimalarials: effects of suxamethonium possibly enhanced by QUININE
        - Antipsychotics: effects of suxamethonium possibly enhanced by PROMAZINE
        - Anxiolytics and Hypnotics: increased sedative effect when baclofen or tizanidine given with ANXIOLYTICS AND HYPNOTICS
          - Beta-blockers: enhanced hypotensive effect when baclofen given with BETA-BLOCKERS; possible enhanced hypotensive effect and bradycardia when tizanidine given with BETA-BLOCKERS; effects of muscle relaxants enhanced by PRопANOLOL
          - Calcium-channel Blockers: enhanced hypotensive effect when baclofen or tizanidine given with CALCIUM-CHANNEL BLOCKERS; effects of non-depolarising muscle relaxants possibly enhanced by CALCIUM-CHANNEL BLOCKERS; possible increased risk of ventricular arrhythmias when intravenous dantrolene given with DILTIAZEM;—manufacturer of diltiazem advises avoid concomitant use; effects of non-depolarising muscle relaxants and suxamethonium enhanced by VERAPAMIL; avoidance of intravenous dantrolene advised by manufacturer of VERAPAMIL
          - Cardiac Glycosides: possible increased risk of bradycardia when tizanidine given with CARDIAC GLYCOSIDES; risk of ventricular arrhythmias when suxamethonium given with CARDIAC GLYCOSIDES

**Moxisylyte**

- Calcium-channel Blockers: enhanced hypotensive effect when moxonidine given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when moxonidine given with CLONIDINE
- Diazoxide: enhanced hypotensive effect when moxonidine given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when moxonidine given with DIURETICS
- Dopaminergic: enhanced hypotensive effect when moxonidine given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
- Methyldopa: enhanced hypotensive effect when moxonidine given with METHYLDOPA
- Moxisylyte: enhanced hypotensive effect when moxonidine given with MOXISYLYTE
- Muscle Relaxants: enhanced hypotensive effect when moxonidine given with BACLOFEN or TIZANIDINE
- Nitrates: enhanced hypotensive effect when moxonidine given with NITRATES
- Oestrogens: hypotensive effect of moxonidine antagonised by OESTROGENS
- Prostaglandins: enhanced hypotensive effect when moxonidine given with ALPROSTADIL
- Vasodilator Anti-hypertensives: enhanced hypotensive effect when moxonidine given with HYDRALAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE

**Moxonidine**

- ACE Inhibitors: enhanced hypotensive effect when moxonidine given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when moxonidine given with ADRENERGIC NEURONE BLOCKERS
  - Alcohol: enhanced hypotensive effect when moxonidine given with ALCOHOL
  - Aldesleukin: enhanced hypotensive effect when moxonidine given with ALDESELEUKIN
  - Alpha-blockers: enhanced hypotensive effect when moxonidine given with ALPHA-BLOCKERS
  - Anaesthetics, General: enhanced hypotensive effect when moxonidine given with GENERAL ANAESTHETICS
  - Analgesics: hypotensive effect of moxonidine antagonised by NSAIDS
  - Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxonidine given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
  - Antidepressants: enhanced hypotensive effect when moxonidine given with MAOIS; hypotensive effect of moxonidine possibly antagonised by TRICYCLICS (manufacturer of moxonidine advises avoid concomitant use)
  - Antipsychotics: enhanced hypotensive effect when moxonidine given with PHENOTHIAZINES
  - Anxiolytics and Hypnotics: enhanced hypotensive effect when moxonidine given with ANXIOLYTICS AND HYPNOTICS; sedative effects possibly increased when moxonidine given with BENZODIAZEPINES
  - Beta-blockers: enhanced hypotensive effect when moxonidine given with BETA-BLOCKERS
  - Calcium-channel Blockers: enhanced hypotensive effect when moxonidine given with CALCIUM-CHANNEL BLOCKERS
  - Clonidine: enhanced hypotensive effect when moxonidine given with CLONIDINE
  - Corticosteroids: hypotensive effect of moxonidine antagonised by CORTICOSTEROIDS
  - Diazoxide: enhanced hypotensive effect when moxonidine given with DIAZOXIDE
  - Diuretics: enhanced hypotensive effect when moxonidine given with DIURETICS
  - Dopaminergic: enhanced hypotensive effect when moxonidine given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
  - Methyldopa: enhanced hypotensive effect when moxonidine given with METHYLDOPA
  - Moxisylyte: enhanced hypotensive effect when moxonidine given with MOXISYLYTE
  - Muscle Relaxants: enhanced hypotensive effect when moxonidine given with BACLOFEN or TIZANIDINE
  - Nitrates: enhanced hypotensive effect when moxonidine given with NITRATES
  - Oestrogens: hypotensive effect of moxonidine antagonised by OESTROGENS
  - Prostaglandins: enhanced hypotensive effect when moxonidine given with ALPROSTADIL
  - Vasodilator Anti-hypertensives: enhanced hypotensive effect when moxonidine given with HYDRALAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE
Muscle Relaxants — Nevirapine

Muscle Relaxants (continued)

- Clonidine: enhanced hypotensive effect when baclofen or tizanidine given with
  CLONIDINE
- Corticosteroids: effects of pancuronium and vecuronium possibly antagonised by
  CORTICOSTEROIDS
- Cytototics: enhanced hypotensive effect when baclofen or tizanidine given with
  DIURETICS
- Dopaminergics: possible agitation, confusion and hallucinations when baclofen given with
  CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
- Lithium: effects of muscle relaxants enhanced by LITHIUM; baclofen possibly aggravates hyperkinesis caused by LITHIUM
- Magnesium (parenteral): effects of non-depolarising muscle relaxants and suxamethonium enhanced by PARENTERAL MAGNESIUM
- Memantine: effects of baclofen and dantrolene possibly modified by MEMANTINE
- Methyldopa: enhanced hypotensive effect when baclofen or tizanidine given with METHYLDOPA
- Metoclopramide: effects of suxamethonium enhanced by METOCLOPRAMIDE
- Minoxidil: enhanced hypotensive effect when baclofen or tizanidine given with
  MINOXIDINE
- Nitrates: enhanced hypotensive effect when baclofen or tizanidine given with NITRATES
- Oestrogens: plasma concentration of tizanidine possibly increased by
  OESTROGENS (increased risk of toxicity)
- Parasympathomimetics: effects of non-depolarising muscle relaxants possibly antagonised by DONEPEZIL; effects of suxamethonium possibly enhanced by DONEPEZIL; effects of suxamethonium enhanced by
  GALANTAMINE, NEOSTIGMINE, PYRIDOSTIGMINE and RIVASTIGMINE; effects of non-depolarising muscle relaxants antagonised by NEOSTIGMINE, PYRIDOSTIGMINE and RIVASTIGMINE
- Progestogens: plasma concentration of tizanidine possibly increased by
  PROGESTOGENS (increased risk of toxicity)
- Symptomimetics, Beta: effects of suxamethonium enhanced by BAMBUTEROL
- Vasodilators, Antihypertensives: enhanced hypotensive effect when baclofen or tizanidine given with HYDRAZALINE; enhanced hypotensive effect when baclofen or tizanidine given with MINOXIDIL; enhanced hypotensive effect when baclofen or tizanidine given with SODIUM NITROPRUSSIDE

Muscle Relaxants, depolarising see Muscle Relaxants

Muscle Relaxants, non-depolarising see Muscle Relaxants

Mycophenolate

- Antacids: absorption of mycophenolate reduced by ANTACIDS
  ● Antibacterials: bioavailability of mycophenolate possibly reduced by
    METRONIDAZOLE and NORFLOXACIN; plasma concentration of mycophenolate possibly reduced by CO-AMOXICLAV; plasma concentration of active metabolite of mycofenolate reduced by ● Rifampicin
- Antifungals: plasma concentration of mycofenolate increased by
  ISAVUCONAZOLE
- Antivirals: mycofenolate increases plasma concentration of
  ACICLOVIR and VALaciclovir, also plasma concentration of inactive metabolite of mycofenolate increased; mycofenolate possibly increases plasma concentration of GANCICLOVIR and VALGANCICLOVIR, also plasma concentration of inactive metabolite of mycofenolate possibly increased
- Iron Salts: absorption of mycofenolate reduced by oral IRON SALTS
- Lipid-regulating Drugs: absorption of mycofenolate reduced by
  COLESTYRAMINE
- Sevelamer: plasma concentration of mycofenolate possibly reduced by SEVELAMER

Nabumetone see NSAIDs

Nadolol see Beta-blockers

Nalidixic Acid see Quinolones

Nalmsene

● Analgesics: manufacturer of nalmefene advises avoid concomitant use with ● OPIOID ANALGESICS

Naloxegol

● Antibacterials: plasma concentration of naloxegol possibly increased by ● CLARITHROMYCIN and ● TELITHROMYCIN —avoid concomitant use; plasma concentration of naloxegol reduced by ● Rifampicin —avoid concomitant use
- Antidepressants: plasma concentration of naloxegol possibly reduced by ● ST JOHN’S Wort —avoid concomitant use
- Antiepileptics: plasma concentration of naloxegol possibly increased by CARBAMAZEPINE —avoid concomitant use
- Antifungals: plasma concentration of naloxegol increased by KETOCONAZOLE —avoid concomitant use; plasma concentration of naloxegol possibly increased by ITRACONAZOLE —avoid concomitant use
- Antivirals: plasma concentration of naloxegol possibly increased by INDINAVIR, RITONAVIR and SAQUINAVIR —avoid concomitant use
  ● Calcium-channel Blockers: plasma concentration of naloxegol increased by DILTIAZEM (reduce dose of naloxegol —see under Naloxegol, p. 61); plasma concentration of naloxegol possibly increased by VERAPAMIL (reduce dose of naloxegol —see under Naloxegol, p. 61)
- Grapefruit Juice: plasma concentration of naloxegol possibly increased by GRAPEFRUIT JUICE —avoid concomitant use

Nandrolone see Anabolic Steroids

Naproxen see NSAIDs

Naratipran see SHT-receptor Agonists (under HT)

Natalizumab

- Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES —avoid concomitant use

Nateglinide see Antidiabetics

Nebivolol see Beta-blockers

Nefopam

- Antidepressants: manufacturer of nefopam advises avoid concomitant use with ● MAOIS; side-effects possibly increased when nefopam given with TRICYCLICS
- Antimuscariotics: increased risk of antimuscarinic side-effects when nefopam given with ANTIMUSCARINICS

Neomycin see Aminoglycosides

Neostigmine see Parasympathomimetics

Netupitant

- Analgesics: manufacturer of netupitant advises caution with MORPHINE
- Antibacterials: netupitant increases plasma concentration of ERYTHROMYCIN; plasma concentration of netupitant reduced by ● Rifampicin —avoid concomitant use
- Anticoagulants: manufacturer of netupitant advises caution with DABIGATRAN
- Antiepileptics: manufacturer of netupitant advises caution with ZIDOVUDINE
- Anxiolytics and Hypnotics: netupitant increases plasma concentration of MIDAZOLAM
- Colchicine: manufacturer of netupitant advises caution with
  COLCHICINE
- Corticosteroids: netupitant increases plasma concentration of DEXAMETHASONE (halve dose of dexamethasone)
- Cytotoxics: netupitant increases plasma concentration of
  DOCEtaxel and ETOPOSIDE

Nevirapine

- Analgesics: nevirapine possibly reduces plasma concentration of METHADONE
- Antibacterials: nevirapine reduces plasma concentration of CLARITHROMYCIN (but concentration of an active metabolite increased), also plasma concentration of nevirapine increased; nevirapine possibly increases plasma concentration of RIFABUTIN; plasma concentration of nevirapine reduced by ● Rifampicin —avoid concomitant use
Nevirapine — Nitrates

Nevirapine (continued)

- Anticoagulants: nevirapine may enhance or reduce anticoagulant effect of - WARFARIN

- Antidepressants: plasma concentration of nevirapine reduced by - ST JOHN'S WORT—avoid concomitant use

- Antiarrythmics: plasma concentration of nevirapine reduced by - CARBAMAZEPINE

- Antifungals: nevirapine reduces plasma concentration of - KETOCONAZOLE—avoid concomitant use; plasma concentration of nevirapine increased by - FLUCONAZOLE; nevirapine possibly reduces plasma concentration of - CASPOFUNGIN and - ITRACONAZOLE—consider increasing dose of caspofungin and itraconazole

- Antipsychotics: nevirapine possibly reduces plasma concentration of - ARIPIPRAZOLE (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature)

- Antivirals: nevirapine possibly reduces plasma concentration of - ATAZANAVIR and - ETRAVIRINE—avoid concomitant use; manufacturer of nevirapine advises avoid concomitant use with - BOCEPREVIR and - RILPİVİRİNE; avoidance of nevirapine advised by manufacturer of - DACLATASVİR (plasma concentration of daclatasvir possibly reduced); avoidance of nevirapine advised by manufacturer of - DASABUVİR, - ELİVİTREATİV, - OMBİTASVİR and - PARİTADEVİR; nevirapine possibly reduces the plasma concentration of - DOLİTREAVİR (see under Dolitreavir, p. 592); nevirapine reduces plasma concentration of - FOSAMPRENAVİR—avoid unboosted fosamprenavir; nevirapine reduces plasma concentration of - INDİNAVİR; nevirapine possibly reduces plasma concentration of - LOPİNAVİR and - TELİPADEVİR—consider increasing dose of lopinavir and telaprevir; nevirapine possibly reduces plasma concentration of - SİMEPRENAVİR—manufacturer of simeprevir advises avoid concomitant use; increased risk of granulocytopenia when nevirapine given with - ZİDOUDİNE

- Dacabazine: manufacturer of nevirapine advises avoid concomitant use with - COBİCİSTAT

- Cytotoxics: avoidance of nevirapine advised by manufacturer of - OLAŞİRİBI

- Guanfacine: nevirapine possibly reduces plasma concentration of - GÜANFACİNE—increase dose of guanfacine

- Oestrogens: nevirapine accelerates metabolism of - OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)

- Orlistat: absorption of nevirapine possibly reduced by - ORLİSTAT

- Progestogens: nevirapine accelerates metabolism of - PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)

Nicolardil (continued)

- Vasodilator Antihypertensives: possible enhanced hypotensive effect when nicorandil given with - HYDRAZİNE, - MINOXİDİL or - SODİUM NİTROPRİSSİDE

Nicotine

- Anti-arrhythmics: nicotine possibly enhances effects of - ADENOSİNE

Nicotinic Acid

- Lipid-regulating Drugs: increased risk of myopathy when nicotinic acid given with - STATİNS (applies to lipid regulating doses of nicotinic acid)

Nifedipine see Calcium-channel Blockers

Nilotinib

- Antibacterials: manufacturer of nilotinib advises avoid concomitant use with - CLARİTHROMİCYİN and - TELİTHROMİCYİN; plasma concentration of nilotinib reduced by - RİFİMPİCİN—avoid concomitant use

- Antifungals: plasma concentration of nilotinib increased by - KETOCONAZOLE—avoid concomitant use; manufacturer of nilotinib advises avoid concomitant use with - ITRACONAZOLE and - VİRİKONAZOLE

- Antipsychotics: avoid concomitant use of cytotoxics with - CLOZAPİNE (increased risk of agranulocytosis)

- Antivirals: avoidance of nilotinib advised by manufacturer of - BOCEPREVİR; plasma concentration of nilotinib possibly increased by - RİTONAVİR—manufacturer of nilotinib advises avoid concomitant use

- Anxiolytics and Hypnotics: nilotinib increases plasma concentration of - MIDAZOLAM

- Grapefruit juice: manufacturer of nilotinib advises avoid concomitant use with - GRAPEFRUIT JUİCE

- Lipid-regulating Drugs: separating administration from nilotinib by 12 hours advised by manufacturer of - LOMİTAİDE

Nimodipine see Calcium-channel Blockers

Nintedanib

- Antibacterials: plasma concentration of nintedanib reduced by - RİFİMPİCİN—avoid concomitant use

- Antifungals: plasma concentration of nintedanib increased by - KETOCONAZOLE

- Antipsychotics: avoid concomitant use of cytotoxics with - CLOZAPİNE (increased risk of agranulocytosis)

Nitrates

- ACE Inhibitors: enhanced hypotensive effect when nitrates given with - ACE INHİBITORS

- Adrenergic Neurone Blockers: enhanced hypotensive effect when nitrates given with - ADRENERGİC NEURON BLOCKERS

- Alcohol: enhanced hypotensive effect when nitrates given with - ALCOHOL

- Aldesleukin: enhanced hypotensive effect when nitrates given with - ALDESLEUKİN

- Alpha-blockers: enhanced hypotensive effect when nitrates given with - ALPHA-BLOCKERS

- Anaesthetics, General: enhanced hypotensive effect when nitrates given with - GENERAL ANAESTHETİCS

- Analgesics: hypotensive effect of nitrates antagonised by - NSAİDS

- Angiotensin II Receptor Antagonists: enhanced hypotensive effect when nitrates given with - ANGIOTENSİNS-II RECEPTOR ANTAGONİSTS

- Anti-arrhythmics: effects of sublingual tablets of nitrates reduced by - DISİPRİMAİDE (failure to dissolve under tongue owing to dry mouth)

- Anticoagulants: infusion of glycyl trinitrate reduces anticoagulant effect of - HEPARİNS

- Antidepressants: enhanced hypotensive effect when nitrates given with - MAOİS; effects of sublingual tablets of nitrates possibly reduced by - TRİCYCLİC-RELATED ANİTDİPESİnts (failure to dissolve under tongue owing to dry mouth); effects of sublingual tablets of nitrates reduced by - TRİCYCLİCS (failure to dissolve under tongue owing to dry mouth)

- Antimuscarinics: effects of sublingual tablets of nitrates possibly reduced by - ANİTDİPESİnts (failure to dissolve under tongue owing to dry mouth)

- Antipsychotics: enhanced hypotensive effect when nitrates given with - PHENOTHİAZİNES
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**NSAIDs**

**NOTE** See also Aspirin. Interactions do not generally apply to topical NSAIDs

- Ace inhibitors: increased risk of renal impairment when NSAIDs given with **ACE INHIBITORS**, also hypotensive effect antagonised
- Adrenergic Neurone Blockers: NSAIDs antagonise hypotensive effect of **ADRENERGIC NEURONE BLOCKERS**
- Aliskiren: NSAIDs possibly antagonise hypotensive effect of **ALISKIREN**
- Alpha-blockers: NSAIDs antagonise hypotensive effect of **ALPHA-BLOCKERS**
- Analgesics: avoid concomitant use of NSAIDs with **NSAIDS** or **ASPIND** (increased side-effects); avoid concomitant use of NSAIDs with **KETOROLAC** (increased side-effects and haemorrhage); ibuprofen possibly reduces antiplatelet effect of **ASPIND**
- Angiotensin-II Receptor Antagonists: increased risk of renal impairment when NSAIDs given with **ANGIOTENSIN-II RECEPTOR ANTAGONISTS**, also hypotensive effect antagonised
- Antacids: absorption of acemetacin possibly reduced by **ANTACIDS**
- Antibacterials: indometacin possibly increases plasma concentration of **AMIKACIN** and **GENTAMICIN** in neonates; plasma concentration of celecoxib, diclofenac and etoricoxib reduced by **RIFAMPICIN**; possible increased risk of convulsions when NSAIDs given with **QUINOLONES**
- Anticoagulants: increased risk of haemorrhage when **intravenous** diclofenac given with **ANTICOAGULANTS** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when ketorolac given with **ANTICOAGULANTS** (avoid concomitant use, including low-dose heparins); NSAIDs possibly enhance anticoagulant effect of **COUMARINS** and **PHENINDIONE**; possible increased risk of bleeding when NSAIDs given with **DABIGATRAN** or **HEPARINS**; increased risk of bleeding when NSAIDs given with **EDOXABAN** (manufacturer of edoxaban advises avoid long-term NSAIDs)
- Antidepressants: increased risk of bleeding when **NSAIDS** given with **SSRIS** or **VENLAFAXINE**
- Antidiabetics: NSAIDs possibly enhance effects of **SULFONYLUREAS**
- Antiepileptics: acemetacin possibly reduces excretion of **FOSPHENTOIN** and **PHENTOIN** (increased risk of toxicity)
- Antiinfungals: plasma concentration of parecoxib increased by **FLUCONAZOLE** (reduce dose of parecoxib); plasma concentration of celecoxib increased by **FLUCONAZOLE** (halve dose of celecoxib); plasma concentration of flurbiprofen and ibuprofen increased by **FLUCONAZOLE**; plasma concentration of diclofenac and ibuprofen increased by **VORICONAZOLE**
- Antipsychotics: possible severe drowsiness when acemetacin or indometacin given with **HALOPERIDOL**
- Antivirals: plasma concentration of NSAIDs possibly increased by **RITONAVIR**; plasma concentration of piroxicam increased by **RITONAVIR** (risk of toxicity)—avoid concomitant use; increased risk of haematological toxicity when NSAIDs given with **ZIDOVUDINE**
- Azathioprine: manufacturer of azathioprine advises possible increased risk of myelosuppression when indometacin given with **AZATHIOPRINE**
- Beta-blockers: NSAIDs antagonise hypotensive effect of **BETA-BLOCKERS**
- Calcium-channel Blockers: NSAIDs antagonise hypotensive effect of **CALCIUM-CHANNEL BLOCKERS**
- Cardiac Glycosides: NSAIDs possibly increase plasma concentration of **CARDIAC GLYCOSIDES**, also possible exacerbation of heart failure and reduction of renal function
- Ciclosporin: increased risk of nephrotoxicity when NSAIDs given with **CICLOSPORIN**; plasma concentration of diclofenac increased by **CICLOSPORIN** (halve dose of diclofenac)
- Clopidogrel: increased risk of bleeding when **NSAIDS** given with **CLOPIDOGREL**
- Corticosteroids: increased risk of gastrointestinal bleeding and ulceration when NSAIDs given with **CORTICOSTEROIDS**
- Cytotoxics: NSAIDs probably reduce excretion of **METHOTREXATE** (increased risk of toxicity); diclofenac,
NSAIDs

- Ibuprofen, indomethacin, ketoprofen, meloxicam and naproxen reduce excretion of metotrexate (increased risk of toxicity); NSAIDs possibly reduce renal excretion of pemetrexed (consult product literature; increased risk of bleeding when NSAIDs given with erlotinib; avoidance of mefenamic acid advised by manufacturer of regorafenib.
- Desmopressin: indomethacin enhances effects of desmopressin.
- Diazoxide: NSAIDs antagonise hypotensive effect of diazoxide.
- Dimethyl sulfoxide: avoid concomitant use of sulindac with dimethyl sulfoxide.
- Diuretics: NSAIDs possibly antagonise diuretic effect of potassium-sparing diuretics; risk of nephrotoxicity of NSAIDs increased by diuretics, also antagonism of diuretic effect; indometacin and ketorolac antagonise effects of diuretics; excetration of acetaminophen possibly increased by furosemide; occasional reports of reduced renal function when indometacin given with triamterene—avoid concomitant use; increased risk of hyperkalaemia when indometacin given with aldosterone antagonists or potassium-sparing diuretics; possible increased risk of hyperkalaemia when NSAIDs given with aldosterone antagonists or potassium-sparing diuretics.
- Iloprost: increased risk of bleeding when NSAIDs given with iloprost.
- Lipid-regulating Drugs: excretion of meloxicam increased by colestyramine.
- Lithium: NSAIDs reduce excretion of lithium (increased risk of toxicity); ketorolac reduces excretion of lithium (increased risk of toxicity)—avoid concomitant use.
- Methyldopa: NSAIDs antagonise hypotensive effect of methyldopa.
- Mifamurtide: avoidance of high doses of NSAIDs advised by manufacturer of mifamurtide.
- Moxonidine: NSAIDs antagonise hypotensive effect of moxonidine.
- Muscle Relaxants: ibuprofen reduces excretion of baclofen (increased risk of toxicity); NSAIDs possibly reduce excretion of baclofen (increased risk of toxicity).
- Nicardipine: increased risk of gastro-intestinal bleeding and ulceration when NSAIDs given with nicardipine.
- Nitrates: NSAIDs antagonise hypotensive effect of nitrates.
- Oestrogens: etoricoxib increases plasma concentration of ethinylestradiol.
- Penicillamine: possible increased risk of nephrotoxicity when NSAIDs given with penicillamine.
- Pentoxifylline: possible increased risk of bleeding when NSAIDs given with pentoxifylline; increased risk of bleeding when ketorolac given with pentoxifylline (avoid concomitant use).
- Prasugrel: possible increased risk of bleeding when NSAIDs given with prasugrel.
- Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs given with tacrolimus; increased risk of nephrotoxicity when ibuprofen given with tacrolimus.
- Vasodilator Antihypertensives: NSAIDs antagonise hypotensive effect of hydralazine, minoxidil and sodium nitroprusside.

Obinutuzumab

- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).
- Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use.

Ocreotide

- Antiadibiotics: ocreotide possibly reduces requirements for antiadibiotics.
- Ciclosporin: ocreotide reduces plasma concentration of ciclosporin.
- Dopaminergics: ocreotide increases plasma concentration of bromocriptine.
- Uler-healing Drugs: ocreotide possibly delays absorption of cimetidine.

Oestrogens

- ACE Inhibitors: oestrogens antagonise hypotensive effect of ACE inhibitors.

Oestrogens (continued)

- Aminophylline: oestrogens increase plasma concentration of aminophylline (consider reducing dose of aminophylline).
- Analgesics: plasma concentration of ethinylestradiol increased by etoricoxib.
- Angiotensin-II Receptor Antagonists: oestrogens antagonise hypotensive effect of angiotensin-II receptor antagonists.
- Antibacterials: plasma concentration of estradiol increased by erythromycin; metabolism of oestrogens accelerated by rifampicin (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC).
- Anticoagulants: oestrogens may enhance or reduce anticoagulant effect of coumarins; oestrogens antagonise anticoagulant effect of phenindione.
- Antidepressants: contraceptive effect of oestrogens reduced by st John's wort (avoid concomitant use); oestrogens antagonise antidepressant effect of tricyclics (but side-effects of tricyclics possibly increased due to increased plasma concentration).
- Antiadibetics: oestrogens antagonise hypoglycaemic effect of antiadibetics.
- Antiepileptics: metabolism of oestrogens accelerated by carbamazepine; eslicarbazepine, fosphenytoin, oxcarbazepine; phenobarbital, phenytoin, primidone; rufinamide and topiramate (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC); oestrogens reduce plasma concentration of lamotrigine—consider increasing dose of lamotrigine; ethinylestradiol possibly reduces plasma concentration of sodium valproate and valproic acid.
- Antifungals: plasma concentration of ethinylestradiol increased by ketoconazole; oestrogens increase plasma concentration of voriconazole; anecdotal reports of contraceptive failure of hormonal contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC; occasional reports of breakthrough bleeding when oestrogens (used for contraception) given with terbinafine.
- Antivirals: plasma concentration of ethinylestradiol increased by atazanavir; avoidance of ethinylestradiol advised by manufacturer of dasabuvir, omibitasvir and paritaprevir—use alternative form of contraception; metabolism of oestrogens accelerated by nevirapine and ritonavir (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC); plasma concentration of ethinylestradiol possibly reduced by telaprevir—manufacturer of telaprevir advises additional contraceptive precautions.
- Anxiolytics and Hypnotics: oestrogens possibly increase plasma concentration of chloridiazepoxide, clidazep and nitrazepam; oestrogens possibly reduce plasma concentration of lorazepam, oxazepam and temazepam; oestrogens increase plasma concentration of melatonin.
- Aprepitant: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with aprepitant (alternative contraception recommended).
- Beta-blockers: oestrogens antagonise hypotensive effect of beta-blockers.
- Bosentan: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with bosentan (alternative contraception recommended).
- Calcium-channel Blockers: oestrogens antagonise hypotensive effect of calcium-channel blockers.
- Ciclosporin: oestrogens possibly increase plasma concentration of ciclosporin.
- Clonidine: oestrogens antagonise hypotensive effect of clonidine.
- Cobicistat: metabolism of oestrogens accelerated by cobicistat (reduced contraceptive effect with combined oral
**Oligocyclines** (continued) concomitantly with other anticonvulsants; the anticonvulsant effect of one is possibly increased by the other.

**Olfatunumah**

- Antipyretics: concomitant use of antipyretics with 
  - **COBICISTAT** (reduced plasma concentration of 
  - **COBICISTAT** (alternative anticonvulsant recommended)

**Olopatadine**

- Progesterone: plasma concentration of olaparib possibly reduced by 
  - **COBICISTAT** (alternative anticonvulsant recommended)

**Oogestrogens**

- **Holocort**: treatment of allergic rhinitis; the anticonvulsant effect of one is possibly increased by the other.

**Olaparib**

- Antifungals: plasma concentration of olaparib possibly reduced by 
  - **CLOzapine** (increased risk of agranulocytosis)

**Omeprazol**

- Antivirals: plasma concentration of olaparib possibly increased by 
  - **BOCEPREVIR**
  - **RTONAVIR** and **TELAPREVIR** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)

**Omeprazol**

- Antifungals: plasma concentration of olaparib possibly reduced by 
  - **CLOzapine** (increased risk of agranulocytosis)

**Omeprazol**

- Antivirals: plasma concentration of olaparib possibly increased by 
  - **BOCEPREVIR**
  - **RTONAVIR** and **TELAPREVIR** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)

**Omeprazol**

- Antifungals: plasma concentration of olaparib possibly increased by 
  - **CLOzapine** (increased risk of agranulocytosis)

**Omeprazol**

- Antivirals: plasma concentration of olaparib possibly increased by 
  - **BOCEPREVIR**
  - **RTONAVIR** and **TELAPREVIR** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)

**Omeprazol**

- Antifungals: plasma concentration of olaparib possibly increased by 
  - **CLOzapine** (increased risk of agranulocytosis)

**Omeprazol**

- Antivirals: plasma concentration of olaparib possibly increased by 
  - **BOCEPREVIR**
  - **RTONAVIR** and **TELAPREVIR** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)

**Omeprazol**

- Antifungals: plasma concentration of olaparib possibly increased by 
  - **CLOzapine** (increased risk of agranulocytosis)

**Omeprazol**

- Antivirals: plasma concentration of olaparib possibly increased by 
  - **BOCEPREVIR**
  - **RTONAVIR** and **TELAPREVIR** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)

**Omeprazol**

- Antifungals: plasma concentration of olaparib possibly increased by 
  - **CLOzapine** (increased risk of agranulocytosis)

**Omeprazol**

- Antivirals: plasma concentration of olaparib possibly increased by 
  - **BOCEPREVIR**
  - **RTONAVIR** and **TELAPREVIR** (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)
A1

Opioid Analgesics

Antifungals:

Antibacterials:

Analgesics

Accelerated by alfentanil, codeine, fentanyl, methadone and morphine; metabolic pathway for increased risk of ventricular arrhythmias when methadone given with delamanid; manufacturer of pethidine advises avoid concomitant use with isoniazid; possible increased risk of ventricular arrhythmias when methadone given with telithromycin; metabolism of oxycodone inhibited by telithromycin.

Anticoagulants: tramadol enhances anticoagulant effect of coumarins.

Antidepressants: plasma concentration of methadone possibly increased by fluoxetine, fluvoxamine, paroxetine and sertraline; possible increased serotonergic effects when pethidine or tramadol given with duloxetine; possible increased serotonergic effects when tramadol given with mirtazapine, venlafaxine or vortioxetine; possible increased serotonergic effects when fentanyl given with MAOIs, SSRI-related antidepressants or SSRIs; possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics with maois; possible CNS excitation or depression (hypertension or hypotension) when tramadol given with maois; possible CNS excitation or depression (hypertension or hypotension) when methadone given with maois, ssris or tricyclics; plasma concentration of methadone possibly reduced by st john’s wort; sedative effects possibly increased when opioid analgesics given with tricyclics.

Antiepileptics: dextropropoxyphene enhances effects of carbamazepine; effects of tramadol reduced by carbamazepine; plasma concentration of methadone reduced by carbamazepine, phenobarbital and primidone; metabolism of fentanyl possibly accelerated by carbamazepine, fosphenytoin and phenytoin (reduced effect); metabolism of methadone accelerated by fosphenytoin and phenytoin (reduced effect and risk of withdrawal effects); possible increased risk of pethidine toxicity when given with fosphenytoin and phenytoin; morphine increases bioavailability of gabapentin.

Antifungals: metabolism of buprenorphine inhibited by ketoconazole, fluconazole and voriconazole; metabolism of alfentanil inhibited by fluconazole; risk of prolonged or delayed respiratory depression; plasma concentration of methadone increased by fluconazole; metabolism of alfentanil possibly inhibited by itraconazole; plasma concentration of methadone possibly increased by itraconazole (increased risk of ventricular arrhythmias); plasma concentration of alfentanil and methadone increased by voriconazole (consider reducing dose of alfentanil and methadone); plasma concentration of fentanyl possibly increased by triazoles.

Antihistamines: sedative effects possibly increased when opioid analgesics given with sedating antihistamines.

Opioid Analgesics (continued)

Antimarial: avoidance of methadone advised by manufacturer of artemirol with piperaquine (possible risk of ventricular arrhythmias).

Antimuscarinics: possible increased risk of antimuscarinic side-effects when codeine given with antimuscarinics.

Antipsyhotics: enhanced hypnotic and sedative effects when opioid analgesics with antipsyhotics; increased risk of ventricular arrhythmias when methadone given with antipsyhotics that prolong the QT interval; increased risk of convulsions when tramadol given with antipsyhotics; increased risk of ventricular arrhythmias when methadone given with amisulpride—avoid concomitant use.

Antivirals: plasma concentration of methadone possibly reduced by abacavir, nevirapine and rilpivirine; plasma concentration of buprenorphine increased by atazanavir; possible increased risk of prolonged sedation and respiratory depression when buprenorphine given with boceprevir; plasma concentration of methadone possibly affected by boceprevir; methadone possibly reduces plasma concentration of didanosine; plasma concentration of methadone reduced by efavirenz, fosamprenavir and ritonavir; plasma concentration of dextropropoxyphene increased by ritonavir (risk of toxicity)—avoid concomitant use; plasma concentration of buprenorphine possibly increased by ritonavir; plasma concentration of alfentanil and fentanyl increased by ritonavir; plasma concentration of pethidine reduced by ritonavir, but plasma concentration of toxic pethidine metabolite increased (avoid concomitant use); plasma concentration of morphine possibly reduced by ritonavir; increased risk of ventricular arrhythmias when methadone given with ritonavir; possible increased risk of prolonged sedation when tramadol given with ritonavir.

Anxiolytics and Hypnotics: increased sedative effect when opioid analgesics given with anxiolytics and hypnotics; fentanyl possibly inhibits metabolism of midazolam.

Antihistaminics: increased risk of ventricular arrhythmias when methadone given with atenolol; possible increased risk of convulsions when tramadol given with atenolol; beta-blockers: morphine possibly increases plasma concentration of esmolol.

Calcium-channel Blockers: metabolism of alfentanil inhibited by diltiazem (risk of prolonged or delayed respiratory depression).

Cytotoxics: possible increased risk of ventricular arrhythmias when methadone given with bosutinib and ceritinib; avoidance of alfentanil and fentanyl advised by manufacturer of ceritinib; caution with alfentanil and fentanyl advised by manufacturer of crizotinib; possible increased risk of ventricular arrhythmias when methadone given with vanetanib—avoid concomitant use.

Dapoxetine: possible increased risk of serotoninergic effects when tramadold given with dapoxetine (manufacturer of dapoxetine advises tramadol should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol).

Domperidone: opioid analgesics antagonise effects of domperidone on gastro-intestinal activity.

Dopaminergic: risk of CNS toxicity when pethidine given with rasagiline (avoid pethidine for 2 weeks after rasagiline); avoid concomitant use of dextromethorphan with rasagiline.

Hyperpyrexia and CNS toxicity reported when pethidine given with selegiline (avoid selegiline; possible increased risk of ventricular arrhythmias; plasma concentration of alfentanil and methadone increased by voriconazole (consider reducing dose of alfentanil and methadone); plasma concentration of fentanyl possibly increased by triazoles.

Hormone Antagonists: plasma concentration of dextromethorphan increased by abiraterone.

SERT inhibitors: effects of tramadol possibly antagonised by ondansetron.

Memantine: increased risk of CNS toxicity when dextromethorphan given with memantine (manufacturer of memantine advises avoid concomitant use).

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Opioid Analgesics (continued)

- Metoclopramide: opioid analgesics antagonise effects of METOCLOPRAMIDE on gastrointestinal activity
- Muscle Relaxants: increased sedative effect when fentanyl or morphine given with BACLOFEN
- Nalmefene: avoidance of opioid analgesics advised by manufacturer of NALMEFENE
- Netuptatin: caution with morphine advised by manufacturer of NETUPITATIN
- Panobinostat: avoidance of dextromethorphan advised by manufacturer of PANOBINOSTAT; possible increased risk of ventricular arrhythmias when methadone given with PANOBINOSTAT—avoid concomitant use
- Sodium Oxybate: opioid analgesics enhance effects of SODIUM OXYBATE (avoid concomitant use)
- Ulcer-healing Drugs: metabolism of opioid analgesics inhibited by CIMETIDINE (increased plasma concentration)

Oritavancin

- Anticoagulants: oritavancin possibly increases plasma concentration of WARFARIN
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Orlistat

- Anti-arhythmics: orlistat possibly reduces plasma concentration of AMIODARONE
- Anticoagulants: manufacturer of orlistat recommends monitoring anticoagulant effect of COUMARINS
- Antidiabetics: manufacturer of orlistat advises avoid concomitant use with ACCARBOSAN
- Antiepileptics: possible increased risk of convulsions when orlistat given with ANTIEPILEPTICS
- Antivirals: orlistat possibly reduces absorption of ABACAVIR, ATAZANAVIR, DARUNAVIR, DIDANOSINE, EFAVIRENZ, ELVITEGRAVIR, EMTRICITABINE, ENFUVIRTIDE, ETATIRINE, FOSAMPRENRAVIR, INDINAVIR, LAMIVUDINE, LOPINAVIR, MARAVIROC, NEVIRAPINE, RALTEGRAVIR, RILPVIRINE, RITONAVIR, SQUAUVINAVIR, STAVUDINE, TENOFOVIR, TIPRANAVIR and ZIDOVUDINE
- Ciclosporin: orlistat possibly reduces absorption of CICLOSPORIN
- Thyroid Hormones: possible increased risk of hypothyroidism when orlistat given with LEVOTHYROXINE

Orphenadrine see Antimuscarinics

Oxaliplatin see Platinum Compounds

Oxandrolone see Anabolic Steroids

Oxazepam see Anxiolytics and Hypnotics

Oxcarbazepine

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRI and TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: oxcarbazepine sometimes reduces plasma concentration of CARBAMAZEPINE (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; avoidance of oxcarbazepine advised by manufacturer of ESLICARBAZEPINE; oxcarbazepine increases plasma concentration of FOSPHENTOIN, PHENOBARBITAL, PHENTYOIN and PRIMIDONE, also plasma concentration of an active metabolite of oxcarbazepine reduced; oxcarbazepine reduces plasma concentration of PERAMPANEL, also plasma concentration of oxcarbazepine increased (see under Perampanel, p. 301); plasma concentration of an active metabolite of oxcarbazepine sometimes reduced by SODIUM VALPROATE and VALPROIC ACID
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by MEFLOQUINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ANTIPSYCHOTICS (convulsive threshold lowered)
- Antivirals: oxcarbazepine possibly reduces plasma concentration of DAJALATASVIR and SIMEPREVIR—manufacturer of daclatasvir and simprevir advises avoid concomitant use; oxcarbazepine possibly reduces the plasma concentration of DULOTEGRAVIR (see under Dolutegavir, oxcarbazepine possibly reduces plasma concentration of CICLOSPORIN
- Clopidogrel: oxcarbazepine possibly reduces antiplatelet effect of CLOPIDOGREL
- Cytotoxics: oxcarbazepine reduces plasma concentration of IMATINIB—avoid concomitant use
- Guanfacine: oxcarbazepine possibly reduces plasma concentration of GUANFACINE—increase dose of guanfacine
- Oestrogens: oxcarbazepine accelerates metabolism of OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ORLISTAT
- Progestogens: oxcarbazepine accelerates metabolism of PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)
- Oxbreitol see Beta-blockers

Oxbutymin see Antimuscarinics

Oxycodone see Opioid Analgesics

Oxymetazoline see Sympathomimetics

Oxytetracycline see Tetracyclines

Oxytocin

- Anaesthetics: General: oxytocic effect possibly reduced, also enhanced hypotensive effect and risk of arrhythmias when oxytocin given with VOLATILE LIQUID GENERAL ANAESTHETICS
- Prostaglandins: uterotonic effect of oxytocin potentiated by PROSTAGLANDINS
- Sympathomimetics: risk of hypertension when oxytocin given with vasconstrictor SYMPATHOMIMETICS (due to enhanced vasopressor effect)

Palitaxel

- Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)
- Antivirals: plasma concentration of paclitaxel increased by RITONAVIR
- Cytotoxics: increased risk of neutropenia when paclitaxel given with LAPATINIB

Paliperidone see Antipsychotics

Palonosetron see 5HT3-receptor Antagonists (under HT)

Pamidronate Disodium see Bisphosphonates

Pancreatin

- Antidiabetics: pancreatin antagonises hypoglycaemic effect of ACARBOSE

Pancuronium see Muscle Relaxants

Panitumumab

- Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)
- Cytotoxics: manufacturer of panitumumab advises avoid concomitant use with BEVACIZUMAB, FLUOROURACIL, IRINOTECAN and OXALIPLATIN
- Folates: manufacturer of panitumumab advises avoid concomitant use with FOLIC ACID
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

Panobinostat

- Antipsychotics: manufacturer of panobinostat advises avoid concomitant use with DEXTROMETHORPHAN; possible increased risk of ventricular arrhythmias when panobinostat given with METHADONE—avoid concomitant use
- Anti-arhythmics: possible increased risk of ventricular arrhythmias when panobinostat given with AMIODARONE or DISOPYRAMIDE—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when panobinostat given with CLARITHROMYCIN—avoid concomitant use; possible increased risk of ventricular arrhythmias when panobinostat given with MOXIFLOXACIN—
Panobinostat
- Antibacterials (continued)
  avoid concomitant use; manufacturer of panobinostat advises avoid concomitant use with • Rifabutin and • Rifampicin
  plasma concentration of panobinostat possibly increased by • Telithromycin (reduce dose of panobinostat—see under Panobinostat, p. 834)
- Antidepressants: manufacturer of panobinostat advises avoid concomitant use with • St John’s Wort
- Antiepileptics: manufacturer of panobinostat advises avoid concomitant use with • Carbamazepine, • fosphenytoin, • Phenobarbital, • phenytoin and • Primidone
- Antifungals: plasma concentration of panobinostat increased by • Ketoconazole (reduce dose of panobinostat—see under Panobinostat, p. 834); plasma concentration of panobinostat possibly increased by • Itraconazole, • Posaconazole and • Voriconazole (reduce dose of panobinostat—see under Panobinostat, p. 834)
- Antimalarials: possible increased risk of ventricular arrhythmias when panobinostat given with • Chloroquine—avoid concomitant use
- Antipsychotics: possible increased risk of ventricular arrhythmias when panobinostat given with • Pimozide—avoid concomitant use
- Antivirals: plasma concentration of panobinostat possibly increased by • Ritonavir and • Saquinavir (reduce dose of panobinostat—see under Panobinostat, p. 834)
- Beta-blockers: possible increased risk of ventricular arrhythmias when panobinostat given with • Sotalol—avoid concomitant use
- Corticosteroids: plasma concentration of panobinostat reduced by • Dexamethasone
- Grapefruit Juice: manufacturer of panobinostat advises avoid concomitant use with • Grapefruit Juice
- SHT₂-receptor Antagonists: possible increased risk of ventricular arrhythmias when panobinostat given with • Granisetron and • Ondansetron
Panotrazole see Proton Pump Inhibitors
Paracetamol
- Anticoagulants: prolonged regular use of paracetamol possibly enhances anticoagulant effect of • Coumarins
- Antidiabetics: absorption of paracetamol possibly reduced when given 1 to 4 hours after • Lixisenatide
- Antiepileptics: metabolism of paracetamol possibly accelerated by • Carbamazepine, • fosphenytoin, • Phenobarbital, • Phenytoin and • Primidone (also isolated reports of hepatotoxicity)
- Antifungals: avoidance of paracetamol advised by manufacturer of • Ketoconazole
- Cytoxics: paracetamol possibly inhibits metabolism of • intravenous Busulfan (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol); caution with paracetamol advised by manufacturer of • Imatinib
- Lipid-regulating Drugs: absorption of paracetamol reduced by • Colestyramine
- Metoclopramide: rate of absorption of paracetamol increased by • Metoclopramide
Paraldehyde
- Alcohol: increased sedative effect when paraldehyde given with • Alcohol
- Disulfiram: risk of toxicity when paraldehyde given with • Disulfiram
Parasymphathomimetics
- Anti-arrhythmics: effects of neostigmine and pyridostigmine possibly antagonised by • Propafenone
- Antibacterials: plasma concentration of galantamine increased by • Erythromycin; effects of neostigmine and pyridostigmine antagonised by • Aminoglycosides; effects of neostigmine and pyridostigmine antagonised by • Clindamycin; effects of neostigmine and pyridostigmine antagonised by • Polymyxins
- Antidepressants: plasma concentration of galantamine increased by • Paroxetine
- Antifungals: plasma concentration of galantamine increased by • Ketoconazole
- Antimalarials: effects of neostigmine and pyridostigmine may be diminished because of potential for • Chloroquine to
Pazopanib
- Antibacterials: plasma concentration of pazopanib possibly increased by clarithromycin and telithromycin (reduce dose of pazopanib); plasma concentration of pazopanib possibly reduced by rifampicin.
- Antifungals: plasma concentration of pazopanib increased by ketoconazole (reduce dose of pazopanib); plasma concentration of pazopanib possibly increased byitraconazole and voriconazole (reduce dose of pazopanib).
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).
- Antivirals: plasma concentration of pazopanib possibly increased by atazanavir, indinavir and ritonavir (reduce dose of pazopanib); avoidance of pazopanib advised by manufacturer of boceprevir; increased risk of ventricular arrhythmias when pazopanib given with saquinavir—avoid concomitant use.
- Cytotoxics: plasma concentration of pazopanib increased by lapatinib.
- Grapefruit Juice: manufacturer of pazopanib advises avoid concomitant use with grapefruit juice.
- Lipid-regulating Drugs: separating administration from pazopanib by 12 hours advised by manufacturer of lomitapide.
- Ulcer-healing Drugs: absorption of pazopanib possibly reduced by histamine H2-antagonists—manufacturer of pazopanib advises give at least 2 hours before or 10 hours after histamine H2-antagonists; absorption of pazopanib possibly reduced by proton pump inhibitors—manufacturer of pazopanib advises give at the same time as proton pump inhibitors.

Pegfilgrastim
- Cytotoxics: neutropenia possibly exacerbated when pegfilgrastim given with capetitabine, fluorouracil or tegafur.

 Peginterferon Alfa see Interferons

Pembrolizumab
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).
- Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use.

Pemetrexed
- Analgesics: renal excretion of pemetrexed possibly reduced by NSAIDs and aspirin—consult product literature.
- Antimalarials: antagonise effect of pemetrexed increased by pyrimethamine.
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).

Penicillamine
- Analgesics: possible increased risk of nephrotoxicity when penicillamine given with NSAIDs.
- Antacids: absorption of penicillamine reduced by antacids.
- Antimalarials: increased risk of haematological toxicity when penicillamine given with antimalarials—manufacturer of penicillamine advises avoid concomitant use.
- Antipsychotics: increased risk of haematological toxicity when penicillamine given with clozapine—manufacturer of penicillamine advises avoid concomitant use.
- Cardiac Glycosides: penicillamine possibly reduces plasma concentration of digoxin.
- Iron Salts: absorption of penicillamine reduced by oral iron salts.

Penicillamine (continued)
- Sodium Aurothiomalate: increased risk of haematological toxicity when penicillamine given with sodium aurothiomalate—see under Penicillamine, p. 964.
- Zinc: penicillamine reduces absorption of zinc, also absorption of penicillamine reduced by zinc.

Penicillins
- Allopurinol: increased risk of rash when amoxicillin, ampicillin or co-amoxiclav given with allopurinol.
- Antibacterials: absorption of phenoxymethylpenicillin reduced by neomycin; effects of penicillins possibly antagonised by tetracyclines.
- Anticoagulants: an interaction between broad-spectrum penicillins and coumarins and phenindione has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered.
- Antiepileptics: manufacturer of pivmecillinam advises avoid concomitant use with sodium valproate and valproic acid.
- Cytotoxics: penicillins reduce excretion of methotrexate (increased risk of toxicity).
- Muscle Relaxants: piperacillin enhances effects of non-depolarising muscle relaxants and suxamethonium.
- Mycophenolate: co-amoxiclav possibly reduces plasma concentration of mycophenolate.
- Sulfinpyrazone: excretion of penicillins reduced by sulfinpyrazone.
- Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF or BNFC.

Pentamidine isetionate
- Anti-arrhythmics: increased risk of ventricular arrhythmias when pentamidine isetionate given with amiodarone—avoid concomitant use; possible increased risk of ventricular arrhythmias when pentamidine isetionate given with disopyramide.
- Antibacterials: increased risk of ventricular arrhythmias when pentamidine isetionate given with parenteral erythromycin; increased risk of ventricular arrhythmias when pentamidine isetionate given with moxifloxacin—avoid concomitant use; increased risk of ventricular arrhythmias when pentamidine isetionate given with delamanid; possible increased risk of ventricular arrhythmias when parenteral pentamidine isetionate given with telithromycin.
- Antidepressants: avoidance of pentamidine isetionate advised by manufacturer of citalopram and escitalopram (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when pentamidine isetionate given with tricyclics.
- Antifungals: possible increased risk of nephrotoxicity when pentamidine isetionate given with amphotericin.
- Antimalarials: avoidance of pentamidine isetionate advised by manufacturer of arteminol with piperacillin (possible risk of ventricular arrhythmias).
- Antipsychotics: increased risk of ventricular arrhythmias when pentamidine isetionate given with droperidol—avoid concomitant use; increased risk of ventricular arrhythmias when pentamidine isetionate given with phenothiazines.
- Antivirals: increased risk of hypocalcaemia when parenteral pentamidine isetionate given with foscarin; increased risk of ventricular arrhythmias when pentamidine isetionate given with saquinavir—avoid concomitant use.
- Cytotoxics: possible increased risk of ventricular arrhythmias when pentamidine isetionate given with vanetanib—avoid concomitant use.
- Ibavradine: increased risk of ventricular arrhythmias when pentamidine isetionate given with ibavradine.

Pentazocine see Opioid Analgesics

Pentostatin
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).
- Cytotoxics: increased toxicity when pentostatin given with high-dose cyclophosphamide—avoid concomitant use; increased pulmonary toxicity when pentostatin given with fluorouracil (unacceptably high incidence of fatalities).
Phenindione (continued)

- Anti-arrhythmics: metabolism of phenindione inhibited by
  - AMIODARONE (enhanced anticoagulant effect); anticoagulant effect of phenindione possibly enhanced by
  \* DRONEDARONE (enhanced anticoagulant effect)
- Antibacterials: experience in anticoagulant clinics suggests that INR possibly altered when phenindione is given with
  - NEOMYCIN (given for local action on gut); anticoagulant effect of phenindione possibly enhanced by
  - LEVOFLOXACIN and TETRACYCLINES; an interaction between phenindione and broad-spectrum PENICILLINS has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered; metabolism of phenindione possibly inhibited by
  \* SULFONAMIDES
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with
  - APIXABAN, \* DABIGATRAN,
  - EDOXABAN and \* RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antivirals: anticoagulant effect of phenindione possibly enhanced by
  \* RITONAVIR
- Clopidogrel: anticoagulant effect of phenindione enhanced due to antiplatelet action of
  \* CLOPIDOGREL
- Corticosteroids: anticoagulant effect of phenindione may be enhanced or reduced by
  \* CORTICOSTEROIDS
- Cytoxics: avoidance of phenindione advised by manufacturer of
  \* IBRUTINIB
- Dipyrindamole: anticoagulant effect of phenindione enhanced due to antiplatelet action of
  \* DIPYRIDAMOLE
- Enteral Feeds: anticoagulant effect of phenindione antagonised by vitamin K (present in some \* ENTERAL FEEDS)
- Iloprost: increased risk of bleeding when phenindione given with
  - ILOPROST
- Lipid-regulating Drugs: anticoagulant effect of phenindione may be enhanced or reduced by
  - COLESTYRAMINE;
  - anticoagulant effect of phenindione possibly enhanced by
  - ROSUVASTATIN;
  - anticoagulant effect of phenindione enhanced by
  - FIBRATES
- Oestrogens: anticoagulant effect of phenindione antagonised by
  \* OESTROGENS
- Prasugrel: possible increased risk of bleeding when phenindione given with
  - PRASUGREL
- Progestogens: anticoagulant effect of phenindione antagonised by
  - PROGESTOGENS
- Testolactone: anticoagulant effect of phenindione enhanced by
  - TESTOLACTONE
- Testosterone: anticoagulant effect of phenindione enhanced by
  - TESTOSTERONE
- Thyroid Hormones: anticoagulant effect of phenindione enhanced by
  - THYROID HORMONES
- Vitamins: anticoagulant effect of phenindione antagonised by
  - VITAMIN K

Phenobarbital

- Alcohol: increased sedative effect when phenobarbital given with
  - ALCOHOL
- Aminophylline: phenobarbital accelerates metabolism of
  - AMINOPHYLLINE (reduced effect)
- Analgesics: phenobarbital reduces plasma concentration of
  - METHADONE; phenobarbital possibly accelerates metabolism of
  - PARACETAMOL (also isolated reports of hepatotoxicity)
- Anthelmintics: phenobarbital reduces plasma concentration of
  - ALBENDAZOLE and \* PRAZIQUANTEL—consider increasing albendazole and praziquantel dose when given for systemic infections
- Anti-arrhythmics: phenobarbital accelerates metabolism of
  - DISOPRIMIDE (reduced plasma concentration); phenobarbital possibly reduces plasma concentration of
  - DRONEDARONE—avoid concomitant use; phenobarbital possibly accelerates metabolism of
  - PROPAFENONE
- Antibacterials: phenobarbital accelerates metabolism of
  - METRONIDAZOLE (reduced effect); phenobarbital possibly reduces plasma concentration of
  - RIFAMPICIN; phenobarbital accelerates metabolism of
  - DISOPRIMIDE (reduced plasma concentration); phenobarbital possibly accelerates metabolism of
  - CHLORAMPHENICOL (reduced plasma concentration); phenobarbital reduces plasma concentration
Phenobarbital
- Antibacterials (continued)
  - Telithromycin (avoid during and for 2 weeks after phenobarbital)
- Anticoagulants: phenobarbital possibly reduces plasma concentration of apixaban and edoxaban; phenobarbital accelerates metabolism of coumarins (reduced anticoagulant effect); phenobarbital possibly reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antidepressants: phenobarbital possibly reduces plasma concentration of reboxetine; phenobarbital reduces plasma concentration of paroxetine; phenobarbital accelerates metabolism of mianserin (reduced plasma concentration); antidepressant effect of antiepileptics possibly antagonised by maoi and tricyclic-related antidepressants (convulsive threshold lowered); antidepressant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered); plasma concentration of phenobarbital possibly reduced by st john's wort—avoid concomitant use; phenobarbital possibly accelerates metabolism of tricyclics (reduced plasma concentration)
- Antiepileptics: phenobarbital reduces plasma concentration of brivaracetam, lamotrigine, tiagabine and zonisamide; plasma concentration of phenobarbital possibly increased by carbamazepine; phenobarbital possibly reduces plasma concentration of ethosuximide, rufinamide and topiramate; plasma concentration of phenobarbital often increased by fosphenytoin and phenytoin, plasma concentration of fosphenytoin and phenytoin often reduced but may be increased; plasma concentration of phenobarbital increased by oxcarbazepine, also plasma concentration of an active metabolite of oxcarbazepine reduced; plasma concentration of phenobarbital increased by sodium valproate and valproic acid (also plasma concentration of sodium valproate and valproic acid reduced); plasma concentration of phenobarbital increased by stiripentol
- Antifungals: phenobarbital possibly reduces plasma concentration of isavuconazole and voriconazole—avoid concomitant use; phenobarbital possibly reduces plasma concentration of itraconazole and posaconazole; phenobarbital reduces absorption of griseofulvin (reduced effect)
- Antiinfectials: avoidance of phenobarbital advised by manufacturer of artemisinin with piperaquine; anticonvulsant effect of antiepileptics antagonised by mefloquine
- Antimucosinics: phenobarbital possibly reduces plasma concentration of active metabolite of fosoterodine—manufacturer of fosoterodine advises avoid concomitant use
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered); phenobarbital accelerates metabolism of haloperidol (reduced plasma concentration); plasma concentration of both drugs reduced when phenobarbital given with chlorpromazine; phenobarbital possibly reduces plasma concentration of aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenobarbital possibly reduces plasma concentration of clozapine; phenobarbital possibly reduces plasma concentration of lurasidone—avoid concomitant use
- Antivirals: phenobarbital possibly reduces plasma concentration of abacavir, darunavir, fosamprenavir, indinavir, lopinavir and saquinavir; avoidance of phenobarbital advised by manufacturer of boceprevir and rilpivirine (plasma concentration of boceprevir and rilpivirine possibly reduced); phenobarbital possibly reduces plasma concentration of daclatasvir and simeprevir—manufacturer of daclatasvir and simeprevir advises avoid concomitant use; phenobarbital possibly reduces plasma concentration of dasabuvir, ombitasvir and paritaprevir—avoid concomitant use; phenobarbital possibly reduces the plasma concentration of dolutegravir (see under dolutegravir, p. 592); avoidance of phenobarbital advised by manufacturer of elvitegravir, etravirine, ledipasvir, sofosbuvir and telaprevir

Phenobarbital (continued)
- Anxiolytics and Hypnotics: increased sedative effect when phenobarbital given with anxiolytics and hypnotics; phenobarbital often reduces plasma concentration of clozapine
- Apremilast: phenobarbital possibly reduces plasma concentration of apremilast—avoid concomitant use
- Aprepitant: phenobarbital possibly reduces plasma concentration of aprepitant
- Avanafil: phenobarbital possibly reduces plasma concentration of avanafil—manufacturer of avanafil advises avoid concomitant use
- Beta-blockers: phenobarbital possibly reduces plasma concentration of propranolol
- Bile Acids: avoidance of phenobarbital advised by manufacturer of cholic acid
- Caffeine citrate: effects of phenobarbital possibly antagonised by caffeïne citrate
- Calcium-channel Blockers: phenobarbital probably reduces effects of calcium-channel blockers; avoidance of phenobarbital advised by manufacturer of nimodipine (plasma concentration of nimodipine reduced)
- Cannabis Extract: phenobarbital possibly reduces plasma concentration of cannabis extract—manufacturer of cannabis extract advises avoid concomitant use
- Ciclosporin: phenobarbital accelerates metabolism of ciclosporin
- Cobimetinib: phenobarbital possibly reduces plasma concentration of cobimetinib—manufacturer of cobimetinib advises avoid concomitant use
- Corticosteroids: phenobarbital accelerates metabolism of corticosteroids (reduced effect)
- Cytotoxics: phenobarbital possibly decreases plasma concentration of axitinib (increase dose of axitinib—consult axitinib product literature); phenobarbital possibly reduces plasma concentration of bortezomib, bosutinib, crizotinib and ponatinib advises avoid concomitant use; phenobarbital possibly reduces plasma concentration of cabozantinib and ceritinib—avoid concomitant use; avoidance of phenobarbital advised by manufacturer of cabazitaxel, dabrafenib, gefitinib and olaparib; avoidance of phenobarbital advised by manufacturer of dasatinib and vandetanib (plasma concentration of dasatinib and vandetanib possibly reduced); phenobarbital possibly reduces plasma concentration of etoposide; phenobarbital reduces plasma concentration of irinotecan and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when phenobarbital given with procarbazine
- Diuretics: phenobarbital reduces plasma concentration of eplerenone—avoid concomitant use; increased risk of osteomalacia when phenobarbital given with carbonic anhydrase inhibitors
- Folates: plasma concentration of phenobarbital possibly reduced by folates
- Fosaprepitant: phenobarbital possibly reduces plasma concentration of fosaprepitant
- Guanfacine: phenobarbital possibly reduces plasma concentration of guanfacine
- Hormone Antagonists: phenobarbital possibly reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; phenobarbital accelerates metabolism of toremifene (reduced plasma concentration)
- Ircavatof: phenobarbital possibly reduces plasma concentration of iravatof—manufacturer of iravatof advises avoid concomitant use
- Leukotriene Receptor Antagonists: phenobarbital reduces plasma concentration of montelukast
- Lumeacof: plasma concentration of phenobarbital possibly reduced by lumeacof—manufacturer of lumeacof advises avoid concomitant use
- Oestrogens: phenobarbital accelerates metabolism of oestrogens (reduced contraceptive effect with combined
Phenobarbital

- Progestogens: phenobarbital accelerates metabolism of progestogens (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)
- Roflumilast: phenobarbital possibly inhibits effects of roflumilast (manufacturer of roflumilast advises avoid concomitant use)
- Sodium Oxybate: avoidance of phenobarbital advised by manufacturer of sodium oxybate

Phenytoin

- Alcohol: plasma concentration of phenytoin possibly reduced by chronic heavy consumption of alcohol
- Aminophylline: plasma concentration of both drugs reduced when phenytoin given with aminophylline
- Analgesics: excretion of phenytoin possibly reduced by acetaminophen (increased risk of toxicity); phenytoin possibly accelerates metabolism of fenoprofen (reduced effect); phenytoin accelerates metabolism of methadone (reduced effect and risk of withdrawal effects); phenytoin possibly increases risk of pethidine toxicity; effects of phenytoin enhanced by aspirin; phenytoin possibly accelerates metabolism of paracetamol (also isolated reports of hepatotoxicity)
- Antacids: absorption of phenytoin reduced by antacids
- Antihelminths: phenytoin reduces plasma concentration of albendazole and praziquantel—consider increasing albendazole and praziquantel dose when given for systemic infections; plasma concentration of phenytoin possibly increased by levamisole
- Anti-arrhythmics: metabolism of phenytoin inhibited by amiodarone (increased plasma concentration); phenytoin reduces plasma concentration of disopyramide; phenytoin possibly reduces plasma concentration of dronedarone—avoid concomitant use
- Antibacterials: metabolism of phenytoin inhibited by clarithromycin (increased plasma concentration); metabolism of phenytoin possibly inhibited by metronidazole (increased plasma concentration); plasma concentration of phenytoin increased or decreased by ciprofloxacin; phenytoin accelerates metabolism of doxycycline (reduced plasma concentration); phenytoin possibly reduces plasma concentration of bedaquiline—manufacturer of bedaquiline advises avoid concomitant use;
Phenytoin

- Antifungals (continued)
  concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity); phenytoin possibly reduces plasma concentration of caspofungin—consider increasing dose of caspofungin

- Antimalarials: avoidance of phenytoin advised by manufacturer of arteninol with piperaquine; anticonvulsant effect of antipilippines antagonised by méfloquine; anticonvulsant effect of phenytoin antagonised by pyrimethamine, also increased antifolate effect

- Antimuscarnics: phenytoin possibly reduces plasma concentration of active metabolite of fosoterodine—manufacturer of fosoterodine advises avoid concomitant use

- Antipsychotics: anticonvulsant effect of antipilippines antagonised by antipsychotics (convulsive threshold lowered); phenytoin reduces plasma concentration of haloperidol; plasma concentration of phenytoin possibly increased or decreased by chlorpromazine; phenytoin possibly reduces plasma concentration of aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenytoin accelerates metabolism of clozapine and quetiapine (reduced plasma concentration); phenytoin possibly reduces plasma concentration of lurasidone—avoid concomitant use

- Antivirals: phenytoin possibly reduces plasma concentration of abacavir, darunavir, lopinavir and saquinavir; avoidance of phenytoin advised by manufacturer of boceprevir and rilpivirine (plasma concentration of boceprevir and rilpivirine possibly reduced); phenytoin possibly reduces plasma concentration of aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenytoin possibly reduces plasma concentration of dapsuburiv and omibitasvir and paritaprevir—avoid concomitant use; phenytoin possibly reduces the plasma concentration of dolugreatriv (see under Dolugreatriv, p. 592); avoidance of phenytoin advised by manufacturer of elvitegravir, etravirine, ledipasvir, sofosbuvir and telaprevir; phenytoin possibly reduces plasma concentration of indinavir; also plasma concentration of phenytoin possibly increased; phenytoin possibly reduces plasma concentration of ritonavir; also plasma concentration of phenytoin possibly affected; plasma concentration of phenytoin increased or decreased by zidovudine

- Anxiolytics and Hypnotics: phenytoin often reduces plasma concentration of clonazepam; plasma concentration of phenytoin increased or decreased by diazepam; plasma concentration of phenytoin possibly increased or decreased by benzodiazepines

- Apremilast: phenytoin possibly reduces plasma concentration of apremilast—avoid concomitant use

- Aprepitant: phenytoin possibly reduces plasma concentration of aprepitant

- Buspropan: phenytoin reduces plasma concentration of buproprion

- Caffeine citrate: phenytoin reduces plasma concentration of caffeine citrate

- Calcium-channel Blockers: phenytoin reduces effects of felodipine and verapamil; avoidance of phenytoin advised by manufacturer of isradipine; avoidance of phenytoin advised by manufacturer of nimodipine (plasma concentration of nimodipine possibly reduced); plasma concentration of phenytoin increased by diltiazem but also effect of diltiazem reduced

- Cannabin Extract: phenytoin possibly reduces plasma concentration of cannabis extract—manufacturer of cannabis extract advises avoid concomitant use

- Cardiac Glycosides: phenytoin possibly reduces plasma concentration of digoxin

- Ciclosporin: phenytoin accelerates metabolism of ciclosporin (reduced plasma concentration)

- Cobicistat: phenytoin possibly reduces plasma concentration of cobicistat—manufacturer of cobicistat advises avoid concomitant use

- Corticosteroids: phenytoin accelerates metabolism of corticosteroids (reduced effect)

- Cytotoxics: phenytoin possibly reduces plasma concentration of doxorubicin, etoposide and oxaliplatin; metabolism of phenytoin possibly inhibited by capetitabine, fluorouracil and tegafur (increased risk of toxicity); phenytoin increases antifolate effect of methotrexate; plasma concentration of phenytoin possibly reduced by cisplatin; phenytoin possibly decreases plasma concentration of axitinib (increase dose of axitinib—consult axitinib product literature); phenytoin possibly reduces plasma concentration of cabazitaxel, dabrafenib, gefitinib, lapatinib, olaparib and vemurafenib; avoidance of phenytoin advised by manufacturer of dasatinib and vismodegib (plasma concentration of dasatinib and vismodegib possibly reduced); phenytoin reduces plasma concentration of imatinib—avoid concomitant use; phenytoin possibly reduces plasma concentration of irinotecan and its active metabolite; manufacturer of procrazone advises possible increased risk of hypersensitivity reactions when phenytoin given with procrazone

- Dexamethasone: absorption of phenytoin possibly reduced by dexamethasone

- Diazoxide: plasma concentration of phenytoin reduced by diazoxide, also effect of diazoxide may be reduced

- Disulfiram: metabolism of phenytoin inhibited by disulfiram (increased risk of toxicity)

- Diuretics: phenytoin reduces plasma concentration of eplerenone—avoid concomitant use; plasma concentration of phenytoin possibly increased by acetazolamide; phenytoin antagonises effects of furosemide; increased risk of osteomalacia when phenytoin given with carbonic anhydrase inhibitors

- Dopaminergics: phenytoin possibly reduces effects of co-beneldopa, co-careldopa and levodopa

- Enteral Feeds: absorption of phenytoin possibly reduced by enteral feeds

- Folic acids: plasma concentration of phenytoin possibly reduced by folates

- Fosaprepitant: phenytoin possibly reduces plasma concentration of fosaprepitant

- Guanfacine: phenytoin possibly reduces plasma concentration of guanfacine—increased dose of guanfacine

- Hormone Antagonists: phenytoin possibly reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; phenytoin possibly accelerates metabolism of toremifene

- HIs1-receptor Antagonists: phenytoin accelerates metabolism of ondansetron (reduced effect)

- Ibravafon: phenytoin possibly reduces plasma concentration of ibravafon—manufacturer of ibravafon advises avoid concomitant use

- Leflunomide: plasma concentration of phenytoin possibly increased by leflunomide

- Lipid-regulating Drugs: absorption of phenytoin possibly reduced by colesevelam; combination of phenytoin with fluvastatin may increase plasma concentration of either drug (or both)

- Lithium: neurotoxicity may occur when phenytoin given with lithium without increased plasma concentration of lithium

- Lumacaftor: plasma concentration of phenytoin possibly reduced by lumacaftor—manufacturer of lumacaftor advises avoid concomitant use

- Macitentan: avoidance of phenytoin advised by manufacturer of macitentan

- Modafinil: plasma concentration of phenytoin possibly increased by modafinil

- Muscle Relaxants: long-term use of phenytoin reduces effects of non-depolarising muscle relaxants (but acute use of
Phenotin
- Muscle Relaxants (continued)
  phenytoin might increase effects of non-depolarising muscle relaxants)
- Oestrogens: phenytoin accelerates metabolism of
  - OESTROGENS (reduced conjugative effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Orlistat: possible increased risk of convulsions when antiepileptics given with • ORLISTAT
- Panobinostat: avoidance of phenytoin advised by manufacturer of • PANOBINOSTAT
- Progestogens: phenytoin accelerates metabolism of
  - PROGESTOGENS (reduced conjugative effect with combined oral contraceptives, progestogen—only oral contraceptives, contraceptive patches, vaginal rings, eutogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)
- Roflumilast: phenytoin possibly inhibits effects of • ROFLUMILAST (manufacturer of roflumilast advises avoid for concomitant use)
- Sulfinpyrazone: plasma concentration of phenytoin increased by • SULFINPYRAZONE
- Sympathomimetics: plasma concentration of phenytoin increased by • METHYLPHENIDATE
- Tacrolimus: phenytoin reduces plasma concentration of TACROLIMUS, also plasma concentration of phenytoin possibly increased
- Theophylline: plasma concentration of both drugs reduced when phenytoin given with • THEOPHYLLINE
- Thyroid Hormones: phenytoin accelerates metabolism of
  - THYROID HORMONES (may increase requirements in hypothyroidism), also plasma concentration of phenytoin possibly increased
- Tibolone: phenytoin accelerates metabolism of TIBOLONE
- Ticagrelor: phenytoin possibly reduces plasma concentration of • TICAGRELOR
- Ulcer-healing Drugs: metabolism of phenytoin inhibited by
  - CIMETIDINE (increased plasma concentration); effects of phenytoin enhanced by • ESOMEPRAZOLE; effects of phenytoin possibly enhanced by • OMEPRAZOLE; absorption of phenytoin reduced by • Sucralfate
- Ulipristal: avoidance of phenytoin advised by manufacturer of • ULIPRISTAL (contraceptive effect of ulipristal possibly reduced)
- Vaccines: effects of phenytoin enhanced by • INFLUENZA VACCINE
- Vitamin D: phenytoin possibly increases requirements for • D3HYDROTACHYSTEROL, • DIHYDROTACHYSTEROL, • CALCITRIOL
- Phosphodiesterase Type-3 Inhibitors
- Pholcodine
  - Antidepressants: manufacturer of pholcodine advises avoid for 2 weeks after stopping MAOIs
- Phosphodiesterase Type-3 Inhibitors
  • ANAGRELIDE, avoidance of exonoxime and milrinone advised by manufacturer of • ANAGRELIDE
- Pilocarpine see Parasympathomimetics
- Pimozone see Antipsychotics
- Pindolol see Beta-blockers
- Pioglitazone see Antidiabetics
- Piperacillin see Penicillins
- Piperazine see Arsenicals with Piperazine
- Pirfenidone
  - Antibacterials: plasma concentration of pirfenidone increased by • CIPROFLOXACIN—see under Pirfenidone, p. 279
  - Antidepressants: plasma concentration of pirfenidone increased by • FLUOXAMINE—manufacturer of pirfenidone advises avoid concomitant use
  - Grapefruit Juice: manufacturer of pirfenidone advises avoid concomitant use with • GRAPEFRUIT JUICE
- Piroxicam see NSAIDs
- Pivmecillinam see Penicillins
- Pixantrone
  - Antipsychotics: avoid concomitant use of cytoxotics with • CLOZAPINE (increased risk of agranulocytosis)
  - Vaccines: risk of generalised infections when cytoxotic antibiotics given with live • VACCINES—avoid concomitant use

Pizotifen
- Adrenergic Neurone Blockers: pizotifen antagonises hypnotic effect of • ADRENERGIC NEURONE BLOCKERS

Platinum Compounds
- Aldesleukin: avoidance of cisplatin advised by manufacturer of • ALDESLEUKIN
- Antibacterials: increased risk of nephrotoxicity and possibly of ototoxicity when platinum compounds given with
  • AMIONOGLYCOSES or • POLYMIXINS; increased risk of nephrotoxicity and ototoxicity when platinum compounds given with • CAPREOMYCIN; increased risk of nephrotoxicity and possibly of ototoxicity when cisplatin given with • VANCOMYCIN
- Antiepileptics: cisplatin possibly reduces plasma concentration of • FOSPHENYTOIN and • PHENYTOIN
- Antipsychotics: avoid concomitant use of cytoxotics with • CLOZAPINE (increased risk of agranulocytosis)
- Cytoxotics: increased risk of ototoxicity when cisplatin given with • IFOSFAМИNE; increased pulmonary toxicity when cisplatin given with • BLEOMYCIN and • METHOTREXATE; avoidance of oxaliplatin advised by manufacturer of • PANITUMUMAB
- Diuretics: increased risk of nephrotoxicity and ototoxicity when platinum compounds given with • DIURETICS

Pneumococcal Vaccine see Vaccines
Polymyxins
- Antibacterials: increased risk of nephrotoxicity when colistimethate sodium or polymyxins given with • AMIONOGLYCOSES; increased risk of nephrotoxicity when colistimethate sodium or polymyxins given with • CAPREOMYCIN; increased risk of nephrotoxicity when polymyxins given with • VANCOMYCIN; increased risk of nephrotoxicity and ototoxicity when colistimethate sodium given with • VANCOMYCIN
- Antifungals: increased risk of nephrotoxicity when polymyxins given with • AMPHOTERICIN
- Ciclosporin: increased risk of nephrotoxicity when polymyxins given with • CICLOSPORIN
- Cytoxotics: increased risk of nephrotoxicity and possibly of ototoxicity when polymyxins given with • PLATINUM COMPOUNDS
- Diuretics: increased risk of ototoxicity when polymyxins given with • LOOP DIURETICS
- Muscle Relaxants: polymyxins enhance effects of • NON-DEPOLARISING MUSCLE RELAXANTS and • SUXAMETHONIUM
- Parasympathomimetics: polymyxins antagonise effects of • NEOGUSTINE and • PYRIDOSTIGMINE
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Polyoxin
- Antacids: risk of intestinal obstruction when polyoxin sulphate given with • ALUMINIUM HYDROXIDE; risk of metabolic alkalosis when polyoxin sulphate given with • ORAL MAGESISIUM SALTS
- Thyroid Hormones: polyoxin sulphate reduces absorption of • LEVOTHYROXINE

Pomalidomide
- Antidepressants: plasma concentration of pomalidomide increased by • FLUOXAMINE

Ponatinib
- Antibacterials: plasma concentration of ponatinib possibly increased by • CITALIROMYCIN and • TELITROMYCIN—consider reducing initial dose of ponatinib (see under Ponatinib, p. 873); plasma concentration of ponatinib possibly reduced by • RIFABUTIN—manufacturer of ponatinib advises avoid concomitant use; plasma concentration of ponatinib reduced by • RIFAMPICIN—manufacturer of ponatinib advises avoid concomitant use
- Antidepressants: plasma concentration of ponatinib possibly reduced by • ST JOHN'S WORT—manufacturer of ponatinib advises avoid concomitant use
- Antiepileptics: plasma concentration of ponatinib possibly reduced by • CARBAMAZEPINE, • FOSPHENYTOIN, • PHENOBARBITAL, • PHENYTOIN and • PRIMIDONE—manufacturer of ponatinib advises avoid concomitant use
Ponatinib (continued)

- Antifungals: plasma concentration of ponatinib increased by **ketoconazole**; plasma concentration of ponatinib possibly increased by **itraconazole** and **voriconazole**—consider reducing initial dose of ponatinib (see under Ponatinib, p. 875)
- Antipsychotics: avoid concomitant use with **clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of ponatinib possibly increased by **indinavir**, **ritonavir** and **saquinavir**—consider reducing initial dose of ponatinib (see under Ponatinib, p. 875)
- Grapefruit Juice: plasma concentration of ponatinib possibly increased by **grapefruit juice**

Prazosin see Alpha-blockers
Prednisolone see Corticosteroids
Prednison see Corticosteroids
Pregabalin
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TCA REL ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **TCA REL ANTIDEPRESSANTS** (convulsive threshold lowered)
- Antimalarias: anticonvulsant effect of antiepileptics antagonised by **TCA REL ANTIDEPRESSANTS** (convulsive threshold lowered)
- Orlstat: possible increased risk of convulsions when antiepileptics given with **orlistat**

Prilosec
- Anti-arrhythmics: increased myocardial depression when prilosec given with **anti-arrhythmics**
- Antibacterials: increased risk of methaemoglobinemia when prilosec given with **sulfonamides**

Primaquine
- Antimalarias: avoidance of antimalaria advised by manufacturer of **artemether with lumefantrine**
- Histamine: avoidance of antimalaria advised by manufacturer of **histamine**
- Mepacrine: plasma concentration of primaquine increased by **mepacrine** (increased risk of toxicity)
- Penicillamine: increased risk of haematological toxicity when antimalarias given with **penicillamine**—manufacturer of penicillamine advises avoid concomitant use
- Vaccines: antimalarias inactivate **oral typhoid vaccine**—see under Typhoid Vaccine in BNF or BNFC

Primidone
- Alcohol: increased sedative effect when primidone given with **alcohol**
- Aminophylline: primidone accelerates metabolism of **aminophylline** (reduced effect)
- Analgesics: primidone reduces plasma concentration of **methadone**; primidone possibly accelerates metabolism of **paracetamol** (also isolated reports of hepatotoxicity)
- Antihelmintics: primidone reduces plasma concentration of **albendazole** and **praziquantel**—consider increasing albendazole and praziquantel dose when given for systemic infections
- Anti-arrhythmics: primidone accelerates metabolism of **disopyramide** (reduced plasma concentration); primidone possibly reduces plasma concentration of **dronedarone**—avoid concomitant use; primidone possibly accelerates metabolism of **propafenone**
- Antibacterials: primidone accelerates metabolism of **metronidazole** (reduced effect); primidone possibly reduces plasma concentration of **rifampicin**; primidone accelerates metabolism of **doxycycline** (reduced plasma concentration); primidone possibly accelerates metabolism of **chloramphenicol** (reduced plasma concentration); primidone reduces plasma concentration of **telithromycin** (avoid during and for 2 weeks after primidone)
- Anticoagulants: primidone possibly reduces plasma concentration of **apixaban** and **edoxaban**; primidone accelerates metabolism of **coumarins** (reduced anticoagulant effect); primidone possibly reduces plasma concentration of **rivaroxaban**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antidepressants: primidone possibly reduces plasma concentration of **reboxetine**; primidone reduces plasma concentration of **paroxetine**; primidone accelerates metabolism of **mianserin** (reduced plasma concentration); anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TCA REL ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **TCA REL ANTIDEPRESSANTS** (convulsive threshold lowered); plasma concentration of
Primidone

- **Antidepressants (continued)**
  - Primidone possibly reduced by: 
    - ST JOHN’S WORT—avoid concomitant use; primidone possibly accelerates metabolism of 
    - **TRICYCLES** (reduced plasma concentration)
  - Antiepileptics: primidone reduces plasma concentration of 
    - BIVARACETAM, LAMOTRIGINE, TIAGABINE and ZONISAMIDE; 
      - Plasma concentration of primidone possibly increased by 
      - CARBARAZEPINE; primidone possibly reduces plasma concentration of 
      - ETHOSUXIMIDE, RUFINAMIDE and TOPIRAMATE; 
      - Plasma concentration of primidone often increased by 
      - FOSPHENYTIN and PHENYTIN, plasma concentration of fosphenytin and phenytin often reduced but may be increased; 
      - Plasma concentration of primidone increased by 
      - OXCARBAZEPINE, also plasma concentration of an active metabolite of oxcarbazepine reduced; plasma concentration of 
      - Primidone increased by 
      - SODIUM VALPROATE and VALPROIC ACID (also plasma concentration of sodium valproate and valproic acid reduced); plasma concentration of primidone increased by 
      - **STIRIPENTOL**
  - Antiinflammatories: use; primidone possibly reduces plasma concentration of 
    - **ISAVUCONAZOLE** and **VORICONAZOLE**—avoid concomitant use; primidone possibly reduces plasma concentration of 
    - **ITRACONAZOLE** and **PIROXONAZOLE**; primidone reduces absorption of 
    - **GRISOFULVIN** (reduced effect)
  - Antimalarials: avoidance of primidone advised by manufacturer of 
    - ARTEMINOL WITH PIPERQUINE; anticonvulsant effect of antiepileptics antagonised by 
    - **MELOQUINE**
  - Antipsychotics: anticonvulsant effect of antiepileptics antagonised by 
    - **ANTIPSYCHOTICS** (convulsive threshold lowered); primidone accelerates metabolism of 
    - **HALOPERIDOL** (reduced plasma concentration); plasma concentration of both drugs reduced when primidone given with 
    - **CHLORPROMAZINE**; primidone possibly reduces plasma concentration of 
    - **ARIPIPRAZOLE** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); primidone possibly reduces plasma concentration of 
    - **CLOZAPINE**; primidone possibly reduces plasma concentration of 
    - **LURASIDONE**—avoid concomitant use
  - Antivirals: primidone possibly reduces plasma concentration of 
    - **ABACAVIR**, **DARUNAVIR**, **FOSAPREVIR**, **INDINAVIR**, 
      - **LORINAVIR** and **SAQUINAVIR**; avoidance of primidone advised by manufacturer of 
      - **BOCEPREVIR** and **RILPIVIRINE** (plasma concentration of boceprevir and rilpivirine possibly reduced); 
      - Primidone possibly reduces plasma concentration of 
      - **DACLATASVIR** and **SIMEPREVIR**—manufacturer of daclatasvir and simeprevir advises avoid concomitant use; primidone possibly reduces plasma concentration of 
      - **DASABUVIR**; primidone possibly reduces plasma concentration of 
      - **OMBITASVIR** and **PARITAPREVIR**—avoid concomitant use; primidone possibly reduces the plasma concentration of 
      - **DOLUTEGRAVIR** (see under Dolutegravir, p. 592); avoidance of 
      - Primidone advised by manufacturer of 
      - **ELVITEGRAVIR**, **ETRARIVINE**, **LEDIPASVIR**, **SOFOSBUVIR** and **TELAPREVIR**
    - Anxiolytics and Hypnotics: increased sedative effect when primidone given with 
      - **ANXIOLYTICS AND HYPNOTICS**; primidone often reduces plasma concentration of 
      - **CLONAZEPAM**; 
      - Aprepitant: primidone possibly reduces plasma concentration of 
      - **APREPIANT**
    - Avasanil: primidone possibly reduces plasma concentration of 
      - **AVANAFIL**—manufacturer of avanafil advises avoid concomitant use
    - Beta-blockers: primidone possibly reduces plasma concentration of 
      - **PROPRANOLOL**
    - Caffeine citrate: effects of primidone possibly antagonised by 
      - **CAFFEINE CITRATE**
    - Calcium-channel Blockers: primidone probably reduces effects of 
      - **CALCIUM-CHANNEL BLOCKERS**; avoidance of primidone advised by manufacturer of 
      - **ISRADIPE**: avoidance of primidone advised by manufacturer of 
      - **NIMODIPINE** (plasma concentration of nimodipine reduced)
    - Cannabis Extract: primidone possibly reduces plasma concentration of 
      - **CANNABIS EXTRACT**—manufacturer of cannabis extract advises avoid concomitant use
    - Ciclosporin: primidone accelerates metabolism of 
      - **CICLOSPORIN** (reduced plasma concentration)

Primidone (continued)

- Cobicitab: primidone possibly reduces plasma concentration of 
  - **COBICISTAT**—manufacturer of cobicitab advises avoid concomitant use
- Corticosteroids: primidone accelerates metabolism of 
  - **CORTICOSTEROIDS** (reduced effect)
- Cytoxics: primidone possibly decreases plasma concentration of 
  - **AXITINIB** (increase dose of axitinib—consult axitinib product literature); primidone possibly reduces plasma concentration of 
  - **BETRIZOMIB**, **BOSUTINIB**, **CRIZOTINIB** and **PONATINIB**—manufacturer of betrizaemb, bosutinib, crizotinib and ponatinib advises avoid concomitant use; primidone possibly reduces plasma concentration of 
  - **CABOZANTINIB** and 
    - **CERITINIB**—avoid concomitant use; avoidance of primidone advised by manufacturer of 
    - **CABAZITAXEL**, **DABRAFENIB** and **GEPITINIB**; avoidance of primidone advised by manufacturer of 
    - **DASATINIB** and **VANDETANIB** (plasma concentration of dasatinib and vandetanib possibly reduced); primidone possibly reduces plasma concentration of 
    - **ETOPOSIDE**; primidone reduces plasma concentration of 
    - **IRINOTECAN** and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when primidone given with 
    - **PROCARBAZINE**
  - Diuretics: primidone reduces plasma concentration of 
    - EPLERENONE—avoid concomitant use; increased risk of osteomalacia when primidone given with 
    - **CARBONIC ANHYDRASE INHIBITORS**
  - Folates: plasma concentration of primidone possibly reduced by 
    - **FOLATES**
  - Fosaprepitant: primidone possibly reduces plasma concentration of 
    - **FOSAPREPIANT**
  - Guanfacine: primidone possibly reduces plasma concentration of 
    - **GUANFACINE**—increase dose of guanfacine
  - Hormone Antagonists: primidone possibly reduces plasma concentration of 
    - **ABIRATERONE**—manufacturer of abiraterone advises avoid concomitant use; primidone accelerates metabolism of 
    - **TOREMIFENE** (reduced plasma concentration)
  - Ivacafar: primidone possibly reduces plasma concentration of 
    - **IVACAFOR**—manufacturer of ivacafrad advises avoid concomitant use
  - Leukotriene Receptor Antagonists: primidone reduces plasma concentration of 
    - **MONTELUKAST**
  - Lumacaftor: plasma concentration of primidone possibly reduced by 
    - **LUMACAFOR**—manufacturer of lumacafrad advises avoid concomitant use
  - Oestrogens: primidone accelerates metabolism of 
    - **ESTROGENS** (reduced oral contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
  - Orlistat: possible increased risk of convulsions when 
    - Antiepileptics given with 
    - **ORLISTAT**
  - Panobinostat: avoidance of primidone advised by manufacturer of 
    - **PANOBINOSTAT**
  - Progestogens: primidone accelerates metabolism of 
    - **PROGESTOGENS** (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)
  - Ponatinib: primidone possibly inhibits effects of 
    - **ROFULIMILAST** (manufacturer of rofufilumast advises avoid concomitant use)
  - Sodium Oxibate: avoidance of primidone advised by manufacturer of 
    - **SODIUM OXIBATE**
  - Sympathomimetics: plasma concentration of primidone possibly increased by 
    - **MEPHENIDATE**
  - Tacrolimus: primidone reduces plasma concentration of 
    - **TACROLIMUS**
  - Theophylline: primidone accelerates metabolism of 
    - **THEOPHYLLINE** (reduced effect)
  - Thyroid Hormones: primidone accelerates metabolism of 
    - **THYROID HORMONES** (may increase requirements for thyroid hormones in hypothyroidism)
  - Ticagrelor: primidone possibly reduces plasma concentration of 
    - **TICAGRELOR**
Progestogens (continued)

Progestogens

Anticholinergics: plasma concentration of norgestrel increased by CILOSPORIN; plasma concentration of norgestrel increased by CILOSPORIN, probenicid, and PHENOBARBITAL. 

Antihistamines: isolated reports that propafenone given with antihistamines may enhance anticoagulant effect of WARFARIN. 

Antimalarials: inactivate artemether with lumefantrine; increased antifolate effect when propafenone given with pyrimethamine. 

Anticoagulants: reduced effect when propafenone given with anticoagulants. 

Antidepressants: increased risk of haematological toxicity when antimalarials given with antimalarials prior to the first cycle. 

Antidiabetics: increased myocardial depression when antimalarials given with antihistamines. 

Antihistamines: isolated reports that propafenone may enhance anticoagulant effect of warfarin. 

Anticoagulants: isolated reports that propafenone may enhance anticoagulant effect of warfarin. 

Antimalarials: avoid concomitant use of antimalarials with propafenone. 

Antidepressants: isolated reports that propafenone may enhance anticoagulant effect of warfarin. 

Anticoagulants: increased risk of haematological toxicity when antimalarials given with antihistamines. 

Antidiabetics: increased myocardial depression when antimalarials given with antihistamines. 

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Antidepressants: isolated reports that propafenone may enhance anticoagulant effect of warfarin. 

Anticoagulants: increased risk of haematological toxicity when antimalarials given with antihistamines. 

Antidiabetics: increased myocardial depression when antmalari
Propafenone (continued)

- Antihistamines: avoidance of propafenone advised by manufacturer of MIZOLASTINE (possible risk of ventricular arrhythmias).
- Anticoagulants: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with.
- ANTIPSYCHOTICS that prolong the QT interval.
- Antivirals: plasma concentration of propafenone possibly increased by POSAMPRINAVIR (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of propafenone increased by RITONAVIR (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when propafenone given with SAQUINAVIR—avoid concomitant use; caution with propafenone advised by manufacturer of TELEPREVIR (risk of ventricular arrhythmias).
- Beta-blockers: increased myocardial depression when anti-arrhythmics given with. BETA-BLOCKERS; propafenone increases plasma concentration of METOPROLOL and PROPRANOLOL.

- Cardiac Glycosides: propafenone increases plasma concentration of DIGOXIN (half-life of digoxin).
- Ciclosporin: propafenone possibly increases plasma concentration of CICLOSPORIN.
- Parasympathomimetics: propafenone possibly antagonises effects of NEOSTIGMINE and PYRIDOSTIGMINE.
- Theophylline: propafenone increases plasma concentration of THEOPHYLLINE.
- Ulcer-healing Drugs: plasma concentration of propafenone increased by CIMETIDINE.

Propradiol see Antiarrhythmics
Propofol see Anaesthetics, General
Proporanolol see Beta-blockers
Prostaglandins
- ACE Inhibitors: enhanced hypotensive effect when alprostadil given with ACE INHIBITORS.
- Adrenergic Neurone Blockers: enhanced hypotensive effect when alprostadil given with ADRENERGIC NEURONE Blockers.
- Alpha-blockers: enhanced hypotensive effect when alprostadil given with ALPHA-BLOCKERS.
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alprostadil given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS.
- Beta-blockers: enhanced hypotensive effect when alprostadil given with BETA-BLOCKERS.
- Calcium-channel Blockers: enhanced hypotensive effect when alprostadil given with CALCIUM-CHANNEL BLOCKERS.
- Clonidine: enhanced hypotensive effect when alprostadil given with CLONIDINE.
- Diazoxide: enhanced hypotensive effect when alprostadil given with DIAZOXIDE.
- Diuretics: enhanced hypotensive effect when alprostadil given with DIURETICS.
- Methyldopa: enhanced hypotensive effect when alprostadil given with METHYLDOPA.
- Moxonidine: enhanced hypotensive effect when alprostadil given with MOXONIDINE.
- Nitrates: enhanced hypotensive effect when alprostadil given with NITRATES.
- Oxycin: prostaglandins potentiate uterotic effect of OXYCIN.
- Vasodilator Antihypertensives: enhanced hypotensive effect when alprostadil given with HYDRAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE.

Protein Kinase Inhibitors see individual drugs

Proton Pump Inhibitors

- Antacids: absorption of lansoprazole possibly reduced by ANTACIDS.
- Antibacterials: plasma concentration of both drugs increased when omeprazole given with CLARITHROMYCIN.
- Anticoagulants: esomeprazole and omeprazole possibly enhance anticoagulant effect of COUMARINS; pantoprazole might enhance the anticoagulant effect of COUMARINS.
- Antidepressants: omeprazole increases plasma concentration of ESCITALOPRAM; plasma concentration of lansoprazole possibly increased by FLUVOXAMINE; plasma concentration of omeprazole possibly reduced by ST JOHN’S WORT.
- Antiarrhythmics: esomeprazole possibly increases plasma concentration of ITRACONAZOLE and KETOCONAZOLE; esomeprazole reduces plasma concentration of POSACONAZOLE—manufacturer of posaconazole suspension advises avoid concomitant use; lansoprazole, omeprazole, pantoprazole and rabeprazole possibly reduce plasma concentration of POSACONAZOLE—manufacturer of posaconazole suspension advises avoid concomitant use; plasma concentration of esomeprazole possibly increased by VORICONAZOLE; plasma concentration of omeprazole increased by VORICONAZOLE (consider reducing dose of omeprazole).
- Antipsychotics: omeprazole possibly reduces plasma concentration of CLOzapine.
- Antibacterials: plasma concentration of both drugs increased when omeprazole given with CLARITHROMYCIN.
- Anticoagulants: esomeprazole and omeprazole possibly enhance anticoagulant effect of COUMARINS; pantoprazole might enhance the anticoagulant effect of COUMARINS.
- Antidepressants: omeprazole increases plasma concentration of ESCITALOPRAM; plasma concentration of lansoprazole possibly increased by FLUVOXAMINE; plasma concentration of omeprazole possibly reduced by ST JOHN’S WORT.
- Antiarrhythmics: esomeprazole possibly increases plasma concentration of ITRACONAZOLE and KETOCONAZOLE; esomeprazole reduces plasma concentration of POSACONAZOLE—manufacturer of posaconazole suspension advises avoid concomitant use; lansoprazole, omeprazole, pantoprazole and rabeprazole possibly reduce plasma concentration of POSACONAZOLE—manufacturer of posaconazole suspension advises avoid concomitant use; plasma concentration of esomeprazole possibly increased by VORICONAZOLE; plasma concentration of omeprazole increased by VORICONAZOLE (consider reducing dose of omeprazole).
- Antipsychotics: omeprazole possibly reduces plasma concentration of CLOzapine.
Pyrazinamide

> Sulfinpyrazone: pyrazinamide antagonises effects of SULFINPYRAZONE.

> Vaccines; antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC.

Pyridostigmine see Parasympathomimetics

Pyridoxine see Vitamins

Pyrimethamine

> Antibacterials: increased antifolate effect when pyrimethamine given with SULFONAMIDES or TRIMETHOPRIM.

> Antiepileptics: pyrimethamine antagonises anticonvulsant effect of FOSPHENYTOIN and PHENYTOIN, also increased antifolate effect.

> Antimalarials: avoidance of antimalarials advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; increased antifolate effect when pyrimethamine given with PROGUANIL.

> Antivirals: increased antifolate effect when pyrimethamine given with ZIDOVUDINE.

> Cytotoxics: pyrimethamine increases antifolate effect of METHOTREXATE and PEMETREXED.

> Histamine: avoidance of antimalarials advised by manufacturer of HISTAMINE.

> Penicillamine: increased risk of haematological toxicity when antimalarials given with PENICILLAMINE—manufacturer of penicillamine advises avoid concomitant use.

> Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC.

Quetiapine see Antipsychotics

Quinagolide

> Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.

> Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.

Quinapril see ACE Inhibitors

Quinoline

> Anti-arrhythmics: increased risk of ventricular arrhythmias when quinine given with AMIODARONE—avoid concomitant use; quinine increases plasma concentration of AMIODARONE.

> Antibacterials: increased risk of ventricular arrhythmias when quinine given with MOXIFLOXACIN—avoid concomitant use; plasma concentration of quinine reduced by sulfamethoxazole.

> Antivirals: increased antifolate effect when quinidine given with SUXAMETHONIUM.

Quinine (continued)

> Penicillamine: increased risk of haematological toxicity when antimalarials given with PENICILLAMINE—manufacturer of penicillamine advises avoid concomitant use.

> Ulcer-healing Drugs: metabolism of quinine inhibited by CITOMIDINE (increased plasma concentration).

> Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC.

Quinolones

> Aminophylline: possible increased risk of convulsions when quinolones given with AMINOPHYLLINE; ciprofloxacin and norfloxacin increase plasma concentration of AMINOPHYLLINE.

> Analgesics: possible increased risk of convulsions when quinolones given with NSAIDS.

> Antacids: absorption of moxifloxacin reduced by ANTACIDS (give at least 6 hours apart); absorption of ciprofloxacin and levofloxacin reduced by ANTACIDS (give at least 2 hours before or 4 hours after ciprofloxacin and levofloxacin); absorption of norfloxacin reduced by ANTACIDS; absorption of ofloxacin reduced by ANTACIDS (give at least 2 hours apart).

> Anti-arrhythmics: increased risk of ventricular arrhythmias when levofloxacin or moxifloxacin given with AMIODARONE; avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with DISOPYRAMIDE—avoid concomitant use.

> Antibacterials: increased risk of ventricular arrhythmias when moxifloxacin given with parenteral ERYTHROMYCIN—avoid concomitant use; avoidance of moxifloxacin advised by manufacturer of BEDAQUILINE; ciprofloxacin possibly increases plasma concentration of BEDAQUILINE—avoid concomitant use if ciprofloxacin given for more than 14 days; increased risk of ventricular arrhythmias when moxifloxacin given with DELAMANID; effects of nalidixic acid possibly antagonised by NITROFURANTOIN; increased possible risk of ventricular arrhythmias when moxifloxacin given with TELITHROMYCIN.

> Anticoagulants: nalidixic acid, norfloxacin and ofloxacin enhance anticoagulant effect of COUMARINS; ciprofloxacin and levofloxacin possibly enhance anticoagulant effect of COUMARINS; levofloxacin possibly enhances anticoagulant effect of PHENINDIONE.

> Antidepressants: avoidance of moxifloxacin advised by manufacturer of CITOLOPRAM, ESCITALOPRAM and VENLAFAXINE (risk of ventricular arrhythmias); ciprofloxacin inhibits metabolism of DULOXETINE—avoid concomitant use; avoidance of ciprofloxacin advised by manufacturer of AGOMELATINE; increased risk of ventricular arrhythmias when moxifloxacin given with TRICYCLICS—avoid concomitant use.

> Antidiabetics: norfloxacin possibly enhances effects of GLIBENCLAMIDE.

> Antiepileptics: ciprofloxacin increases or decreases plasma concentration of FOSPHENYTOIN and PHENYTOIN.

> Antihistamines: increased risk of ventricular arrhythmias when moxifloxacin given with MIZOLASTINE—avoid concomitant use.

> Antimalarials: avoidance of quinolones advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; avoidance of moxifloxacin advised by manufacturer of ARTEMIDIL WITH PIPERAQUINE (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when moxifloxacin given with CHLOROQUINE, HYDROXYCHLOROQUINE, MEFLOQUINE or QUININE—avoid concomitant use.

> Antipsychotics: increased risk of ventricular arrhythmias when moxifloxacin given with BENPERIDOL—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with DROPERIDOL, HALOPERIDOL, PHENOTHIAZINES, PIMOZIDE or ZUCLOPENTHIXOL—avoid concomitant use; ciprofloxacin increases plasma concentration of CLOZAPINE; ciprofloxacin possibly increases plasma concentration of OLANzapine.

> Antivirals: manufacturer of moxifloxacin advises give DIDanosine tablets at least 6 hours before or after moxifloxacin; manufacturer of norfloxacin advises give DIDanosine tablets at least 2 hours before or after norfloxacin; manufacturer of levofloxacin advises give DIDanosine tablets at least 2 hours before or after levofloxacin; absorption of ciprofloxacin reduced by DIDanosine tablets (give at least......
Quinolones

Antivirals (continued)
2 hours before or 4 hours after ciprofloxacin); increased risk of ventricular arrhythmias when moxifloxacin given with
- SAQUINAVIR—avoid concomitant use
- Amoxicillin and clavulanic acid: avoidance of ciprofloxacin advised by manufacturer of ZOLIDEPID
- Atorvastatin: increased risk of ventricular arrhythmias when moxifloxacin given with● ATOMOXETINE
- Beta-blockers: increased risk of ventricular arrhythmias when moxifloxacin given with● SOTALOL—avoid concomitant use
- Calcium Salts: absorption of ciprofloxacin reduced by CALCIUM SALTS (give at least 2 hours before or 4 hours after ciprofloxacin)
- Ciclosporin: increased risk of nephrotoxicity when quinolones given with● CICLOSPORIN
- Clopidogrel: ciprofloxacin possibly reduces antiplatelet effect of● CLOPIDODGER
- Cytotoxics: nalidixic acid increases risk of MELPHALAN toxicity; ciprofloxacin possibly reduces excretion of METHOTREXATE (increased risk of toxicity); possible increased risk of ventricular arrhythmias when moxifloxacin given with● BOSUTINIB and● CERTINIB; ciprofloxacin possibly increases the plasma concentration of● BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; ciprofloxacin increases plasma concentration of ERLOTINIB; ciprofloxacin possibly increases the plasma concentration of● IBRUTINIB—reduce dose of ibrutinib (see under Ibrutinib, p. 867); possible increased risk of ventricular arrhythmias when levofloxacin or moxifloxacin given with● ARSENIC TRIOXIDE; ciprofloxacin possibly increases plasma concentration of● OLAPARIB (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)
- Dairy Products: absorption of ciprofloxacin reduced by DAIRY PRODUCTS (give at least 2 hours apart); absorption of norfloxacin reduced by DAIRY PRODUCTS
- Dapomimetics: ciprofloxacin increases plasma concentration of● RASAGILINE; ciprofloxacin inhibits metabolism of● RANOLAZINE (increased plasma concentration)
- SH2-receptor Agonists: quinolones possibly inhibit metabolism of● ZOLMITRIPTAN (reduce dose of zolmitriptan)
- Iron Salts: absorption of moxifloxacin reduced by oral IRON SALTS (give at least 6 hours apart); absorption of ciprofloxacin reduced by oral IRON SALTS (give at least 2 hours before or 4 hours after ciprofloxacin); absorption of levofloxacin, norfloxacin and ofloxacin reduced by oral IRON SALTS (give at least 2 hours apart)
- Lanthanum: absorption of quinolones possibly reduced by● LANTHANUM (give at least 2 hours before or 4 hours after lanthanum)
- Muscle Relaxants: norfloxacin possibly increases plasma concentration of● TIZANIDINE (increased risk of toxicity); ciprofloxacin increases plasma concentration of● TIZANIDINE (increased risk of toxicity)—avoid concomitant use
- Mycophenolate: norfloxacin possibly reduces bioavailability of● MYCOPHENOLATE
- Panobinostat: possible increased risk of ventricular arrhythmias when moxifloxacin given with● PANOBINOSTAT—avoid concomitant use
- Pentamidine ietionate: increased risk of ventricular arrhythmias when moxifloxacin given with● PENTAMIDINE ISETONATE—avoid concomitant use
- Perifedone: ciprofloxacin increases plasma concentration of● PERIFEDONE—see under Perifedone, p. 279
- Sevelamer: absorption of ciprofloxacin reduced by● SEVELAMER (give at least 2 hours before or 4 hours after ciprofloxacin)
- Strontium Ranelate: absorption of quinolones reduced by● STRONTIUM RANELATE (manufacturer of strontium ranelate advises avoid concomitant use)
- Theophylline: possible increased risk of convulsions when quinolones given with● THEOPHYLLINE; ciprofloxacin and norfloxacin increase plasma concentration of● THEOPHYLLINE
- Ulcer-healing Drugs: absorption of levofloxacin, norfloxacin and ofloxacin reduced by● SUCRALFATE (give at least 2 hours

Quinolones

Ulcer-healing Drugs (continued)
- absorption of ciprofloxacin reduced by● SUCRALFATE (give at least 2 hours before or 4 hours after ciprofloxacin); absorption of moxifloxacin reduced by● SUCRALFATE (give at least 6 hours apart)
- Vaccines: antibacterials inactivate● ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC
- Zinc: absorption of moxifloxacin reduced by● ZINC (give at least 6 hours apart); absorption of ciprofloxacin, levofloxacin, norfloxacin and ofloxacin reduced by● ZINC (give at least 2 hours apart)

Rabeprazole see Proton Pump Inhibitors

Rabies Vaccine see Vaccines

Raloxifene

- Anticoagulants: raloxifene antagonises anticoagulant effect of● COUMARINS
- Lipid-regulating Drugs: absorption of raloxifene reduced by● COLESTYRAMINE (manufacturer of raloxifene advises avoid concomitant administration)

Raltitrexed

- Antipsychotics: avoid concomitant use of cytotoxics with● CLOzapine (increased risk of agranulocytosis)
- Folates: manufacturer of raltitrexed advises avoid concomitant use with● FOLATES

Ramipril see ACE Inhibitors

Ramucirumab

- Antibacterials: plasma concentration of raltegravir reduced by● ALUMINIUM HYDROXIDE and● ORAL MAGNESIUM SALTS—manufacturer of raltegravir advises avoid concomitant use
- Antivirals: plasma concentration of raltegravir reduced by● RIFAPICIN—consider increasing dose of raltegravir
- Antivirals: increased risk of rash when raltegravir given with● DARUNAVIR; avoidance of raltegravir advised by manufacturer of● FOSAMPRENAVIR
- Oralstat: absorption of raltegravir possibly reduced by● ORALSTAT
- Ulcer-healing Drugs: plasma concentration of raltegravir increased by● FAMOTIDINE and● OMEPRAZOLE

Raltitrexed

- Antipsychotics: avoid concomitant use of cytotoxics with● CLOzapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live● VACCINES—avoid concomitant use

Ranitidine see Histamine H2-antagonists

Ranolazine

- Anti-arrhythmics: manufacturer of ranolazine advises avoid concomitant use with● DISOPYRAMIDE
- Antibacterials: plasma concentration of ranolazine possibly increased by● CLARITHROMYCIN and● TELITHROMYCIN—manufacturer of ranolazine advises avoid concomitant use; plasma concentration of ranolazine reduced by● RIFAPICIN—manufacturer of ranolazine advises avoid concomitant use
- Antidepressants: plasma concentration of ranolazine increased by● PAROXETINE
- Antifungals: plasma concentration of ranolazine increased by● KETOCONAZOLE—avoid concomitant use; plasma concentration of ranolazine possibly increased by● ITRACONAZOLE,● POSaconazole and● voriconazole—manufacturer of ranolazine advises avoid concomitant use
- Antivirals: plasma concentration of ranolazine possibly increased by● ATAZANAVIR,● DARUNAVIR,● FOSAMPRENAVIR,● INIDINAVIR,● LOPINAVIR,● RITONAVIR,● SAQUINAVIR and● TIPRANAVIR—manufacturer of ranolazine advises avoid concomitant use
- Beta-blockers: manufacturer of ranolazine advises avoid concomitant use with● SOTALOL
- Calcium-channel Blockers: plasma concentration of ranolazine increased by● Diltiliazem and● VERAPAMIL (consider reducing dose of ranolazine)
- Cardiac Glycosides: ranolazine increases plasma concentration of● DIGOXIN
- Ciclosporin: plasma concentration of both drugs may increase when ranolazine given with● CICLOSPORIN

Corrections:
Ranolazine (continued)

- Grapefruit Juice: plasma concentration of ranolazine possibly increased by grapefruit juice—manufacturer of ranolazine advises avoid concomitant use
- Lipid-regulating Drugs: ranolazine increases plasma concentration of simvastatin (see under simvastatin, p. 194); separating administration from ranolazine by 12 hours advised by manufacturer of lomitapide
- Tacrolimus: ranolazine increases plasma concentration of tacrolimus

Rasagiline

**NOTE** Rasagiline is a MAO-B inhibitor

- Analgesics: avoid concomitant use of rasagiline with dextromethorphan; risk of CNS toxicity when rasagiline given with pethidine (avoid pethidine for 2 weeks after rasagiline)
- Antibacterials: plasma concentration of rasagiline increased by ciprofloxacin
- Antidepressants: after stopping rasagiline do not start fluoxetine for 2 weeks, also rasagiline should not be started until at least 5 weeks after stopping fluoxetine; after stopping rasagiline do not start fluvoxamine for 2 weeks; risk of hypertensive crisis when rasagiline given with MAOIs, avoid MAOIs for at least 2 weeks after stopping rasagiline; increased risk of CNS toxicity when rasagiline given with SSRIs or tricyclics; risk of CNS excitation and hypertention when rasagiline given with vortioxetine
- Dopaminergics: plasma concentration of rasagiline possibly reduced by entacapone
- Memantine: effects of dopaminergics possibly enhanced by memantine
- Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by methyl dopa
- Symptomhmetics: avoid concomitant use of rasagiline with sympathomimetics

Reboxetine

- Antibacterials: manufacturer of reboxetine advises avoid concomitant use with macrolides
- Antidepressants: manufacturer of reboxetine advises avoid concomitant use with fluvoxamine; increased risk of hypertention and CNS excitation when reboxetine given with MAOIs (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs)
- Antiepileptics: plasma concentration of reboxetine possibly reduced by carbamazepine, phenobarbital and primidone
- Antifungals: manufacturer of reboxetine advises avoid concomitant use with imidazoles and triazoles
- Antimalarials: avoidance of antidepressants advised by manufacturer of artemether with lumefantrine and artemiinol with piperaquine
- Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine
- Diuretics: possible increased risk of hypokalaemia when reboxetine given with loop diuretics and thiazides and related diuretics
- Ergot alkaloids: possible risk of hypertention when reboxetine given with ergotamine

Regorafenib

- Analgesics: manufacturer of regorafenib advises avoid concomitant use with mefenamic acid
- Antibacterials: plasma concentration of regorafenib reduced by rifampicin—manufacturer of regorafenib advises avoid concomitant use
- Anticoagulants: increased risk of bleeding when regorafenib given with warfarin
- Antifungals: plasma concentration of regorafenib increased by ketoconazole—avoid concomitant use
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Cytotoxics: regorafenib increases plasma concentration of irinotecan

Remifentanil see Opioid Analgesics

Repaglinide see Antidiabetics

Retigabine

- Alcohol: increased risk of blurred vision when retigabine given with alcohol
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered)
- Antiepileptics: plasma concentration of retigabine possibly reduced by carbamazepine, fosphenytoin and phenytoin
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by mephaquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered)
- Orlstat: possible increased risk of convulsions when antiepileptics given with orlistat

Retinoids

- Alcohol: etretinate formed from acitretin in presence of alcohol (increased risk of teratogenicity in women of child-bearing potential)
- Antibacterials: possible increased risk of benign intracranial hypertension when retinoids given with tetracyclines (avoid concomitant use)
- Anticoagulants: acitretin possibly reduces anticoagulant effect of coumarins
- Antiepileptics: isotretinoin possibly reduces plasma concentration of carbamazepine
- Antifungals: plasma concentration of alitretinoin increased by ketoconazole; possible increased risk of retinoid toxicity when given with fluconazole, ketoconazole and voriconazole
- Cytotoxics: acitretin increases plasma concentration of methotrexate (also increased risk of hepatotoxicity)—avoid concomitant use
- Lipid-regulating Drugs: alitretinoin reduces plasma concentration of simvastatin
- Vitamins: risk of hypervitaminosis A when retinoids given with vitamin A—avoid concomitant use

Ribavirin

- Antivirals: effects of ribavirin possibly reduced by abacavir, increased risk of side-effects when ribavirin given with didanosine—avoid concomitant use; increased risk of toxicity when ribavirin given with stavudine; increased risk of anaemia when ribavirin given with zidovudine—avoid concomitant use
- Azathioprine: ribavirin possibly enhances myelosuppressive effects of azathioprine

Rifabutin see Rifamycins

Rifampicin see Rifamycins

Rifamycins

**NOTE** Interactions do not apply to rifaximin

- ACE Inhibitors: rifampicin reduces plasma concentration of active metabolite of imidapril (reduced antihypertensive effect)
- Alfiskiren: rifampicin reduces plasma concentration of aliskiren
- Ambrisentan: rifampicin possibly increases plasma concentration of ambrisentan
- Aminophylline: rifampicin accelerates metabolism of aminophylline (reduced plasma concentration)
- Analgesics: rifampicin reduces plasma concentration of celecoxib, diclofenac and etoricoxib; rifampicin accelerates metabolism of alfentanil, codeine, fentanyl, methadone and morphine (reduced effect); rifampicin possibly accelerates metabolism of oxycodone
- Angiotensin-II Receptor Antagonists: rifampicin reduces plasma concentration of losartan and its active metabolite
- Antacids: absorption of rifampicin reduced by antacids
- Antihelminetics: rifampicin reduces plasma concentration of praziquantel—avoid concomitant use
- Anti-arrhythmics: rifampicins accelerate metabolism of disopyramide (reduced plasma concentration); rifampicin reduces plasma concentration of brendaron—avoid concomitant use; rifampicin accelerates metabolism of propafenone (reduced effect)
Rifamycins

Rifamycins (continued)
- Antimicrobials: increased risk of side-effects including neutropenia when rifabutin given with azithromycin; rifampicin reduces plasma concentration of clarithromycin and dапsone; plasma concentration of rifabutin increased by clarithromycin (increase risk of toxicity—reduce rifabutin dose); plasma concentration of rifabutin possibly increased by erythromycin (increased risk of toxicity—reduce rifabutin dose); rifampicin possibly reduces plasma concentration of tinidazole and trimethoprime; rifampicin reduces plasma concentration of doxycycline—consider increasing dose of doxycycline; rifampicin reduces plasma concentration of bedaquiline—manufacturer of bedaquiline advises avoid concomitant use; rifabutin possibly reduces plasma concentration of bedaquiline—manufacturer of bedaquiline advises avoid concomitant use; rifampicin accelerates metabolism of chloramphenicol (reduced plasma concentration); rifampicin reduces plasma concentration of delamanid; increased risk of hepatotoxicity when rifampicin given with isoniazid; rifampicin reduces plasma concentration of telithromycin (avoid during and for 2 weeks after rifampicin).
- Anticoagulants: rifampicin possibly reduces plasma concentration of apixaban—manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism; rifampicins accelerate metabolism of coumarins (reduced anticoagulant effect); rifampicin reduces plasma concentration of dabigatran—manufacturer of dabigatran advises avoid concomitant use; rifampicin reduces plasma concentration of edoxaban; rifampicin reduces plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis.
- Antidepressants: rifampicin reduces plasma concentration of linezolid (possible therapeutic failure of linezolid); rifampicin reduces plasma concentration of vortioxetine—consider increasing dose of vortioxetine.
- Antidiabetics: rifampicins accelerate metabolism of tolbutamide (reduced effect); rifampicin reduces plasma concentration of canagliflozin and nateglinide; rifampicin possibly reduces effects of linagliptin; rifampicin possibly antagonises hypoglycaemic effect of repaglinide; rifampicins possibly accelerate metabolism of sulfonyleureas (reduced effect).
- Antiepileptics: rifampicin reduces plasma concentration of brivaracetam and lamotrigine; rifabutin reduces plasma concentration of carbamazepine; rifampicins accelerate metabolism of fosphenytoin and phenytoin (reduced plasma concentration); plasma concentration of rifampicin possibly reduced by phenobarbital and primidone.
- Antifungals: rifampicin accelerates metabolism of ketoconazole (reduced plasma concentration, also plasma concentration of rifampicin may be reduced by ketoconazole; plasma concentration of rifabutin increased by fluconazole (increased risk of uveitis—reduce rifabutin dose); rifampicin accelerates metabolism of fluconazole (reduced plasma concentration); rifabutin possibly reduces plasma concentration of isavuconazole—avoid concomitant use; rifampicin reduces plasma concentration of isavuconazole and voriconazole—avoid concomitant use; rifabutin and rifampicin reduce plasma concentration of itraconazole—manufacturer of itraconazole advises avoid concomitant use; plasma concentration of rifabutin increased by posaconazole (also plasma concentration of posaconazole reduced); rifampicin reduces plasma concentration of posaconazole and terbinafine; plasma concentration of rifabutin increased by voriconazole, also rifabutin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for signs of toxicity); rifampicin initially increases and then reduces plasma concentration of caspofungin (consider increasing dose of caspofungin); plasma concentration of rifabutin possibly increased by triazoles (increased risk of uveitis—reduce rifabutin dose).
- Antihistamines: rifampicin possibly reduces effects of fexofenadine.

Rifamycins (continued)
- Antimalarials: avoidance of rifampicin advised by manufacturer of artenandin with piperaquine; rifampicin reduces plasma concentration of mefloquine—avoid concomitant use; rifampicin reduces plasma concentration of quinidine.
- Antimycobacterials: rifampicin reduces plasma concentration of active metabolite of fosfonidine—avoid concomitant use.
- Antipsychotics: rifampicin accelerates metabolism of haloperidol (reduced plasma concentration); rifabutin and rifampicin possibly reduce plasma concentration of aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); rifampicin possibly reduces plasma concentration of clozapine; rifampicin reduces plasma concentration of lurasidone—avoid concomitant use.
- Antivirals: rifampicin possibly reduces plasma concentration of abacavir; rifampicin reduces plasma concentration of atazanavir, daplatasvir, lopinavir, nevirapine and rilpivirine—avoid concomitant use; plasma concentration of rifabutin increased by atazanavir, darunavir, fosamprenavir and tipranavir (reduce dose of rifabutin); avoidance of rifampicin advised by manufacturer of boceprevir (plasma concentration of boceprevir possibly reduced); rifabutin possibly reduces plasma concentration of daclatasvir and simprevir—manufacturer of daclatasvir and simprevir advises avoid concomitant use; rifampicin significantly reduces plasma concentration of darunavir, fosamprenavir and telaprevir—avoid concomitant use; rifampicin possibly reduces plasma concentration of dasabuvir, omibitasvir, paritaprevir and tipranavir—avoid concomitant use; rifampicin reduces the plasma concentration of dolutegravir (see under Dolutegravir, p. 592); rifampicin reduces plasma concentration of efavirenz—increase dose of efavirenz; plasma concentration of rifabutin reduced by efavirenz—increase dose of rifabutin; avoidance of rifampicin advised by manufacturer of elvitegravir, etravirine, ledipasvir, sofosbuvir and zidovudine; rifabutin reduces plasma concentration of elvitegravir also plasma concentration of active metabolite of rifabutin increased—reduce dose of rifabutin; plasma concentration of both drugs reduced when rifabutin given with etravirine; plasma concentration of rifabutin increased by indinavir, also plasma concentration of indinavir decreased (reduce dose of rifabutin and increase dose of indinavir); rifampicin accelerates metabolism of indinavir (reduced plasma concentration—avoid concomitant use); avoidance of rifampicin advised by manufacturer of ledipasvir, sofosbuvir and telaprevir; rifampicin reduces plasma concentration of maraviroc and raltegravir—consider increasing dose of maraviroc and raltegravir; plasma concentration of ritonavir possibly increased by nevirapine—rifabutin decreases plasma concentration of rilpivirine (increase dose of rilpivirine—consult rilpivirine product literature); plasma concentration of rifabutin increased by ritonavir (increased risk of toxicity—reduce rifabutin dose); rifampicin reduces plasma concentration of ritonavir; rifampicin significantly reduces plasma concentration of saquinavir, also risk of hepatotoxicity—avoid concomitant use; plasma concentration of ritonavir possibly increased by saquinavir (also plasma concentration of saquinavir reduced)—reduce rifabutin dose; rifampicin reduces plasma concentration of simprevir—manufacturer of simprevir advises avoid concomitant use.
- Anxiolytics and Hypnotics: rifampicin accelerates metabolism of diazepam and zaleplon (reduced plasma concentration); rifampicin possibly accelerates metabolism of benzodiazepines (reduced plasma concentration); rifampicin possibly accelerates metabolism of butorphanol; rifampicin accelerates metabolism of zolpidem (reduced plasma concentration and reduced effect); rifampicin significantly reduces plasma concentration of zopiclone.
- Apremilast: rifampicin reduces plasma concentration of apremilast.
- Aprepiant: rifampicin reduces plasma concentration of aprepitant.
Cytotoxics:

- Bosentan:
- Avanafil:
- Atovaquone:
- Rifamycins

Rifamycins (continued)

- Atovaquone: avoidance of concomitant rifabutin advised by manufacturer of ATOVUQUONE (plasma concentration of both drugs reduced); rifampicin reduces plasma concentration of ATOVUQUONE (and concentration of rifampicin increased)—avoid concomitant use
- Avanafil: rifampicin possibly reduces plasma concentration of AVANAFIL—manufacturer of avanafil advises avoid concomitant use
- Beta-blockers: rifampicin accelerates metabolism of BISOPROLOL and PROPRANOLOL (plasma concentration significantly reduced); rifampicin reduces plasma concentration of CARVEDILOL, CELIPROLOL and METOPROLOL; rifampicin possibly reduces plasma concentration of oral TIMOLOL
- Bosentan: rifampicin reduces plasma concentration of BOSENTAN—avoid concomitant use
- Calcium-channel blockers: rifampicin possibly reduces plasma concentration of FELODIPINE; rifampicin possibly accelerates metabolism of ISRADIPINE and NICARDIPINE (possible significantly reduced plasma concentration); rifampicin accelerates metabolism of DILTIAZEM, NIFEDIPINE, NIMODIPINE and VERAPAMIL (plasma concentration significantly reduced)
- Cannabis Extract: rifampicin reduces plasma concentration of CANNABIS EXTRACT—manufacturer of cannabis extract advises avoid concomitant use
- Ciclosporin: rifampicin accelerates metabolism of CICLOSPORIN (reduced plasma concentration)
- Cocisistat: rifabutin reduces plasma concentration of COCISTAT (adjust dose—consult product literature); rifampicin possibly reduces plasma concentration of COCISTAT—manufacturer of cocistat advises avoid concomitant use
- Corticosteroids: rifamycins accelerate metabolism of CORTICOSTEROIDS (reduced effect)
- Diuretics: rifampicin possibly reduces effects of BRENTOXIMAVEDOTIN; rifampicin reduces plasma concentration of AFATINIB, RUXOLITINIB, SORAFENIB and TRABECTEDIN; rifabutin possibly reduces plasma concentration of AXITINIB (increase dose of axitinib—consult axitinib product literature); rifampicin reduces plasma concentration of AXITINIB (increase dose of axitinib—consult axitinib product literature); rifabutin possibly reduces plasma concentration of BORTezOMIB, BOsUTINIB, CRIZOTINIB and PONATINIB—manufacturer of bosutinib, crizotinib and ponatinib advises avoid concomitant use; rifampicin reduces plasma concentration of BOSUTINIB, CRIZOTINIB and PONATINIB—manufacturer of bosutinib, crizotinib and ponatinib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB and PONATINIB—manufacturer of bosutinib, crizotinib and ponatinib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BOsUTINIB, CRIZOTINIB, PONATINIB, REGORAFENIB and VANDETANIB—manufacturer of bortezomib, bosutinib, cabazitaxel, crizotinib, ponatinib, regorafenib and vandetanib advises avoid concomitant use; rifampicin reduces plasma concentration of BORTezOMIB, BOsUTINIB, CRIZOTINIB and PONATINIB—manufacturer of bosutinib, crizotinib and ponatinib advises avoid concomitant use; rifampicin reduces plasma concentration of CRIZOTINIB and PONATINIB—manufacturer of crizotinib and ponatinib advises avoid concomitant use; rifampicin reduces plasma concentration of ERLOTINIB and SUNITINIB (reduced plasma concentration); rifampicin reduces plasma concentration of EVEROLIMUS (avoid concomitant use or consider increasing the dose of everolimus—consult everolimus product literature); avoidance of rifabutin advised by manufacturer of CABAZITAXEL, LAPATINIB, OLAPARIB and VEMURAFENIB; rifampicin accelerates metabolism of DASATINIB (reduced plasma concentration—avoid concomitant use); rifampicin accelerates metabolism of ERLOTINIB and SUNITINIB (reduced plasma concentration); rifampicin reduces plasma concentration of EVerOLIMUS (avoid concomitant use or consider increasing the dose of everolimus—consult everolimus product literature); avoidance of rifabutin advised by manufacturer of CABAZITAXEL, LAPATINIB, OLAPARIB and VEMURAFENIB; rifampicin possibly reduces plasma concentration of ERIBULIN and PAZOPANIB; rifampicin reduces plasma concentration of active metabolite of TEMSIROLIMUS—avoid concomitant use; rifampicin possibly reduces plasma concentration of VINFLUNINE—manufacturer of vinflunine advises avoid concomitant use; avoidance of rifampicin advised by manufacturer of VISMODEGIB (plasma concentration of vismodegib possibly reduced)

Rifamycins (continued)

- Deferasirox: rifampicin reduces plasma concentration of DEFERASIROX
- Diuretics: rifampicin reduces plasma concentration of EPLERENONE—avoid concomitant use
- Fosaprepitant: rifampicin reduces plasma concentration of FOSAPREPITAN
- Guanfacine: rifabutin possibly reduces plasma concentration of GUANFACINE—increase dose of guanfacine; rifampicin reduces plasma concentration of GUANFACINE—increase dose of guanfacine
- Hormone Antagonists: rifampicin reduces plasma concentration of ABRIRERONE—manufacturer of abiraterone advises avoid concomitant use; rifabutin possibly reduces plasma concentration of ABRIRERONE—manufacturer of abiraterone advises avoid concomitant use; rifampicin possibly reduces plasma concentration of EXEMESTANE; rifampicin accelerates metabolism of TAMOXIFEN (reduced plasma concentration)
- HST1-receptor Antagonists: rifampicin accelerates metabolism of ONDANSETRON (reduced effect)
- Icavafor: rifabutin possibly reduces plasma concentration of IVACAFOR—manufacturer of icavafor advises avoid concomitant use; rifampicin reduces plasma concentration of IVACAFOR—manufacturer of icavafor advises avoid concomitant use
- Lefunomide: rifampicin possibly reduces plasma concentration of active metabolite of LEFLUNOMIDE
- Lipid-regulating Drugs: rifampicin possibly reduces plasma concentration of ATOVASTATIN and SIMVASTATIN; rifampicin accelerates metabolism of FLUVASTATIN (reduced effect)
- Lumacaftor: plasma concentration of rifabutin possibly reduced by LUMACAFOR—avoid concomitant use
- Macitentan: rifampicin reduces plasma concentration of MACITENANT—avoid concomitant use
- Muscle Relaxants: rifampicin possibly reduces plasma concentration of TIZANIDINE
- Mycophenolate: rifampicin reduces plasma concentration of active metabolite of MYCOPHENOLATE
- Naloxegol: rifampicin reduces plasma concentration of NALOXEGOL—avoid concomitant use
- Netupitant: rifampicin reduces plasma concentration of NETUPITANT—avoid concomitant use
- Oestrogens: rifamycins accelerate metabolism of OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Panobinostat: avoidance of rifabutin and rifampicin advised by manufacturer of PANOBINOSTAT
- Progestogens: rifamycins accelerate metabolism of PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)
- Ranolazine: rifampicin reduces plasma concentration of RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
- Roflumilast: rifampicin inhibits effects of ROFLUMILAST (manufacturer of roflumilast advises avoid concomitant use)
- Sirolimus: rifabutin and rifampicin reduce plasma concentration of SIROLIMUS—avoid concomitant use
- Tacrolimus: rifabutin possibly reduces plasma concentration of TACROLIMUS; rifampicin reduces plasma concentration of TACROLIMUS
- Tadalafil: rifampicin reduces plasma concentration of TADALAFIL—manufacturer of tadalafil advises avoid concomitant use
- Teriflunomide: rifampicin reduces plasma concentration of TERIFLUNOMIDE
- Theophylline: rifampicin accelerates metabolism of THEOPHYLLINE (reduced plasma concentration)
- Thyroid Hormones: rifampicin accelerates metabolism of LEVOTHYROIDINE (may increase requirements for levothyroxine in hypothyroidism)
- Tibolone: rifampicin accelerates metabolism of TIBOLONE (reduced plasma concentration)
Rifaximin

- Ticagrelor: rifampicin reduces plasma concentration of ticagrelor; avoid concomitant use
- Tolovaptan: rifampicin reduces plasma concentration of tolvaptan
- Ulcer-healing Drugs: rifampicin accelerates metabolism of cimetidine (reduced plasma concentration)
- Ulipristal: avoidance of rifampicin advised by manufacturer of ulipristal (contraceptive effect of ulipristal possibly reduced)
- Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF or BNFC

Rifaximin

Note: Rifaximin interactions do not apply to rifaximin.
- Anticoagulants: rifaximin possibly reduces anticoagulant effect of warfarin
- Ciclosporin: plasma concentration of rifaximin increased by ciclosporin
- Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF or BNFC

Rilpivirine

- Antacids: manufacturer of rilpivirine advises give antacids 2 hours before or 4 hours after rilpivirine
- Antimonials: manufacturer of rilpivirine advises avoid concomitant use with carbarsazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin
- Dabigatran: rilpivirine possibly increases plasma concentration of dabigatran
- Antidepressants: manufacturer of rilpivirine advises avoid concomitant use with St John’s Wort (plasma concentration of rilpivirine possibly reduced)
- Antiepileptics: manufacturer of rilpivirine advises avoid concomitant use with carbamazepine, fosphenytoin, oxcarsazepine, phenobarbital, phenytoin
- Primidone: rilpivirine product literature
- Antivirals: manufacturer of rilpivirine advises give didanosine 2 hours before or 4 hours after rilpivirine; avoidance of rilpivirine advised by manufacturer of nevirapine
- Calcium: manufacturer of rilpivirine advises give calcium salts 2 hours before or 4 hours after rilpivirine
- Corticosteroids: manufacturer of rilpivirine advises avoid concomitant use with dexamethasone (except when given as a single dose)
- Orlistat: absorption of rilpivirine possibly reduced by orlistat
- Ulcer-healing Drugs: manufacturer of rilpivirine advises avoid concomitant use with esomeprazole, lansoprazole, pantoprazole and rabeprazole (plasma concentration of rilpivirine possibly reduced); plasma concentration of rilpivirine reduced by omeprazole—avoid concomitant use; manufacturer of rilpivirine advises avoid histamine H2-antagonists for 12 hours before or 4 hours after rilpivirine—consult product literature

Riociguat

- Antacids: absorption of riociguat reduced by antacids (give at least 2 hours before or 1 hour after riociguat)
- Antifungals: manufacturer of riociguat advises avoid concomitant use with itraconazole, ketoconazole and voriconazole
- Antivirals: manufacturer of riociguat advises avoid concomitant use with riociguat
- Avanafil: possible enhanced hypotensive effect when riociguat given with avanafil—avoid concomitant use
- Bosentan: plasma concentration of riociguat reduced by bosentan
- Nicorandil: possible enhanced hypotensive effect when riociguat given with nicorandil—avoid concomitant use
- Nitrates: possible enhanced hypotensive effect when riociguat given with nitrates—avoid concomitant use
- Sildenafil: enhanced hypotensive effect when riociguat given with sildenafil—avoid concomitant use
- Tadalafil: possible enhanced hypotensive effect when riociguat given with tadalafil—avoid concomitant use
- Vardenafil: possible enhanced hypotensive effect when riociguat given with vardenafil—avoid concomitant use
- Risedronate sodium: see Bisphosphonates
- Risperidone: see Antipsychotics

Ritonavir

- Alpha-blockers: ritonavir possibly increases plasma concentration of alfuzosin—avoid concomitant use
- Aminophylline: ritonavir accelerates metabolism of aminophylline (reduced plasma concentration)
- Analgesics: ritonavir possibly increases plasma concentration of nsaids and buproprionphine; ritonavir increases plasma concentration of dextropropoxyphene and piroxicam (risk of toxicity)—avoid concomitant use; ritonavir increases plasma concentration of alfenatal and fentanyl; ritonavir reduces plasma concentration of methadone; ritonavir possibly reduces plasma concentration of morphine; ritonavir reduces plasma concentration of methadone; ritonavir possibly reduces plasma concentration of morphine; ritonavir possibly reduces plasma concentration of pethidine; but increases plasma concentration of toxic metabolite of pethidine (avoid concomitant use)
- Anthelminetics: ritonavir possibly reduces plasma concentration of active metabolite of albendazole—consider increasing albendazole dose when given for systemic infections
- Antiarrhythmics: ritonavir increases plasma concentration of amiodarone and propafenone (increased risk of ventricular arrhythmias—avoid concomitant use); ritonavir possibly increases plasma concentration of disopyramide (increased risk of toxicity); avoidance of ritonavir advised by manufacturer of dronedarone; ritonavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antibacterials: ritonavir possibly increases plasma concentration of azithromycin and erythromycin; ritonavir increases plasma concentration of clarithromycin (reduce dose of clarithromycin in renal impairment); ritonavir increases plasma concentration of rifabutin (increased risk of toxicity); ritonavir possibly increases plasma concentration of rilpivirine reduced by rilpamipine; ritonavir possibly increases plasma concentration of bedaquiline—manufacturer of ritonavir advises avoid concomitant use; ritonavir increases plasma concentration of delamanid; plasma concentration of both drugs increased when ritonavir given with fusidic acid—avoid concomitant use; avoidance of concomitant ritonavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
- Anticoagulants: ritonavir may enhance or reduce anticoagulant effect of warfarin; avoidance of ritonavir advised by manufacturer of apixaban; ritonavir possibly enhances anticoagulant effect of coumarins and phenindione; ritonavir increases plasma concentration of rivaroxaban—avoid concomitant use
- Antidepressants: ritonavir possibly reduces plasma concentration of paroxetine; ritonavir increases plasma concentration of trazodone (increased risk of toxicity); ritonavir possibly increases plasma concentration of SSRIs and tricyclics; plasma concentration of ritonavir reduced by St John’s Wort—avoid concomitant use
- Antidiabetics: ritonavir possibly increases plasma concentration of tolbutamide
- Antiepileptics: ritonavir possibly increases plasma concentration of carbamazepine; plasma concentration of ritonavir possibly reduced by fosphenytoin and phenytoin; also plasma concentration of fosphenytoin and phenytoin possibly affected; ritonavir possibly reduces plasma concentration of lamotrigine, sodium valproate and valproic acid
- Antifungals: ritonavir increases plasma concentration of ketoconazole (reduce dose of ketoconazole); plasma concentration of ritonavir increased by fluconazole; ritonavir increases plasma concentration of isavuconazole (also plasma concentration of ritonavir reduced)—avoid concomitant use of high-dose ritonavir; combination of
Ritonavir

- Antifungals (continued)
  - Ritonavir with ITRACONAZOLE may increase plasma concentration of either drug (or both); ritonavir reduces plasma concentration of Voriconazole—avoid concomitant use
- Antiarrhythmics: ritonavir possibly increases plasma concentration of NON-SEDATING ANTIHISTAMINES
- Antiarrhythmials: caution with ritonavir advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; plasma concentration of ritonavir possibly reduced by MEFLOQUINE; ritonavir increases plasma concentration of QUININE (increased risk of toxicity)
- Antiarrhythmics: avoidance of ritonavir advised by manufacturer of DARIFENACIN and TOLERTODINE; manufacturer of fesoterodine advises dose reduction when ritonavir given with FESOTERODINE—consult fesoterodine product literature; ritonavir possibly increases plasma concentration of SOLIFENACIN—see under Solifenacin, p. 713
- Antipsychotics: ritonavir possibly increases plasma concentration of ANTI PSYCHOTICS; ritonavir possibly increases plasma concentration of ARIPIPRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); manufacturer of ritonavir advises avoid concomitant use with CLOzapine (increased risk of toxicity); ritonavir possibly increases plasma concentration of LURASIDONE—avoid concomitant use; ritonavir reduces plasma concentration of OLANZAPINE—consider increasing dose of olanzapine; ritonavir increases plasma concentration of PIMOZIDE (increased risk of ventricular arrhythmias—avoid concomitant use); ritonavir possibly increases plasma concentration of QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
- Antiarrhythmics: plasma concentration of both drugs reduced when ritonavir given with BOPEPREVIR; manufacturer of ritonavir advises ritonavir and DIDANOSINE should be taken 2.5 hours apart; ritonavir increases the toxicity of EFAVirenz, monitor liver function tests—manufacturer of Atripla® advises avoid concomitant use with high-dose ritonavir; ritonavir increases plasma concentration of INDINAVIR, MARAVIROC and SAQUINAVIR; ritonavir increases plasma concentration of SIMEPREVIR—manufacturer of simeprevir advises avoid concomitant use
- Antivirals: ritonavir possibly increases plasma concentration of ANTI HEPATITIS V/HIV ANTIVIRALS; ritonavir possibly increases plasma concentration of ALPRAZOLAM, DIAZEPAM, FLURAZEPAM and ZOLPIDEM (risk of extreme sedation and respiratory depression—avoid concomitant use); ritonavir possibly increases plasma concentration of MIDAZOLAM (risk of prolonged sedation—avoid concomitant use of oral midazolam); ritonavir increases plasma concentration of BUSPIRONE (increased risk of toxicity)
- Aprepitant: ritonavir possibly increases plasma concentration of APREPITANT
- Atovaquone: ritonavir possibly reduces plasma concentration of ATOV AQUONE—manufacturer of atovaquone advises avoid concomitant use
- Avanafil: ritonavir significantly increases plasma concentration of AVANAFIL—avoid concomitant use
- Bosentan: ritonavir increases plasma concentration of BOSENTAN (consider reducing dose of bosentan)
- Bupropion: ritonavir reduces plasma concentration of BUPROPION
- Calcium-channel blockers: ritonavir possibly increases plasma concentration of CALCIUM-CHANNEL BLOCKERS; ritonavir increases plasma concentration of AMLODIPINE (reduce dose of amlopridine); avoidance of ritonavir advised by manufacturer of LERCANIDIPINE
- Cardiac Glycosides: ritonavir possibly increases plasma concentration of DIGOXIN
- Ciclosporin: ritonavir possibly increases plasma concentration of CICLOSPORIN
- Cilostazol: ritonavir possibly increases plasma concentration of CILOSTAZOL (see under Cilostazol, p. 221)
- Cobimetinib: avoidance of ritonavir advised by manufacturer of COBICISTAT

Ritonavir (continued)

- Colchicine: ritonavir possibly increases risk of COLCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: ritonavir possibly increases plasma concentration of CORTICOSTEROIDS—increased risk of adrenal suppression; ritonavir possibly increases plasma concentration of Budesonide (including inhaled, intranasal, and rectal budesonide)—increased risk of adrenal suppression; ritonavir increases plasma concentration of inhaled and intranasal Fluticasone—increased risk of adrenal suppression; ritonavir reduces plasma concentration of TRIAMCINOLONE injection—increased risk of adrenal suppression
- Cytotoxics: ritonavir increases the plasma concentration of AFINATIN—manufacturer of afatinib advises separating administration of ritonavir by 6 to 12 hours; ritonavir possibly increases plasma concentration of Axitinin (reduce dose of axitinib—consult axitinib product literature); ritonavir possibly increases the plasma concentration of Bosutinib and CABAZITAXEL—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; ritonavir possibly increases plasma concentration of Cabozantinib and Vinblastine; ritonavir possibly increases plasma concentration of Cetirinin—avoid concomitant use or consider reducing the dose of cetirinin (see under Cetirinin, p. 861); ritonavir possibly increases plasma concentration of Crizotinib, Everolimus, Nilotinib and Vinflunine—manufacturer of crizotinib, everolimus, nilotinib and vinflunine advises avoid concomitant use; avoidance of ritonavir advised by manufacturer of Dasatinib (plasma concentration of dasatinib possibly increased); ritonavir possibly increases the plasma concentration of Brutinib—reduce dose of lbrutinib (see under Ibrutinib, p. 867); avoidance of ritonavir advised by manufacturer of Lapatinib; ritonavir possibly increases plasma concentration of Pazopanib (reduce dose of pazopanib); ritonavir possibly increases plasma concentration of Ponatinib—consider reducing initial dose of ponatinib (see under Ponatinib, p. 873); manufacturer of ruxolitinib advises dose reduction when ritonavir given with RUXOLITINIB—consult ruxolitinib product literature; ritonavir possibly increases plasma concentration of Docetaxel—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose; ritonavir increases plasma concentration of Paclitaxel; ritonavir possibly increases plasma concentration of Olaparib (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)
- Daopetine: avoidance of ritonavir advised by manufacturer of DOPOXETINE (increased risk of toxicity)
- Diuretics: ritonavir increases plasma concentration of Eplerenone—avoid concomitant use
- Domperidone: possible increased risk of ventricular arrhythmias when ritonavir given with Domperidone—avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when ritonavir given with Ergot Alkaloids—avoid concomitant use
- Fosaprepitant: ritonavir possibly increases plasma concentration of Fosaprepitant
- Ganciclovir: ritonavir possibly increases plasma concentration of Ganciclovir (half-life of ganciclovir)
- H1-receptor Agonists: ritonavir increases plasma concentration of Eletriptan (risk of toxicity)—avoid concomitant use
- Ibrud: ritonavir possibly increases plasma concentration of Ibrud
- Lipid-regulating Drugs: ritonavir possibly increases plasma concentration of Atorvastatin (use lowest possible dose of atorvastatin); possible increased risk of myopathy when ritonavir given with Rosuvastatin—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when ritonavir given with Simvastatin (avoid concomitant use); avoidance of ritonavir advised by manufacturer of Lomitapide (plasma concentration of lomitapide possibly increased)

Interactions | Appendix 1
Ritonavir (continued)

- Mirabegron: when given with ritonavir avoid or reduce dose of Mirabegron in hepatic or renal impairment—see Mirabegron, p. 715
- Haloxegol: ritonavir possibly increases plasma concentration of Haloxegol—avoid concomitant use
- Oestrogens: ritonavir accelerates metabolism of Oestrogens (reduced concomitant effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Orlisstat: absorption of rimonavir possibly reduced by Orlisstat
- Panobinostat: ritonavir possibly increases plasma concentration of Panobinostat (reduce dose of panobinostat—see under Panobinostat, p. 834)
- Ranolazine: rimonavir possibly increases plasma concentration of Ranolazine—manufacturer of ranolazine advises avoid concomitant use
- Riociguat: avoidance of rimonavir advised by manufacturer of Riociguat
- Sildenafil: ritonavir significantly increases plasma concentration of Sildenafil—avoid concomitant use of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction (consult sildenafil product literature)
- Symathomimetics: rimonavir possibly increases plasma concentration of Dexamfetamine
- Symathomimetics, Beta2: manufacturer of rimonavir advises avoid concomitant use with Salbutamol
- Tacrolimus: rimonavir possibly increases plasma concentration of Tacrolimus
- Tadalafil: rimonavir increases plasma concentration of Tadalafil—avoid concomitant use of tadalafil for pulmonary hypertension
- Theophylline: rimonavir accelerates metabolism of Theophylline (reduced plasma concentration)
- Ticagrelor: rimonavir possibly increases plasma concentration of Ticagrelor—manufacturer of ticagrelor advises avoid concomitant use
- Ulipristal: avoidance of rimonavir advised by manufacturer of Ulipristal (contraceptive effect of ulipristal possibly reduced)
- Vardenafil: rimonavir increases plasma concentration of Vardenafil—avoid concomitant use

Rituximab

- Antipsychotics: avoid concomitant use of cytotoxics with Rituximab
- Clozapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monocular antibodies given with live Vaccines—avoid concomitant use

Rivaroxaban

- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with Ketorolac (avoid concomitant use, including low-dose heparins)
- Anti-arhythmics: manufacturer of rivaroxaban advises avoid concomitant use with Dronedarone
- Anticoagulants: plasma concentration of rivaroxaban reduced by Rifampicin—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Anticoagulants: increased risk of haemorrhage when rivaroxaban given with other Anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with Apixaban, Darapladin and Edoxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antidepressants: plasma concentration of rivaroxaban possibly reduced by St John’s Wort—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antiepileptics: plasma concentration of rivaroxaban possibly reduced by Carbamazepine, Phenytoin, Phenobarbital, Phenytoin and Primidone—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antifungals: plasma concentration of rivaroxaban increased by Fosamprenavir, Saquinavir and Tipranavir; manufacturers advise concomitant use of rivaroxaban with Lopinavir; plasma concentration of rivaroxaban increased by Ritonavir—avoid concomitant use
- Antibacterials: effects of rivaroxaban possibly inhibited by Ciprofloxacin (manufacturer of rivaroxaban advises avoid concomitant use)
- Antidepressants: metabolism of rivaroxaban inhibited by Fluvoxamine
- Antiepileptics: effects of rivaroxaban possibly inhibited by Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone (manufacturer of rivaroxaban advises avoid concomitant use)
- Theophylline: manufacturer of rivaroxaban advises avoid concomitant use with Theophylline
- Ulcer-healing Drugs: metabolism of rivaroxaban inhibited by Cimetidine

Roflumilast

- Aminophylline: manufacturer of roflumilast advises avoid concomitant use with Aminophylline
- Antibacterials: effects of roflumilast inhibited by Ciprofloxacin (manufacturer of roflumilast advises avoid concomitant use)
- Antidepressants: metabolism of roflumilast by Fluvoxamine
- Antiepileptics: effects of roflumilast possibly inhibited by Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone (manufacturer of rivaroxaban advises avoid concomitant use)
- Theophylline: manufacturer of rivaroxaban advises avoid concomitant use with Theophylline
- Ulcer-healing Drugs: metabolism of roflumilast inhibited by Cimetidine

Ropinirole

- Antipsychotics: metabolism of ropinirole inhibited by Ciprofloxacin (increased plasma concentration)
- Antipsychotics: manufacturer of ropinirole advises avoid concomitant use of Antipsychotics (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by Memantine
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by Methyldopa
- Metoclopramide: manufacturer of ropinirole advises avoid concomitant use of Metoclopramide (antagonism of effect)
- Oestrogens: plasma concentration of ropinirole increased by Oestrogens

Ropivacaine

- Anti-arhythmics: increased myocardial depression when ropivacaine given with Anti-arhythmics
- Antidepressants: metabolism of ropivacaine inhibited by Fluvoxamine—avoid prolonged administration of ropivacaine

Rousuvastatin: see Statins

Rotavirus Vaccine: see Vaccines

Rotigotine

- Antipsychotics: manufacturer of rotigotine advises avoid concomitant use of Antipsychotics (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by Memantine
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by Methyldopa
- Metoclopramide: manufacturer of rotigotine advises avoid concomitant use of Metoclopramide (antagonism of effect)

Rufinamide

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and Tricyclic-related Antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and Tricyclics (convulsive threshold lowered)
- Antiepileptics: plasma concentration of both drugs possibly reduced when rufinamide given with Carbamazepine; plasma concentration of rufinamide possibly reduced by Fosphenytoin and Phenytoin, also plasma concentration of fosphenytoin and phenytoin possibly increased; plasma concentration of rufinamide possibly reduced by Phenobarbital and Primidone; plasma concentration of rufinamide possibly increased by Sodium Valproate and Valproic Acid (reduce dose of rufinamide)
Rufinamide (continued)

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by • MEfloquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by • ANTiPSYCHOTICS (convulsive threshold lowered)
- Oestrogens: rufinamide accelerates metabolism of • OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Oralistat: possible increased risk of convulsions when antiepileptics given with • ORLISTAT
- Progestogens: rufinamide accelerates metabolism of • PROGESTOGENs (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)

Ruxolitinib

- Antibacterials: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with • CLARITHROMYCIN and • TELITHROMYCIN—consult ruxolitinib product literature; plasma concentration of ruxolitinib reduced by • RIFAMPICIN
- Antifungals: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with • FLUCONAZOLE, • ITRACONAZOLE, • KETOCONAZOLE, • POSaconazole and • voriconazole—consult ruxolitinib product literature
- Antipsychotics: avoid concomitant use of cytotoxics with • clozapine (increased risk of agranulocytosis)
- Antivirals: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with • boceprevir, • indinavir, • lopinavir, • ritonavir, • saquinavir and • telaprevir—consult ruxolitinib product literature

Sacubitril

- ACE Inhibitors: manufacturer of sacubitril advises avoid • ACE INHIBITORS for 36 hours before or after sacubitril
- Diuretics: sacubitril reduces plasma concentration of • Furosemide
- Lipid-regulating Drugs: sacubitril increases plasma concentration of • atorvastatin

St John’s Wort

- Aminophylline: St John’s wort possibly reduces plasma concentration of • aminophylline
- Analgesics: St John’s wort possibly reduces plasma concentration of • Methadone
- Anti-arrhythmics: St John’s wort possibly reduces plasma concentration of • Dronedarone—avoid concomitant use
- Antibacterials: St John’s wort possibly reduces plasma concentration of • Bedaquiline—manufacturer of bedaquiline advises avoid concomitant use; St John’s wort reduces plasma concentration of • Telithromycin (avoid during and for 2 weeks after St John’s wort)
- Anticoagulants: St John’s wort possibly reduces plasma concentration of • Apixaban—manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism; St John’s wort reduces anticoagulant effect of • edaravone (avoid concomitant use); St John’s wort possibly reduces plasma concentration of • dabigatran—manufacturer of dabigatran advises avoid concomitant use; St John’s wort possibly reduces plasma concentration of • edoxaban; St John’s wort possibly reduces plasma concentration of • rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antidepressants: possible increased serotoninergic effects when St John’s wort given with • duloxetine, • venlafaxine or • Vortioxetine; St John’s wort reduces plasma concentration of • Amitriptyline; increased serotoninergic effects when St John’s wort given with • SSRIs—avoid concomitant use
- Antiepileptics: St John’s wort possibly reduces plasma concentration of • carbamazepine; St John’s wort possibly reduces plasma concentration of • fosphenytoin, • phenobarbital, • phenytoin and • primidone—avoid concomitant use
- Antifungals: St John’s wort possibly reduces plasma concentration of • isavuconazole—avoid concomitant use;

St John’s Wort (continued)

- Antifungals (continued)
  - St John’s wort reduces plasma concentration of • voriconazole—avoid concomitant use
- Antimalarials: avoidance of antidepressants advised by manufacturer of • arteether with lumefantrine and • artemisinol with piperaquine
- Antimuscarnicinas: St John’s wort possibly reduces plasma concentration of active metabolite of • fesoterodine—manufacturer of fesoterodine advises avoid concomitant use
- Antipsychotics: St John’s wort possibly reduces plasma concentration of • aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); St John’s wort possibly reduces plasma concentration of • lurasidone—avoid concomitant use
- Antivirals: St John’s wort reduces plasma concentration of • atazanavir, • darunavir, • efavirenz, • fosamprenavir, • indinavir, • lopinavir, • nevirapine, • ritonavir and • saquinavir—avoid concomitant use; St John’s wort possibly reduces plasma concentration of • dalatafazin, • dasabuvir, • ombitasvir, • paritaprevir and • simprevir—manufacturer of dalatafazin, dasabuvir, ombitasvir, paritaprevir and simprevir advises avoid concomitant use; St John’s wort possibly reduces the plasma concentration of • dolugetavir (see under Dolugetavir, p. 592); avoidance of St John’s wort advised by manufacturer of • elvitegravir, • etravirine, • ledipasvir, • sofosbuvir and • telaprevir; St John’s wort possibly reduces plasma concentration of • maraviroc and • tirapavir—avoid concomitant use; avoidance of St John’s wort advised by manufacturer of • rilpivirine (plasma concentration of rilpivirine possibly reduced)
- Anxiolytics and Hypnotics: St John’s wort possibly reduces plasma concentration of oral midazolam
- Apremilast: St John’s wort possibly reduces plasma concentration of • apremilast—avoid concomitant use
- Aprepitant: avoidance of St John’s wort advised by manufacturer of • aprepitant
- Atomoxetine: possible increased risk of convulsions when antidepressants given with • atomoxetine
- Calcium-channel Blockers: St John’s wort possibly reduces plasma concentration of • amiodopine and • felodipine; St John’s wort reduces plasma concentration of • nifedipine; St John’s wort significantly reduces plasma concentration of • verapamil
- Cannabis Extract: St John’s wort possibly reduces plasma concentration of • cannabis extract—manufacturer of cannabis extract advises avoid concomitant use
- Cardiac Glicoses: St John’s wort reduces plasma concentration of • digoxin—avoid concomitant use
- Ciclosporin: St John’s wort reduces plasma concentration of • ciclosporin—avoid concomitant use
- Cobicitab: St John’s wort possibly reduces plasma concentration of • cobicitab—manufacturer of cobicitab advises avoid concomitant use
- Cytotoxic: St John’s wort possibly reduces plasma concentration of • axitinib—consider increasing dose of axitinib; St John’s wort possibly reduces plasma concentration of • bortezomib, • bosutinib, • cabozantinib, • crizotinib, • everolimus, • ibritinib, •idelalisib, • ponatinib and • vinflunine—manufacturer of bortezomib, bosutinib, cabozantinib, crizotinib, everolimus, ibritinib, idelalisib, ponatinib and vinflunine advises avoid concomitant use; St John’s wort possibly reduces plasma concentration of • ceritinib—avoid concomitant use; avoidance of St John’s wort advised by manufacturer of • cabazitaxel, • dabrafenib, • gefitinib, • lapatinib, • olaparib and • vemurafenib; St John’s wort reduces plasma concentration of • matinib—avoid concomitant use; avoidance of St John’s wort advised by manufacturer of • vandetanib and • vismodegib (plasma concentration of vandetanib and vismodegib possibly reduced); St John’s wort possibly reduces plasma concentration of • eribulin; St John’s wort accelerates metabolism of • irinotecan (reduced plasma concentration—avoid concomitant use)
St John's Wort – Saquinavir

Interactions

Dapoxetine: possible increased risk of serotonergic effects when St John's Wort is given with dapoxetine (manufacturer of dapoxetine advises St John's Wort should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping St John's Wort)

Diuretics: St John's Wort reduces plasma concentration of eplerenone — avoid concomitant use

Fingolimod: St John's Wort possibly reduces plasma concentration of fingolimod — manufacturer of fingolimod advises avoid concomitant use

Fosaprepitant: avoidance of St John's Wort advised by manufacturer of fosaprepitant

Panobinostat:
Naloxegol:
Macitentan:
SHT; receptor Agonists: increased serotonergic effects when St John's Wort is given with SHT, agonists — avoid concomitant use

Ivabradine: St John's Wort reduces plasma concentration of ivabradine — avoid concomitant use

Ivacaftor: manufacturer of ivacaftor advises avoid concomitant use

Lipid-regulating Drugs: St John's Wort reduces plasma concentration of simvastatin

Lumacaftor: avoidance of St John's Wort advised by manufacturer of lumacaftor

Macitentan: avoidance of St John's Wort advised by manufacturer of macitentan

Naloxegol: St John's Wort possibly reduces plasma concentration of naloxegol — avoid concomitant use

Oestrogens: St John's Wort reduces contraceptive effect of oestrogens

Panobinostat: avoidance of St John's Wort advised by manufacturer of panobinostat

Progestogens: St John's Wort reduces contraceptive effect of progestogens — avoid concomitant use

Tacrolimus: St John's Wort reduces plasma concentration of tacrolimus — avoid concomitant use

Theophylline: St John's Wort possibly reduces plasma concentration of theophylline

Ulcerc-healing Drugs: St John's Wort possibly reduces plasma concentration of omeprazole

Ulipristal: avoidance of St John's Wort advised by manufacturer of ulipristal (contraceptive effect of ulipristal possibly reduced)

Salmeterol
Salbutamol
Saquinavir

Analgesics: increased risk of ventricular arrhythmias when saquinavir is given with alfentanil, fentanyl, of methadone — avoid concomitant use

Anti-arrhythmics: increased risk of ventricular arrhythmias when saquinavir is given with amiodarone, disopyramide, dofetilide, flecainide, lidocaine or propafenone — avoid concomitant use

Antibacterials: plasma concentration of both drugs possibly increased when saquinavir is given with clarithromycin (increased risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when saquinavir is given with dapsone, erythromycin or moxifloxacin — avoid concomitant use; saquinavir increases plasma concentration of rifabutin (also plasma concentration of saquinavir reduced) — reduced rifabutin dose; plasma concentration of saquinavir significantly reduced by rifampicin, also risk of hepatotoxicity — avoid concomitant use; increased risk of ventricular arrhythmias when saquinavir is given with delamanid; plasma concentration of both drugs may increase when saquinavir is given with fusidic acid; avoidance of saquinavir advised by manufacturer of telithromycin (risk of ventricular arrhythmias)

Anticoagulants: saquinavir possibly enhances anticoagulant effect of warfarin — avoid of saquinavir advised by manufacturer of apixaban and rivaroxaban

Antidepressants: increased risk of ventricular arrhythmias when saquinavir is given with trazodone or tricyclics — avoid concomitant use; plasma concentration of saquinavir reduced by St John's Wort — avoid concomitant use

Antiepileptics: plasma concentration of saquinavir possibly reduced by carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone

Antifungals: plasma concentration of saquinavir increased by ketoconazole — manufacturer of ketoconazole advises avoid concomitant use; plasma concentration of saquinavir possibly increased by imidazoles and triazoles

Antihistamines: increased risk of ventricular arrhythmias when saquinavir with mizolastine — avoid concomitant use

Antimalaria: caution with saquinavir advised by manufacturer of arteether with lumefantrine; avoidance of saquinavir advised by manufacturer of arteminol with piperaquine (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when saquinavir is given with quinine — avoid concomitant use

Antimuscarinics: avoidance of saquinavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advices dose reduction when saquinavir given with fesoterodine — consult fesoterodine product literature

Antipsychotics: increased risk of ventricular arrhythmias when saquinavir is given with clozapine, haloperidol or phenothiazines — avoid concomitant use; saquinavir possibly increases plasma concentration of aripiprazole (reduce dose of aripiprazole — consult aripiprazole product literature); saquinavir possibly increases plasma concentration of luraside — avoid concomitant use; saquinavir possibly increases plasma concentration of pimozone (increased risk of ventricular arrhythmias — avoid concomitant use); saquinavir possibly increases plasma concentration of quetiapine — manufacturer of quetiapine advises avoid concomitant use

Antivirals: increased risk of ventricular arrhythmias when saquinavir is given with atazanavir or lopinavir — avoid concomitant use; saquinavir reduces plasma concentration of darunavir — avoid concomitant use; plasma concentration of saquinavir significantly reduced by efavirenz; plasma concentration of saquinavir increased by indinavir and ritonavir; saquinavir increases plasma concentration of maraviroc (consider reducing dose of maraviroc); avoidance of saquinavir advised by manufacturer of paritaprevir; plasma concentration of saquinavir reduced by ritonavir

Antioxidics and Hypnotics: saquinavir increases plasma concentration of midazolam (risk of prolonged sedation — avoid concomitant use of oral midazolam)

Avanafil: saquinavir possibly increases plasma concentration of avanafil — manufacturer of avanafil advises avoid concomitant use

Beta-blockers: increased risk of ventricular arrhythmias when saquinavir is given with sotalol — avoid concomitant use

Ciclosporin: plasma concentration of both drugs increased when saquinavir given with ciclosporin

Corticosteroids: plasma concentration of saquinavir possibly reduced by dexamethasone

Cytotoxics: saquinavir possibly increases the plasma concentration of afatinib — manufacturer of afatinib advises separating administration of saquinavir by 6 to 12 hours; saquinavir possibly increases plasma concentration of afatinib (reduce dose of afatinib — consult afatinib product literature); saquinavir possibly increases the plasma concentration of bosutinib and cabazitaxel — manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; saquinavir possibly increases plasma concentration of ceritinib — avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 861); saquinavir possibly increases plasma concentration of crizotinib and everolimus — manufacturer of crizotinib and everolimus advises avoid concomitant use; saquinavir possibly increases...
**Saxagliptin**

- **Cytopotitics** (continued): the plasma concentration of • IBRUTINIB—reduce dose of ibritinib (see under ibritinib, p. 867); avoidance of saxagliptin advised by manufacturer of • LAPATINIB; increased risk of ventricular arrhythmias when saxagliptin given with • RANITIDINE—avoid concomitant use; saxagliptin possibly increases plasma concentration of • DOXOTAXEL—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose by 50%.

- Dapoxetine: avoidance of saxagliptin advised by manufacturer of • DAPoxetine (increased risk of toxicity).

- Diuretics: saxagliptin increases plasma concentration of • EPLERENONE (reduce dose of eplerenone).

- Domperidone: possible increased risk of ventricular arrhythmias when saxagliptin given with • DOMPERIDON—avoid concomitant use.

- Ergot Alkaloids: increased risk of ergotism when saxagliptin given with • ERGOTAMINE—avoid concomitant use.

- Guanfacine: saxagliptin possibly increases plasma concentration of • GUANFACINE (halve dose of guanfacine).

- Lipid-regulating Drugs: possible increased risk of myopathy when saxagliptin given with • SIMVASTATIN (avoid concomitant use); avoidance of saxagliptin advised by manufacturer of • LOMITAPIDE (plasma concentration of lomitapide possibly increased).

- Naloxegol: saxagliptin possibly increases plasma concentration of • NALOXEGOL—avoid concomitant use.

- Orlitast: absorption of saxagliptin possibly reduced by • ORLISTAT.

- Panobinostat: saxagliptin possibly increases plasma concentration of • PANOBINOSTAT (reduce dose of panobinostat—see under Panobinostat, p. 854).

- Pentamidine Isetionate: increased risk of ventricular arrhythmias when saxagliptin given with • PENTAMIDINE ISETIONATE—avoid concomitant use.

- Ranolazine: saxagliptin possibly increases plasma concentration of • RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use.

- Sildenafil: increased risk of ventricular arrhythmias when saxagliptin given with • SILDENAFIL—avoid concomitant use.

- Tacrolimus: saxagliptin increases plasma concentration of • Tacrolimus (consider reducing dose of tacrolimus).

- Tadalafil: increased risk of ventricular arrhythmias when saxagliptin given with • TADALAFIL—avoid concomitant use.

- Ulcer-healing Drugs: plasma concentration of saxagliptin possibly increased by • Cimetidine; plasma concentration of saxagliptin possibly increased by • ESOMEPRAZOLE, • Lansoprazole, • Pantoprazole and • Rabeprazole—manufacturer of saxagliptin advises avoid concomitant use; plasma concentration of saxagliptin increased by • OMEPRAZOLE—manufacturer of saxagliptin advises avoid concomitant use.

- Vardenafil: increased risk of ventricular arrhythmias when saxagliptin given with • VARDENAFIL—avoid concomitant use.

**Selegiline**

- **Antidepressants:** manufacturer of selegiline advises avoid concomitant use with • CITALOPRAM and • ESICITALOPRAM; increased risk of hypertension and CNS excitation when selegiline given with • FLUOXETINE (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with • FLUOXAMINE, • SERTRALINE or • VENLAFAXINE (selegiline should not be started until 1 week after stopping fluvoxamine, sertraline or venlafaxine, avoid fluvoxamine, sertraline or venlafaxine for 2 weeks after stopping selegiline); enhanced hypotensive effect when selegiline given with • MAOIS—manufacturer of selegiline advises avoid concomitant use; avoid concomitant use of selegiline with • MOLOBEMIDE; CNS toxicity reported when selegiline given with • TRICYCLICS; risk of CNS excitation and hypertension when selegiline given with • VORTIXETINE.

- **Dopaminergics:** selegiline enhances effects and increases toxicity of • CO-BENEDOPA, • CO-CARELDOPA or • LEVODOPA (reduce dose of co-benedopa, co-carel dopa or levodopa); max. dose of 10 mg selegiline advised by manufacturer of • ENTACAPONE if used concomitantly.

- 5HT-receptor Agonists: manufacturer of selegiline advises avoid concomitant use with 5HT, AGONISTS.

- Memantine: effects of dopaminergics and selegiline possibly enhanced by • MEMARTINE.

- Methylidopa: antiparkinsonian effect of dopaminergics antagonised by • METHYLDOPA.

- Oestrogens: plasma concentration of selegiline increased by • OESTROGENS—manufacturer of selegiline advises avoid concomitant use.

- Progestogens: plasma concentration of selegiline increased by • PROGESTOGENS—manufacturer of selegiline advises avoid concomitant use.

- **Sympathomimetics:** manufacturer of selegiline advises avoid concomitant use with • SYMPATHOMIMETICS; risk of hypertensive crisis when selegiline given with • DOPAMINE.

**Selenium**

- Eltrombopag: selenium possibly reduces absorption of • ELTROMBOPAG (give at least 4 hours apart).

- Vitamins: absorption of selenium possibly reduced by • ASCORBIC ACID (give at least 4 hours apart).

**Sertraline**

- **Antidepressants,** SSRIs.

- **Sevelamer**

- **Antibacterials:** sevelamer reduces absorption of • CIPROFLOXACIN (at least 2 hours before or 4 hours after ciprofloxacin).

- Ciclosporin: sevelamer possibly reduces plasma concentration of • CICLOSPORIN.

- Mycophenolate: sevelamer possibly reduces plasma concentration of • MYCOPHENOLATE.

- Tacrolimus: sevelamer possibly reduces plasma concentration of • TACROLIMUS.

- Thyroid Hormones: sevelamer possibly reduces absorption of • LEVOTHYROXINE.

- Vitamins: sevelamer reduces absorption of • CALCITRIOL (give at least 1 hour before or 3 hours after sevelamer).

**Sevoflurane**

- **Anaesthetics,** General.

- **Sildenafil**

- **Alpha-blockers:** enhanced hypotensive effect when sildenafil given with • ALPHA-BLOCKERS (avoid alpha-blockers for 4 hours after sildenafil)—when patient is stable on the alpha blocker initiate sildenafil at the lowest possible dose.

- **Anti-arrhythmics:** avoidance of sildenafil advised by manufacturer of • DISOPYRAMIDE (risk of ventricular arrhythmias).

- **Antibacterials:** plasma concentration of sildenafil increased by • CLARITHROMYCIN—consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension; plasma concentration of sildenafil increased by • ERITHROMYCIN—reduce initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to twice daily for pulmonary hypertension; plasma
Sildenafil

- **Antibacterials** (continued): concentration of sildenafil possibly increased by **TELITHROMYCIN**—consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension.
- **Antifungals**: plasma concentration of sildenafil increased by **KETOCONAZOLE**—reduce initial dose of sildenafil for erectile dysfunction and avoid concomitant use of sildenafil for pulmonary hypertension; plasma concentration of sildenafil increased by **ITRACONAZOLE**—reduce initial dose of sildenafil.
- **Antivirals**: plasma concentration of sildenafil increased by **ETRAVIRINE**; plasma concentration of sildenafil possibly increased by **fosamprenavir**; plasma concentration of sildenafil possibly increased by **INDINAVIR**—reduce initial dose of sildenafil; plasma concentration of sildenafil significantly increased by **RITONAVIR**—avoid concomitant use of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction (consult sildenafil product literature); increased risk of ventricular arrhythmias when sildenafil given with **SAQUINAVIR**—avoid concomitant use; avoidance of sildenafil advised by manufacturer of **TELAPREvir**; avoidance of sildenafil for pulmonary arterial hypertension advised by manufacturer of **TIRPAVENIR**.
- **Basal Hypertensive Agents**: plasma concentration of sildenafil reduced by **BOSENTAN**, also plasma concentration of bosentan increased.
- **Calcium-channel Blockers**: enhanced hypotensive effect when sildenafil given with **AMLODINE**.
- **Cobicistat**: plasma concentration of sildenafil possibly increased by **Cobicistat**—manufacturer of cobicistat advises avoid concomitant use of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction—consult cobicistat product literature.
- **Cytotoxics**: avoidance of sildenafil for pulmonary arterial hypertension advised by manufacturer of **IDEALISIB**.
- **Dapoxetine**: avoidance of sildenafil advised by manufacturer of **DAPOXETINE**.
- **Grapefruit Juice**: plasma concentration of sildenafil possibly increased by **GRAPFruit JUICE**.
- **Niacinamide**: sildenafil significantly enhances hypotensive effect of **NICTARDIN** (avoid concomitant use).
- **Nitrates**: sildenafil significantly enhances hypotensive effect of **NITRATES** (avoid concomitant use).
- **Riociguat**: enhanced hypotensive effect when sildenafil given with **RIOCIgUAT**—avoid concomitant use.
- **Ulcer-Healing Drugs**: plasma concentration of sildenafil increased by **CIMETIDINE**—consider reducing dose of sildenafil for erectile dysfunction.

Silmiximab

- **Antipsychotics**: avoid concomitant use of cytotoxics with **CLOZAPINE** (increased risk of agranulocytosis).
- **Vaccines**: risk of generalised infections when monoclonal antibodies given with live **VACCINES**—avoid concomitant use.

Simeprevir

- **Anti-arrhythmics**: possible increased risk of bradycardia when simeprevir (with sofosbuvir) given with **AMIODARONE**—see under Amiodarone, p. 99.
- **Antibacterials**: plasma concentration of simeprevir possibly increased by **CLAIRITHROMYCIN** and **TELITHROMYCIN**—manufacturer of simeprevir advises avoid concomitant use; plasma concentration of both drugs increased when simeprevir given with **ERYTHROMYCIN**—manufacturer of simeprevir advises avoid concomitant use; plasma concentration of simeprevir possibly reduced by **RIFABUTIN**—manufacturer of simeprevir advises avoid concomitant use; plasma concentration of simeprevir possibly reduced by **RIFAMPICIN**—manufacturer of simeprevir advises avoid concomitant use.
- **Antidepressants**: plasma concentration of simeprevir possibly reduced by **ST JOHN’S WORT**—manufacturer of simeprevir advises avoid concomitant use.
- **Antiepileptics**: plasma concentration of simeprevir possibly reduced by **CARBAMAZEPINE**, **FOSPHENYTOIN**, **OXCARBAZEPINE**, **PHENOBARBITAL**, **PHENYTOIN** and **PRIMIDONE**—manufacturer of simeprevir advises avoid concomitant use.
- **Antifungals**: manufacturer of simeprevir advises avoid concomitant use with **KETOCONAZOLE**; plasma concentration of simeprevir possibly increased by **FLUCONAZOLE**.
- **Antivirals**: plasma concentration of simeprevir possibly increased by **ITRACONAZOLE**, **POSACONAZOLE** and **VORICONAZOLE**—manufacturer of simeprevir advises avoid concomitant use.
- **Antiwars**: plasma concentration of both drugs increased when simeprevir given with **DARUNAVIR**—manufacturer of simeprevir advises avoid concomitant use; plasma concentration of simeprevir reduced by **ETRAVIRINE**; plasma concentration of both drugs increased when simeprevir given with **LEDIPASVIR**—manufacturer of ledipasvir advises avoid concomitant use; plasma concentration of simeprevir possibly reduced by **NEVIRAPINE**—manufacturer of simeprevir advises avoid concomitant use; plasma concentration of simeprevir increased by **RITONAVIR**—manufacturer of simeprevir advises avoid concomitant use.
- **Anxiolytics and Hypnotics**: simeprevir increases plasma concentration of **ORAL MIDAZOLAM**.
- **Cardiac Glycosides**: simeprevir increases plasma concentration of **DIGOXIN**.
- **Cobicistat**: plasma concentration of simeprevir possibly increased by **Cobicistat**—manufacturer of simeprevir advises avoid concomitant use.
- **Corticosteroids**: plasma concentration of simeprevir possibly reduced by **Dexamethasone**—manufacturer of simeprevir advises avoid concomitant use.
- **Lipid-regulating Drugs**: simeprevir increases plasma concentration of **ATORVASTATIN**, **ROSUVASTATIN** and **SIMVASTATIN** (consider reducing dose of atorvastatin, rosuvastatin and simvastatin).

Simvastatin see Statins

Siroliimus

- **Anti-arrhythmics**: caution with sirolimus advised by manufacturer of **DRONEDARONE**.
- **Antibacterials**: plasma concentration of sirolimus increased by **CLAIRITHROMYCIN** and **TELITHROMYCIN**—avoid concomitant use; plasma concentration of both drugs increased when sirolimus given with **ERYTHROMYCIN**; plasma concentration of sirolimus reduced by **RIFABUTIN** and **RIFAMPICIN**—avoid concomitant use.
- **Antifungals**: plasma concentration of sirolimus increased by **ITRACONAZOLE**, **KETOCONAZOLE** and **VORICONAZOLE**—avoid concomitant use; plasma concentration of sirolimus possibly increased by **ISAVUCONAZOLE**, **MICAFUNGIN** and **MICONAZOLE**; plasma concentration of sirolimus possibly increased by **FLUCONAZOLE** and **POSACONAZOLE**.
- **Antiwars**: plasma concentration of sirolimus possibly increased by **BOCEPREVIR** (increased risk of toxicity—reduce sirolimus dose); plasma concentration of both drugs increased when sirolimus given with **TELAPREvir**—reduce dose of sirolimus.
- **Calcium-channel Blockers**: plasma concentration of sirolimus possibly increased by **MICARDIPINE**; plasma concentration of sirolimus increased by **DILTIAZEM**; plasma concentration of both drugs increased when sirolimus given with **VERAPAMIL**.
- **Ciclosporin**: plasma concentration of sirolimus increased by **CICLOSPORIN**.
- **Cytotoxics**: avoidance of sirolimus advised by manufacturer of **CERITINIB**—with caution with sirolimus advised by manufacturer of **CRIZOTINIB**.
- **Grapefruit Juice**: plasma concentration of sirolimus increased by **Grapefruit juice**—avoid concomitant use.
- **Lumacaftor**: avoidance of sirolimus advised by manufacturer of **LUMACAFTOR**.

Sitagliptin see Antidiabetics

Smallpox Vaccine see Vaccines

Sodium Aurothiomalate

- **ACE Inhibitors**: flushing and hypotension reported when sodium aurothiomalate given with **ACE INHIBITORS**.
- **Penicillamine**: increased risk of haematological toxicity when sodium aurothiomalate given with **PENICILLAMINE**—see under Penicillamine, p. 964).
Sodium Benzoate
- Antiepileptics: effects of sodium benzoate possibly reduced by SODIUM VALPROATE and VALPROIC ACID
- Antipsychotics: effects of sodium benzoate possibly reduced by HALOPERIDOL
- Corticosteroids: effects of sodium benzoate possibly reduced by CORTICOSTEROIDS

Sodium Citrate
- Antibacterials: avoid concomitant use of sodium citrate with METHENAMINE
- Ulcer-healing Drugs: avoidance of sodium citrate advised by manufacturer of SUCRALFATE

Sodium Clodronate see Bisphosphonates

Sodium Desferalate see Iron salts

Sodium Nitroprusside see Vasodilator Antihypertensives

Sodium Oxybate
- Analgesics: effects of sodium oxybate enhanced by OPIOID ANALGESICS (avoid concomitant use)
- Antidepressants: increased risk of side-effects when sodium oxybate given with TRICYCLICS
- Antiepileptics: manufacturer of sodium oxybate advises giving 14 days apart
- Anticoagulants: increased risk of side-effects when sodium oxybate given with RUFINAMIDE
- Antihypnotics and Hypnotics: plasma concentration of sodium oxybate possibly reduced by BENZODIAZEPINES (avoid concomitant use)
- Antimicrobials: effects of sodium oxybate possibly reduced by SODIUM PHENYLBUTYRATE
- Antipsychotics: effects of sodium oxybate possibly enhanced by VALPROIC ACID

Sodium Phenytoin
- Antiepileptics: effects of sodium phenytoin possibly reduced by SODIUM VALPROATE and VALPROIC ACID
- Antipsychotics: effects of sodium phenytoin possibly reduced by HALOPERIDOL
- Corticosteroids: effects of sodium phenytoin possibly reduced by CORTICOSTEROIDS

Sodium Stibogluconate
- Antifungals: possible increased risk of arrhythmias when sodium stibogluconate given before AMPHOTERICIN—manufacturer of sodium stibogluconate advises giving 14 days apart

Sodium Valproate
- Analgesics: effects of sodium valproate enhanced by ASPIRIN
- Antibacterials: metabolism of sodium valproate possibly inhibited by ERYTHROMYCIN (increased plasma concentration); avoidance of sodium valproate advised by manufacturer of PIPEMICILLIN; plasma concentration of sodium valproate reduced by CARBABENEMES—avoid concomitant use
- Anticoagulants: sodium valproate possibly enhances anticoagulant effect of COUMARINS
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIS and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: plasma concentration of sodium valproate reduced by CARBAMAZEPINE, also plasma concentration of active metabolite of carbamazepine increased; sodium valproate possibly increases plasma concentration of ETHOSUXIMIDE; sodium valproate increases or possibly decreases plasma concentration of FOSPHENYTOIN and PHTHYDON, also plasma concentration of sodium valproate reduced; sodium valproate increases plasma concentration of LAMOTRIGINE (increased risk of toxicity—reduce lamotrigine dose); sodium valproate sometimes reduces plasma concentration of an active metabolite of OXCARBAZEPINE; sodium valproate increases plasma concentration of PHENOBARBITAL and PRIMIDONE (also plasma concentration of sodium valproate reduced); sodium valproate possibly increases plasma concentration of RUFINAMIDE (reduce dose of rufinamide); hyperammonaemia and CNS toxicity reported when sodium valproate given with TOPRIMATE
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by MEFLOQUINE

Sodium Valproate (continued)
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by CLOZAPINE, RITONAVIR, OLANZAPINE
- Antivirals: plasma concentration of sodium valproate possibly reduced by RITONAVIR; sodium valproate possibly increases plasma concentration of ZIDOVUDINE (increased risk of toxicity)
- Antioxidants and Hypnotics: plasma concentration of sodium valproate possibly increased by CLOBAZAM; increased risk of side-effects when sodium valproate given with LAMOTRIGINE, PHENYTOIN and PRIMIDONE

Sodium Benzoate—Statins

Sofosbuvir
- Anti-arrhythmics: possible increased risk of bradycardia when sofosbuvir given with AMIODARONE—see under Amiodarone, p. 99
- Antibacterials: manufacturer of sofosbuvir advises avoid concomitant use with RIFABUTIN and RIFAMPICIN
- Antidepressants: manufacturer of sofosbuvir advises avoid concomitant use with ST JOHN’S WORT
- Antiepileptics: manufacturer of sofosbuvir advises avoid concomitant use with CARBAMAZEPINE, OXCARBAZEPINE, PHENOBARBITAL and PRIMIDONE
- Anticoagulants: sodium valproate possibly reduces effects of SODIUM OXYBATE
- Antipsychotics: increased risk of toxicity when sofosbuvir given with OLANZAPINE

Solifenacin see Antimuscarinics

Somatropin
- Corticosteroids: growth-promoting effect of somatropin may be inhibited by CORTICOSTEROIDS
- Oestrogens: increased doses of somatropin may be needed when given with OESTROGENS (when used as oral replacement therapy)

Sorafenib
- Anti-arrhythmics: bioavailability of sorafenib reduced by NEOMYCIN; plasma concentration of sorafenib reduced by RIFAMPICIN
- Anticoagulants: sorafenib possibly enhances anticoagulant effect of COUMARINS
- Antipsychotics: avoid concomitant use of cytotoxics with CLOZAPINE (increased risk of agranulocytosis)
- Antivirals: avoidance of sorafenib advised by manufacturer of ZIDOVUDINE
- Anticoagulants: sorafenib possibly reduces plasma concentration of IRINOTECAN
- Anticoagulants: sorafenib possibly reduces plasma concentration of DOXETAXEL and DOROXUBICIN; sorafenib possibly increases plasma concentration of IRINOTECAN

Sotalol see Beta-blockers

Spiroponolactone see Diuretics

Statin
- Antacids: absorption of rosuvastatin reduced by ANTAGONISTS
- Antiarhythmics: increased risk of myopathy when simvastatin given with AMIODARONE (see under Simvastatin, p. 194); increased risk of myopathy when simvastatin given with DRONEDARONE; plasma concentration of atorvastatin
Antivirals:• Antiepileptics: • Antidiabetics:

Possible increased risk of myopathy when atorvastatin or simvastatin given with: • AZITHROMYCIN; plasma concentration of atorvastatin and pravastatin increased by • CLARITHROMYCIN; increased risk of myopathy when simvastatin given with • CLARITHROMYCIN, • ERYTHROMYCIN or • TELITHROMYCIN (avoid concomitant use); plasma concentration of rosuvastatin reduced by • ERYTHROMYCIN or • KETOCONAZOLE; increased risk of myopathy when atorvastatin given with • ERYTHROMYCIN; plasma concentration of pravastatin increased by • AZITHROMYCIN; plasma concentration of atorvastatin and simvastatin possibly reduced by • RIFAMPICIN; metabolism of fluvastatin accelerated by • RIFAMPICIN (reduced effect); increased risk of myopathy when statins given with • DAPTOMYCIN (preferably avoid concomitant use); risk of myopathy and rhabdomyolysis when statins given with • FUSIDIC ACID—avoid concomitant use and for 7 days after last fusidic acid dose; increased risk of myopathy when atorvastatin given with • TELITHROMYCIN (avoid concomitant use); possible increased risk of myopathy when pravastatin given with • TELITHROMYCIN

Anticoagulants: atorvastatin may transiently reduce anticoagulant effect of • WARFARIN; simvastatin can enhance the anticoagulant effect of • COUMARINS; fluvastatin enhances anticoagulant effect of • COUMARINS; rosuvastatin possibly enhances anticoagulant effect of • COUMARINS and • PHENINDIONE

Antidepressants: plasma concentration of simvastatin reduced by • ST JOHN’S WORT

Antidiabetics: fluvastatin possibly increases plasma concentration of • GLIBENCLAMIDE

Antiepileptics: plasma concentration of simvastatin reduced by • CARBAMAZEPINE and • ESICLABAZEPINE—consider increasing dose of simvastatin; plasma concentration of rosuvastatin reduced by • ESICLABAZEPINE; combination of fluvastatin with • FOSAMPRENAVIR or • PHENYTOIN may increase plasma concentration of either drug (or both)

Antifungals: possible increased risk of myopathy when atorvastatin given with • KETOCONAZOLE—manufacturer of ketoconazole advises avoid concomitant use; increased risk of myopathy when simvastatin given with • ITRACONAZOLE, • KETOCONAZOLE or • POSACONAZOLE (avoid concomitant use); possible increased risk of myopathy when simvastatin given with • FLUCONAZOLE or • MICONAZOLE; possible increased risk of myopathy when atorvastatin given with • FLUCONAZOLE or • IMIDAZOLES; possible concentration of simvastatin increased by • FLUCONAZOLE—possibly increased risk of myopathy; plasma concentration of atorvastatin increased by • ISAUCONAZOLE; plasma concentration of rosuvastatin increased by • ITRACONAZOLE—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when atorvastatin given with • ITRACONAZOLE, • POSACONAZOLE or • VORICONAZOLE; increased risk of myopathy when simvastatin given with • VORICONAZOLE

Antivirals: increased risk of myopathy when atorvastatin or pravastatin given with • ATAZANAVIR; plasma concentration of rosuvastatin increased by • ATAZANAVIR, • DARUNAVIR, • LOPINAVIR and • TIPRANAVIR—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when simvastatin given with • ATAZANAVIR, • INDINAVIR, • RITONAVIR or • SAQUINAVIR (avoid concomitant use); plasma concentration of atorvastatin increased by • BOCEPREVIR (reduce dose of atorvastatin); manufacturers advise avoid atorvastatin use of simvastatin with • BOCEPREVIR and • TELAPREVIR; plasma concentration of pravastatin possibly increased by • BOCEPREVIR; plasma concentration of rosuvastatin increased by • DACLATASVIR; plasma concentration of pravastatin possibly increased by • DARUNAVIR (use lowest possible dose of pravastatin); possible increased risk of myopathy when atorvastatin given with • DARUNAVIR, • FOSAMPRENAVIR, • INDINAVIR, • LOPINAVIR or • SAQUINAVIR; avoidance of atorvastatin and simvastatin advised by • ETRAVIRINE; possible increased risk of myopathy when rosuvastatin given with • FOSAMPRENAVIR, • INDINAVIR, • RITONAVIR and • SAQUINAVIR—manufacturer of rosuvastatin advises avoid concomitant use; possible increased risk of myopathy when simvastatin given with • FOSAMPRENAVIR or • LOPINAVIR—avoid concomitant use; avoidance of rosuvastatin advised by manufacturer of • LEDIPASVIR; possible increased risk of myopathy when atorvastatin, fluvastatin and simvastatin given with • LEDIPASVIR—manufacturer of ledipasvir advises consider reducing dose of atorvastatin, fluvastatin and simvastatin; avoidance of atorvastatin and simvastatin advised by manufacturer of • OMBITASVIR; avoidance of atorvastatin, fluvastatin and simvastatin advised by manufacturer of • PARITAPREVIR; plasma concentration of pravastatin increased by • PARITAPREVIR (reduce dose of pravastatin); plasma concentration of atorvastatin possibly increased by • RITONAVIR (use lowest dose of atorvastatin); plasma concentration of atorvastatin, rosuvastatin and simvastatin increased by • SIMEPREVIR (consider reducing dose of atorvastatin, rosuvastatin and simvastatin); avoidance of atorvastatin advised by manufacturer of • TELAPREVIR; plasma concentration of simvastatin possibly increased by • TIPRANAVIR—avoid concomitant use; increased risk of myopathy when atorvastatin given with • TIPRANAVIR (see under Atorvastatin, p. 191)

Anxiolytics and Hypnotics: atorvastatin increases plasma concentration of • INTRAVENOUS MIDAZOLAM

Bosentan: plasma concentration of simvastatin reduced by • BOSENTAN

Calcium-channel Blockers: possible increased risk of myopathy when simvastatin given with • AMLODIPINE and • DILTIAZEM— • DILTIAZEM (see under Simvastatin, p. 194); plasma concentration of atorvastatin increased by • DILTIAZEM—possibly increased risk of myopathy; increased risk of myopathy when simvastatin given with • VERAPAMIL (see under Simvastatin, p. 194); atorvastatin increases plasma concentration of • VERAPAMIL, also possible increased risk of myopathy (consider reducing dose of atorvastatin)

Cardiac Glycosides: atorvastatin possibly increases plasma concentration of • DIGOXIN

Ciclosporin: increased risk of myopathy when rosuvastatin or simvastatin given with • CICLOSPORIN (avoid concomitant use); increased risk of myopathy when simvastatin given with • CICLOSPORIN (see under Atorvastatin, p. 191); increased risk of myopathy when fluvastatin or pravastatin given with • CICLOSPORIN

Clodigrel: plasma concentration of rosuvastatin increased by • CLOPIDOGREL—adjust dose of rosuvastatin (consult product literature)

Cobicistat: plasma concentration of atorvastatin possibly increased by • Cobicistat—manufacturer of cobicistat advises reduce dose of atorvastatin; avoidance of simvastatin advised by manufacturer of • Cobicistat

Colchicine: possible increased risk of myopathy when statins given with • COLCHICINE

Cytotoxics: plasma concentration of simvastatin possibly increased by • DASATINIB; avoidance of simvastatin advised by manufacturer of • IDELALISIB; plasma concentration of simvastatin increased by • IMATINIB

Elotrombopag: plasma concentration of rosuvastatin increased by • ELTROMBOPAG—adjust dose of rosuvastatin (consult product literature)

Grapefruit juice: plasma concentration of atorvastatin possibly increased by • GRAPEFRUIT JUICE; plasma concentration of simvastatin increased by • GRAPEFRUIT JUICE—avoid concomitant use
Statins (continued)
- Hormone Antagonists: possible increased risk of myopathy when simvastatin given with a DANAZOL—avoid concomitant use
- Enzyme-regulating Drugs: possible increased risk of myopathy when simvastatin given with b BEZAFIBRATE (see under Simvastatin, p. 194); possible increased risk of myopathy when simvastatin given with c CIPIROBIZOL (see under Simvastatin, p. 194); when given with statins reduce maximum dose of FENOFIBRATE—see under Fenofibrate, p. 188; increased risk of myopathy when atorvastatin, fluvastatin or pravastatin given with d GEMFIBROZIL (preferably avoid concomitant use); increased risk of myopathy when simvastatin given with e GEMFIBROZIL (avoid concomitant use); plasma concentration of rosuvastatin increased by f EZEZIMIBE—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when rosuvastatin given with g FIBRATES (see under Rosuvastatin, p. 195); increased risk of myopathy when statins given with h FIBRATES; plasma concentration of atorvastatin increased by i LOMITAPIDE—manufacturer of lomitapide advises reduce dose of atorvastatin by half or separate administration by 12 hours; plasma concentration of simvastatin increased by j LOMITAPIDE (see under Simvastatin, p. 194); increased risk of myopathy when statins given with k NICOTINIC ACID (applies to lipid regulating doses of nicotinic acid)
- Oestrogens: atorvastatin and rosuvastatin increase plasma concentration of ETHINYLESTRADEOLOL
- Progestogens: atorvastatin increases plasma concentration of NORETHISTERONE; rosuvastatin increases plasma concentration of active metabolite of NORGESTIMATE; rosuvastatin increases plasma concentration of NORGESTREL
- Ranolazine: plasma concentration of simvastatin increased by l RANOLAZINE (see under Simvastatin, p. 194)
- Retinoids: plasma concentration of simvastatin reduced by m ALITRETININOX
- Sacubitril: plasma concentration of atorvastatin increased by n SUCUBITRIL
- Teriflunomide: plasma concentration of rosuvastatin increased by o TERIFLUNOMIDE (consider reducing dose of rosuvastatin)
- Ticagrelor: plasma concentration of simvastatin increased by p TICARAGRELOR (increased risk of toxicity)

Stavudine
- Antivirals: increased risk of side-effects when stavudine given with a DIDANOSINE; increased risk of toxicity when stavudine given with b RIBAVIRIN; effects of stavudine possibly inhibited by c ZIDOVUDINE (manufacturers advise avoid concomitant use)
- Cytotoxics: effects of stavudine possibly inhibited by d DOXORUBICIN; increased risk of toxicity when stavudine given with e HYDROXYCARBAMIDE—avoid concomitant use
- Orlstat: absorption of stavudine possibly reduced by f ORLISTAT

Stiripentol
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by a MAOIS and b TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by c SSRIS and d TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: stiripentol increases plasma concentration of e CARBAMAZEPINE, f FOSPHENYTIN, g PHENOBARBITAL, h PHENYTOIN and i PRIMIDONE
- Antimalariais: anticonvulsant effect of antiepileptics antagonised by j MEFLOQUINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by k ANTIPSYCHOTICS (convulsive threshold lowered)
- Anxiolytics and Hypnotics: stiripentol increases plasma concentration of l CLOBAZAM
- Orlstat: possible increased risk of convulsions when antiepileptics given with m ORLISTAT

Streptomycin see Aminoglycosides

Strontium Ranelate
- Antibacterials: strontium ranelate reduces absorption of a QUINOLONES and b TETRACYCLINES (manufacturer of strontium ranelate advises avoid concomitant use)

Sucralfate
- Aminophylline: sucralfate possibly reduces absorption of a AMINOPHYLLINE (give at least 2 hours apart)
- Antibacterials: sucralfate reduces absorption of b CIPROFLOXACIN (give at least 2 hours before or 4 hours after ciprofloxacin); sucralfate reduces absorption of c LEVOFLOXACIN, d NORFLOXACIN and e OFLOXACIN (give at least 2 hours apart); sucralfate reduces absorption of f MOXIFLOXACIN (give at least 6 hours apart); sucralfate reduces absorption of g TETRACYCLINES
- Anticoagulants: sucralfate possibly reduces absorption of h COUMARINS (reduced anticoagulant effect)
- Antiepileptics: sucralfate reduces absorption of i FOSPHENYTIN and j PHENYTOIN
- Antifungals: sucralfate reduces absorption of k KETOCONAZOLE
- Antipsychotics: sucralfate reduces absorption of l SULPIRIDE
- Cardiac Glycosides: sucralfate possibly reduces absorption of m CARDIAC GLYCOSIDES
- Potassium Salts: manufacturer of sucralfate advises avoid concomitant use with n POTASSIUM CITRATE
- Sodium Citrate: manufacturer of sucralfate advises avoid concomitant use with o SODIUM CITRATE
- Theophylline: sucralfate possibly reduces absorption of p THEOPHYLLINE (give at least 2 hours apart)
- Thyroid Hormones: sucralfate reduces absorption of q LEVOTHYROXINE
- Ulcer-healing Drugs: sucralfate possibly reduces absorption of r Lansoprazole

Sucroferric Oxyhydroxide see Iron Salts

Sugammadex
- Antibacterials: response to sugammadex possibly reduced by s FUSIDIC ACID
- Prostaglandins: sugammadex possibly reduces plasma concentration of t PROGESTOGENS—manufacturer of sugammadex advises additional contraceptive precautions

Sulfadiazine see Sulfonamides

Sulfadoxine see Sulfonamides

Sulfamethoxazole see Sulfonamides

Sulfasalazine
- Cardiac Glycosides: sulfasalazine possibly reduces absorption of u DIGOXIN
- Folates: sulfasalazine possibly reduces absorption of v FOLIC ACID

Sulfapyrazine
- Aminophylline: sulfapyrazine reduces plasma concentration of w AMINOPHYLLINE
- Analgesics: effects of sulfapyrazine antagonised by x ASPIRIN
- Antibacterials: sulfapyrazine reduces excretion of y NITROFURANTOIN (increased risk of toxicity); sulfapyrazine reduces excretion of z PENCILLINS; effects of sulfapyrazine antagonised by a PYRAZINAMIDE
- Anticoagulants: increased risk of bleeding when sulfapyrazine given with b APIXABAN; sulfapyrazine enhances anticoagulant effect of c COUMARINS; possible increased risk of bleeding when sulfapyrazine given with d DABIGATRAN
- Antidiabetics: sulfapyrazine enhances effects of e SULFONYLUREAS
- Antiepileptics: sulfapyrazine increases plasma concentration of f FOSPHENYTIN and g PHENYTOIN
- Calcium-channel Blockers: sulfapyrazine reduces plasma concentration of h VERAPAMIL
- Ciclosporin: sulfapyrazine reduces plasma concentration of i CICLOSPORIN
- Theophylline: sulfapyrazine reduces plasma concentration of j THEOPHYLLINE

Sulfonamides
- Anaesthetics, General: sulfonamides enhance effects of k THIOPENTAL
- Anaesthetics, Local: effects of sulfonamides possibly inhibited by l CHLOROPROCAINE (manufacturer of chloroprocaine advises avoid concomitant use); increased risk of methaemoglobinemia when sulfonamides given with m PRilocaine
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when sulfamethoxazole (as co-trimoxazole) given with AMIODARONE—manufacturer of amiodarone advises avoid concomitant use of co-trimoxazole
**Sulfonamides** (continued)
- Antibacterials: increased risk of crystalluria when sulfonamides given with ▶ METHENAMINE
- Anticoagulants: sulfonamides enhance anticoagulant effect of ▶ COUMARINS; sulfonamides possibly inhibit metabolism of
  ▶ PHENINDIONE
- Antidiabetics: sulfonamides rarely enhance the effects of
  ▶ SULFONYLUREAS
- Antiepileptics: sulfonamides possibly increase plasma concentration of ▶ FOSPHENYTOIN and ▶ PHENYTOIN
- Antimalarials: increased antifolate effect when sulfonamides given with ▶ PYRIMETHAMINE
- Antiparkinsonian: avoid concomitant use of sulfonamides with ▶ CLOzapine (increased risk of agranulocytosis)
- Azathioprine: increased risk of haematological toxicity when sulfamethoxazole (as co-trimoxazole) given with ▶ AZATHIOPRINE
- Cilostazol: increased risk of necrotising enterocolitis when sulfonamides given with ▶ CILOSTAZOLE; sulfadiazine possibly reduces plasma concentration of ▶ CILOSTAZOLE
- Cytoxics: increased risk of haematological toxicity when sulfamethoxazole (as co-trimoxazole) given with ▶ MERCAPTOPURINE; sulfonamides increase risk of METHOTREXATE toxicity; increased risk of severe bone marrow depression (fatalities reported) and other haematological toxicities when sulfamethoxazole (as co-trimoxazole) given with ▶ METHOTREXATE
- Potassium Aminobenzoate: effects of sulfonamides inhibited by ▶ POTASSIUM AMINOBENZOATE
- Tacrolimus: possible increased risk of nephrotoxicity when sulfamethoxazole given with ▶ TACROLIMUS
- Vaccines: antibacterials inactivate ▶ ORAL TYPHOID VACCINE — see under Typhoid Vaccine in BNF or BNFC

**Sulfonamides** see Antidiabetics

**Sulindac** see NSAIDs

**Sulpiride** see Antipsychotics

**Sumatriptan** see 5HT₁-receptor Agonists (under HT)

**Sunitinib**
- Antibacterials: metabolism of sunitinib accelerated by ▶ RIFAMPICIN (reduced plasma concentration).
- Anthraquinones: metabolism of sunitinib inhibited by ▶ KETOCONAZOLE (increased plasma concentration).
- Antipsychotics: avoid concomitant use of cytoxotics with ▶ CLOzapine (increased risk of agranulocytosis)
- Antivirals: avoidance of sunitinib advised by manufacturer of ▶ BOCEPREVIR

**Suxamethonium** see Muscle Relaxants

**Sympathomimetics**
- Adrenergic Neurone Blockers: ephedrine, isometheptene, metaraminol, methylphenidate, noradrenaline (norepinephrine), oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline antagonise hypertensive effect of ▶ ADRENERGIC NEURONE BLOCKERS; manufacturer of midodrine advises avoid concomitant use with ▶ GUANETHIDINE; dexametammin and lisdexametammin antagonise hypertensive effect of ▶ GUANETHIDINE; increased risk of hypertensive crisis when adrenaline (epinephrine) given with ▶ GUANETHIDINE
- Alcohol: effects of methylphenidate possibly enhanced by ▶ ALCOHOL
- Alpha-adrrenoreceptor Stimulants: avoidance of sympathomimetics advised by manufacturer of ▶ APRACLONIDINE
- Alpha-blockers: effects of midodrine possibly antagonised by ▶ ALPHA-BLOCKERS; avoid concomitant use of adrenaline (epinephrine) or dopamine with ▶ TOLAZOLINE
- Aminophylline: avoidance of aminophylline in children advised by manufacturer of ▶ AMINOPHYLLINE
- Anaesthetics, General: avoidance of sympathomimetics advised by manufacturer of ▶ ISOFLURANE (risk of ventricular arrhythmias); increased risk of hypertension when methylphenylidate given with ▶ VOLATILE LIQUID GENERAL ANAESTHETICS; increased risk of arrhythmias when adrenaline (epinephrine) or noradrenaline (norepinephrine) given with ▶ VOLATILE LIQUID GENERAL ANAESTHETICS.
- Antacids: absorption of pseudoephedrine possibly increased by ▶ ALUMINIUM HYDROXIDE

**Sympathomimetics** (continued)
- Anticoagulants: methylphenidate possibly enhances anticoagulant effect of ▶ COUMARINS
- Antidepressants: risk of hypertensive crisis when dexametammin, ephedrine, isometheptene, lisdexametammin, metaraminol, methylphenidate, phenylephrine or pseudoephedrine given with ▶ MAOIS, avoid dexametammin, ephedrine, isometheptene, lisdexametammin, metaraminol, methylphenidate, phenylephrine or pseudoephedrine for at least 2 weeks after stopping MAOIs; manufacturer of midodrine advises avoid concomitant use with ▶ MAOIS and ▶ TRICYCLICS; risk of hypertensive crisis when adrenaline (epinephrine), dobutamine, dopamine, noradrenaline (norepinephrine) or xylometazoline given with ▶ MAOIS; risk of hypertensive crisis when oxymetazoline given with ▶ MAOIS, some manufacturers advise avoid oxymetazoline for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when sympathomimetics given with ▶ MOCLOBEMIDE; methylphenidate possibly inhibits metabolism of ▶ SSRS and ▶ TRICYCLICS; increased risk of hypertension and arrhythmias when noradrenaline (norepinephrine) or phenylephrine given with ▶ TRICYCLICS; increased risk of hypertension and arrhythmias when adrenaline (epinephrine) given with ▶ TRICYCLICS (but local anaesthetics with adrenaline appear to be safe)
- Antiepileptics: methylphenidate increases plasma concentration of ▶ FOSPHENYTOIN and ▶ PHENYTOIN; methylphenidate possibly increases plasma concentration of ▶ PHENOBARBITAL and ▶ PRIMIDONE
- Antihistamines: manufacturer of midodrine advises avoid concomitant use with ▶ ANTIHISTAMINES
- Antipsychotics: hypertensive effect of sympathomimetics antagonised by ▶ ANTIPSYCHOTICS; effects of lisdexametamine possibly reduced by ▶ CHLORPROMAZINE; dexametamine possibly antagonises antipsychotic effects of ▶ CHLORPROMAZINE; methylphenidate possibly increases side-effects increased by ▶ RISPERIDONE
- Antivirals: plasma concentration of dexametammin possibly increased by ▶ RITONAVIR
- Beta-blockers: increased risk of severe hypertension and bradycardia when adrenaline (epinephrine) given with non-cardioselective ▶ BETA-BLOCKERS, also response to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when dobutamine given with non-cardioselective ▶ BETA-BLOCKERS; possible increased risk of severe hypertension and bradycardia when noradrenaline (norepinephrine) given with non-cardioselective ▶ BETA-BLOCKERS
- Cardiac Glycosides: manufacturer of midodrine advises avoid concomitant use with ▶ DIGOXIN
- Clonidine: possible risk of hypertension when adrenaline (epinephrine) or noradrenaline (norepinephrine) given with ▶ CLONIDINE; serious adverse events reported with concomitant use of methylphenidate and ▶ CLONIDINE (causality not established)
- Corticosteroids: possible risk of hypertension when midodrine given with ▶ CORTICOSTEROIDS; ephedrine accelerates metabolism of ▶ DXAMETAMIN.
- Dopaminergics: risk of toxicity when isometheptene given with ▶ BROMOCRIPTINE; effects of adrenaline (epinephrine), dobutamine, dopamine and noradrenaline (norepinephrine) possibly enhanced by ▶ ENTACAPONE; avoid concomitant use of sympathomimetics with ▶ RASAGILINE; risk of hypertensive crisis when dopamine given with ▶ SELEGILINE; avoidance of sympathomimetics advised by manufacturer of ▶ SELEGILINE
- Ergot Alkaloids: increased risk of ergotism when sympathomimetics given with ▶ ERGOTALKALOIDS
- Oxytocin: risk of hypertension when vasoconstrictor sympathomimetics given with ▶ OXYTOCIN (due to enhanced vasopressor effect)
- Sympathomimetics: effects of adrenaline (epinephrine) possibly enhanced by ▶ DOPEXAMINE; dexamphetamine possibly enhances effects of ▶ NORADRENLINE (NOREPINEPHRINE)
Sympathomimetics (continued)
- Theophylline: avoidance of ephedrine in children advised by manufacturer of THEOPHYLLINE
- Thyroid Hormones: manufacturer of midodrine advises avoid concomitant use with THYROID HORMONES
- Uter-healing Drugs: metabolism of dobutamine possibly inhibited by CIMETIDINE

Sympathomimetics, Beta2
- Aminophylline: increased risk of hypokalaemia when high doses of beta2-sympathomimetics given with AMINOPHYLLINE
- Antifungals: plasma concentration of olopatadine increased by KETOCONAZOLE; metabolism of salmeterol inhibited by KETOCONAZOLE (increased plasma concentration)
- Antivirals: increased risk of nephrotoxicity when tacrolimus given with ACICLOVIR, GANCICLOVIR, VALCICLOVIR or VALGANCICLOVIR; plasma concentration of tacrolimus possibly increased by ATAZANAVIR and RITONAVIR; plasma concentration of tacrolimus increased by BOCEPREVIR (reduce dose of tacrolimus); plasma concentration of tacrolimus possibly affected by EFAVIRENZ; plasma concentration of tacrolimus increased by FOSAMPRENAVIR; plasma concentration of tacrolimus increased by SAQUINAVIR (consider reducing dose of tacrolimus); plasma concentration of both drugs increased when tacrolimus given with TELAPREVI (reduce dose of tacrolimus)
- Calcium-channel Blockers: plasma concentration of tacrolimus possibly increased by FELODIPINE and VERAPAMIL; plasma concentration of tacrolimus increased by DILTIAZEM, NICARDIPINE and NIFEDIPINE
- Ciclosporin: tacrolimus increases plasma concentration of CICLOSPORIN (increased plasma concentration)
- Cytotoxics: increased risk of nephrotoxicity—avoid concomitant use
- Cytotoxics: tacrolimus possibly increases the plasma concentration of AFATINIB—manufacturer of afatinib advises separating administration of tacrolimus by 6 to 12 hours; avoidance of tacrolimus advised by manufacturer of IMATINIB; caution with tacrolimus advised by manufacturer of CRIZOTINIB; plasma concentration of tacrolimus increased by IMATINIB
- Dексазозан: increased risk of immunosuppression with tacrolimus advised by manufacturer of DEXRAZOXANE
- Diuretics: increased risk of hyperkalaemia when tacrolimus given with ALDOSTERONE ANTAGONISTS or POTASSIUM-SPARING DIURETICS
- Grapefruit Juice: plasma concentration of tacrolimus increased by GRAPEFRUIT JUICE
- Hormone Antagonists: plasma concentration of tacrolimus possibly increased by DANAziel
- Lipid-regulating Drugs: separating administration from tacrolimus by 12 hours advised by manufacturer of LOMITAPIDE
- Lumacaftor: avoidance of tacrolimus advised by manufacturer of LUMACAFTOR
- Mifamurtide: avoidance of tacrolimus advised by manufacturer of MIFAMURTIDE
- Oestroprogestins: plasma concentration of tacrolimus possibly increased by ETHINYLESTRADIOL
- Potassium Salts: increased risk of hyperkalaemia when tacrolimus given with POTASSIUM SALTS
- Ranolazine: plasma concentration of tacrolimus increased by RANOLAZINE
- Sevelamer: plasma concentration of tacrolimus possibly reduced by SEVELAMER
- Uter-healing Drugs: plasma concentration of tacrolimus possibly increased by OMPEZRAZOLE

Tacrolimus
- Antifungals (continued): nephrotoxicity when tacrolimus given with AMPHOTERICIN; plasma concentration of tacrolimus increased by ISAVICONAZOLE; plasma concentration of tacrolimus reduced by CASPOFUNGIN and DROPERIDOL (risk of ventricular arrhythmias)
- Antivirals: possible increased risk of nephrotoxicity when tacrolimus given with ACICLOVIR, GANCICLOVIR, VALCICLOVIR or VALGANCICLOVIR; plasma concentration of tacrolimus possibly increased by ATAZANAVIR and RITONAVIR; plasma concentration of tacrolimus increased by BOCEPREVIR (reduce dose of tacrolimus); plasma concentration of tacrolimus possibly affected by EFAVIRENZ; plasma concentration of tacrolimus increased by FOSAMPRENAVIR; plasma concentration of tacrolimus increased by SAQUINAVIR (consider reducing dose of tacrolimus); plasma concentration of both drugs increased when tacrolimus given with TELAPREVI (reduce dose of tacrolimus)
- Calcium-channel Blockers: plasma concentration of tacrolimus possibly increased by FELODIPINE and VERAPAMIL; plasma concentration of tacrolimus increased by DILTIAZEM, NICARDIPINE and NIFEDIPINE
- Cytotoxics: increased risk of nephrotoxicity—avoid concomitant use
- Cytotoxics: tacrolimus possibly increases the plasma concentration of AFATINIB—manufacturer of afatinib advises separating administration of tacrolimus by 6 to 12 hours; avoidance of tacrolimus advised by manufacturer of IMATINIB; caution with tacrolimus advised by manufacturer of CRIZOTINIB; plasma concentration of tacrolimus increased by IMATINIB
- Dексазозан: increased risk of immunosuppression with tacrolimus advised by manufacturer of DEXRAZOXANE
- Diuretics: increased risk of hyperkalaemia when tacrolimus given with ALDOSTERONE ANTAGONISTS or POTASSIUM-SPARING DIURETICS
- Grapefruit Juice: plasma concentration of tacrolimus increased by GRAPEFRUIT JUICE
- Hormone Antagonists: plasma concentration of tacrolimus possibly increased by DANAziel
- Lipid-regulating Drugs: separating administration from tacrolimus by 12 hours advised by manufacturer of LOMITAPIDE
- Lumacaftor: avoidance of tacrolimus advised by manufacturer of LUMACAFTOR
- Mifamurtide: avoidance of tacrolimus advised by manufacturer of MIFAMURTIDE
- Oestroprogestins: plasma concentration of tacrolimus possibly increased by ETHINYLESTRADIOL
- Potassium Salts: increased risk of hyperkalaemia when tacrolimus given with POTASSIUM SALTS
- Ranolazine: plasma concentration of tacrolimus increased by RANOLAZINE
- Sevelamer: plasma concentration of tacrolimus possibly reduced by SEVELAMER
- Uter-healing Drugs: plasma concentration of tacrolimus possibly increased by OMPEZRAZOLE

Tadalafil
- Alpha-blockers: enhanced hypotensive effect when tadalafil given with DOXAZOSIN—manufacturer of tadalafil avoids avoid concomitant use; enhanced hypotensive effect when tadalafil given with ALPHA-BLOCKERS—when patient is stable on the alpha blocker initiate tadalafil at the lowest possible dose
- Anti-arhythmic/s: avoidance of tadalafil advised by manufacturer of DISOPYRAMIDE (risk of ventricular arrhythmias)
- Antibacterials: plasma concentration of tadalafil possibly increased by CLARITHROMYCIN and ERITHROMYCIN; plasma concentration of tadalafil reduced by Rifampicin; possible increased risk of nephrotoxicity when tacrolimus given with SULFAMETHOXAZOLE, TRIMETHOPRIM or VANCOMYCIN; increased risk of nephrotoxicity when tacrolimus given with AMINOLYCOSIDES; plasma concentration of tacrolimus possibly increased by CHLORAMPHENICOL and TELITHROMYCIN
- Anticoagulants: tadalafil possibly increases plasma concentration of DABIGATRAN—manufacturer of dabigatran advises avoid concomitant use
- Antidepressants: plasma concentration of tadalafil reduced by ST JOHN'S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of tacrolimus reduced by FOSPHENYTOIN and PHENYTOIN, also plasma concentration of phenytoin possibly increased; plasma concentration of tacrolimus reduced by PHENOBARBITAL and PRIMIDONE
- Antifungals: plasma concentration of tacrolimus increased by FLUCONAZOLE, ITRACONAZOLE, KETOCONAZOLE, POSaconazole and VORICONAZOLE (consider reducing dose of tacrolimus); plasma concentration of tacrolimus possibly increased by MICONAZOLE oral gel; increased risk of
Tegafur
- Antiarrhythmics: metabolism of tegafur inhibited by
  - PENTOXIFYLBAN
- Anticoagulants: metabolism of tegafur inhibited by
  - RIFAMPICIN
- Antibacterials: plasma concentration of tegafur possibly increased when telaprevir given (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with
  - RIFABUTIN
- Antiepileptics: manufacturer of telaprevir advises avoid concomitant use with
  - CARBAMAZEPINE, PHENOBARBITAL, PHENYTOIN, PRIMIDONE
- Antifungals: plasma concentration of tegafur possibly increased when telaprevir given (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with
  - KETOCONAZOLE
- Antioxidants: plasma concentration of tegafur possibly increased when telaprevir given (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with
  - THEOPHYLLINE
- Antiparkinsonians: metabolism of tegafur possibly increased when telaprevir given (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with
  - L-DOPA
- Antipsychotics: plasma concentration of tegafur possibly increased when telaprevir given (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with
  - LITHUANIAN, PHENOTIPIR
- Antiulcer: manufacturer of telaprevir advises caution with
  - TACAMIPRIDE (risk of ventricular arrhythmias); manufacturer of telaprevir advises caution with
  - ORAL TYPHOID VACCINE
- Anxiolytics and Hypnotics: plasma concentration of tegafur possibly increased when telaprevir given (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with
  - LORAZEPAM
- Beta-blockers: manufacturer of telaprevir advises caution with
  - CARBAMAZEPINE, PHENOBARBITAL, PHENYTOIN, PRIMIDONE
- Beta-blockers: manufacturer of telaprevir advises caution with
  - LIRICA
- Beta-blockers: manufacturer of telaprevir advises caution with
  - TRAMadol
- Calcium-channel Blockers: manufacturer of telaprevir advises caution with
  - KETONORBNIC DILATE
- Calcium-channel Blockers: manufacturer of telaprevir advises caution with
  - LIVMOC
- Calcium-channel Blockers: manufacturer of telaprevir advises caution with
  - AMIODARONE, DISOPYRAMIDE (risk of ventricular arrhythmias); manufacturer of telaprevir
Telaprevir (continued)

- Colchicine: telaprevir possibly increases risk of colchicine toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: telaprevir possibly increases plasma concentration of inhaled and intranasal budesonide and fluticasone; plasma concentration of telaprevir possibly reduced by dexamethasone
- Cytotoxics: telaprevir possibly increases the plasma concentration of bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; manufacturer of ruxolitinib advises dose reduction when telaprevir given with ruxolitinib—consult ruxolitinib product literature; telaprevir possibly increases plasma concentration of olaparib (avoid concomitant use or reduce dose of olaparib—see under Olaparib, p. 881)
- Domperidone: possible increased risk of ventricular arrhythmias when telaprevir given with domperidone—avoid concomitant use
- Ergot Alkaloids: manufacturer of telaprevir advises avoid concomitant use with ergot alkaloids
- Guanfacine: telaprevir possibly increases plasma concentration of guanfacine (half-life of guanfacine)
- Lipid-regulating Drugs: manufacturer of telaprevir advises avoid concomitant use with atorvastatin; manufacturers advise avoid concomitant use of telaprevir with simvastatin; avoidance of telaprevir advised by manufacturer of lomitapide (plasma concentration of lomitapide possibly increased)
- Oestrogens: telaprevir possibly reduces plasma concentration of ethinylestradiol—manufacturer of telaprevir advises additional contraceptive precautions
- Sildenafil: manufacturer of telaprevir advises avoid concomitant use with sildenafil
- Sirolimus: plasma concentration of both drugs increased when telaprevir given with sirolimus (reduce dose of sirolimus)
- Pimozide: possible increased risk of ventricular arrhythmias when telaprevir given with pimozide—avoid concomitant use; telaprevir possibly increases plasma concentration of quetiapine
- Antivirals: manufacturer of telaprevir advises avoid concomitant use with atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir and tipranavir in severe renal and hepatic impairment; telaprevir possibly increases the plasma concentration of darunavir—reduce dose of darunavir (see under Darunavir, p. 577); avoidance of telaprevir advised by manufacturer of darunavir and ritonavir; telaprevir possibly increases plasma concentration of maraviroc (consider reducing dose of maraviroc); manufacturer of telaprevir advises avoid concomitant use with saquinavir (risk of ventricular arrhythmias); telaprevir possibly increases plasma concentration of simprevir—manufacturer of simprevir advises avoid concomitant use; plasma concentration of elotuzumab possibly increased when telaprevir given with elotuzumab (increased risk of ventricular arrhythmias)
- Anxiolytics and Hypnotics: telaprevir possibly increases metabolism of midazolam (increased plasma concentration with increased sedation)
- Aprepitant: telaprevir possibly increases plasma concentration of aprepitant
- Avanafil: telaprevir possibly increases plasma concentration of avanafil—manufacturer of avanafil advises avoid concomitant use
- Calcium-channel Blockers: telaprevir possibly increases plasma concentration of nifedipine.
- Ciclosporin: telaprevir possibly increases plasma concentration of ciclosporin
- Colchicine: telaprevir possibly increases risk of colchicine toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Cytotoxics: telaprevir possibly increases plasma concentration of axitinib (reduce dose of axitinib—consult axitinib product literature); telaprevir possibly increases the plasma concentration of bosutinib and cabazitaxel—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; telaprevir possibly increases plasma concentration of ceritinib—avoid concomitant use or consider reducing the dose of ceritinib (see under Ceritinib, p. 861); telaprevir possibly increases plasma concentration of crizotinib and everolimus—manufacturer of crizotinib and everolimus advises avoid concomitant use; avoidance of telaprevir by manufacturer of crizotinib and everolimus advised; telaprevir possibly increases plasma concentration of pazopanib (reduce dose of pazopanib); telaprevir possibly increases plasma concentration of ponatinib—consider reducing initial dose of ponatinib (see under Ponatinib, p. 873); manufacturer of ruxolitinib advises dose reduction when telaprevir given with ruxolitinib—consult ruxolitinib product literature; telaprevir possibly increases plasma concentration of telithromycin (continued)

Telithromycin (continued)

- Antidepressants: possible increased risk of ventricular arrhythmias when telithromycin given with citalopram and tricyclics; plasma concentration of telithromycin reduced by st john’s wort (avoid during and for 2 weeks after st john’s wort)
- Antiepileptics: plasma concentration of telithromycin reduced by carbamazepine, fosphenytoin, omeprazole and phenobarbital
Telithromycin
Cytotoxics (continued)
increases plasma concentration of docetaxel — manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose; temsirolimus possibly increases plasma concentration of olaparib (avoid concomitant use or reduce dose of olaparib — see under Olaparib, p. 881)
Dapoxetine: avoidance of telithromycin advised by manufacturer of dapoxetine (increased risk of toxicity)
Diuretics: telithromycin increases plasma concentration of eplerenone — avoid concomitant use
Domeridone: possible increased risk of ventricular arrhythmias when telithromycin given with damperidone — avoid concomitant use
Ergot Alkaloids: increased risk of ergotism when telithromycin given with ergot alkaloids — avoid concomitant use
Fosaprepitant: telithromycin possibly increases plasma concentration of fosaprepitant
Guanfacine: telithromycin possibly increases plasma concentration of guanfacine (halve dose of guanfacine)
Ivabradine: telithromycin possibly increases plasma concentration of ivabradine — avoid concomitant use
Ivacaftor: telithromycin possibly decreases plasma concentration of ivacaftor (see under Ivacaftor in BNF or BNFC, and Lumacaftor with Ivacaftor in BNF or BNFC)
Lipid-regulating Drugs: telithromycin possibly increases plasma concentration of panobinostat
Lumacaftor: telithromycin increases plasma concentration of lumacaftor (plasma concentration of lomitapide possibly increased)
Panobinostat: telithromycin possibly increases plasma concentration of panobinostat (reduce dose of panobinostat — see under Panobinostat, p. 834)
Pentamidine i setionate: possible increased risk of ventricular arrhythmias when telithromycin given with pentamidine i setionate
Pentamidine i setionate
Ranolazine: telithromycin possibly increases plasma concentration of ranolazine — manufacturer of ranolazine advises avoid concomitant use
Sildenafil: telithromycin possibly increases plasma concentration of sildenafil — consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension
Sirolimus: telithromycin increases plasma concentration of sirolimus — avoid concomitant use
Tacrolimus: telithromycin possibly increases plasma concentration of tacrolimus
Ulipristal: avoidance of telithromycin advised by manufacturer of low-dose ulipristal
Vaccines: antibacterials inactivate oral typhoid vaccine — see under Typhoid Vaccine in BNF or BNFC
Temsirolimus (continued)
Antibacterials: plasma concentration of active metabolite of temsirolimus reduced by rifampicin — avoid concomitant use
Antifungals: plasma concentration of active metabolite of temsirolimus increased by ketoconazole — avoid concomitant use; manufacturer of temsirolimus advises avoid concomitant use with iraconazole (plasma concentration of temsirolimus possibly increased)
Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
Tenovir
Antivirals: manufacturer of tenovir advises avoid concomitant use with adebovir; tenovir reduces plasma concentration of atazanavir, also plasma concentration of tenofovir possibly increased; tenofovir increases plasma concentration of didanosine (increased risk of toxicity) — avoid concomitant use; plasma concentration of tenofovir increased by lopinavir and telaprevir
Orosiata: absorption of tenofovir possibly reduced by orlistat
Terbinafine
Antibacterials: plasma concentration of terbinafine reduced by rifampicin
Antidepressants: terbinafine possibly increases plasma concentration of paroxetine and tricyclics
Antifungals: terbinafine increases plasma concentration of fluconazole
Ciclosporin: terbinafine possibly reduces plasma concentration of ciclosporin
Oestrogens: occasional reports of breakthrough bleeding when terbinafine given with oestrogens (when used for contraception)
Progestogens: occasional reports of breakthrough bleeding when terbinafine given with progestogens (when used for contraception)
Ulcer-healing Drugs: plasma concentration of terbinafine increased by cinetidine
Terbutaline see Sympathomimetics, Beta2
Teriflunomide
Antibacterials: teriflunomide increases plasma concentration of cefaclor; plasma concentration of teriflunomide reduced by rifampicin
Antidiabetics: teriflunomide increases plasma concentration of repaglinide
Lipid-regulating Drugs: the effect of teriflunomide is significantly decreased by colestyramine (enhanced elimination) — avoid unless drug elimination desired; teriflunomide increases plasma concentration of rosuvastatin (consider reducing dose of rosuvastatin)
Oestrogens: teriflunomide increases plasma concentration of ethinylestadiol
Progestogens: teriflunomide increases plasma concentration of levonorgestrel
Vaccines: risk of generalised infections when teriflunomide given with live vaccines — avoid concomitant use
Testolactone
Anticoagulants: testolactone enhances anticoagulant effect of coumarins and phenindione
Testosterone
Anticoagulants: testosterone enhances anticoagulant effect of coumarins and phenindione
Antidiabetics: testosterone possibly enhances hypoglycaemic effect of antidiabetics
Tetrabenazine
Antidepressants: risk of CNS toxicity when tetrabenazine given with maois (avoid tetrabenazine for 2 weeks after MAOIs)
Antipsychotics: increased risk of extrapyramidal side-effects when tetrabenazine given with antipsychotics
Dopaminergics: increased risk of extrapyramidal side-effects when tetrabenazine given with amantadine
Metoclopramide: increased risk of extrapyramidal side-effects when tetrabenazine given with metoclopramide
Tetracosactide see Corticosteroids
Tetracyclines see Tetracyclines
Theophylline

ACE Inhibitors: absorption of tetracyclines reduced by quinapril tablets (quinapril tablets contain magnesium carbonate)

Adsorbents: absorption of tetracyclines possibly reduced by kaolin

Antacids: absorption of tetracyclines possibly reduced by antacids (give at least 2 to 3 hours apart)

Antibacterials: plasma concentration of doxycycline reduced by rifampicin — consider increasing dose of doxycycline; tetracyclines possibly antagonise effects of penicillins

Anticoagulants: tetracyclines possibly enhance anticoagulant effect of coumarins and phenindione

Antidiabetics: tetracyclines possibly increased risk of ergotism when tetracyclines given with ergotamine

Iron Salts: absorption of tetracyclines possibly reduced by calcium salts (give at least 2 to 3 hours apart)

Cytotoxics: doxycycline or tetracycline increase risk of hypokalaemia when theophylline given with doxycycline or tetracycline increase risk of hypokalaemia when theophylline given with rifampicin (increased risk of toxicity)

Calcium-channel Blockers: plasma concentration of theophylline possibly increased by calcium-channel blockers (enhanced effect)

Calcium-channel Blockers: plasma concentration of theophylline increased by ritonavir (reduced plasma concentration)

Caffeine and Hypnotics: theophylline possibly reduces effects of benzodiazepines

Antivirals: plasma concentration of theophylline possibly increased by aciclovir and valaciclovir; metabolism of theophylline accelerated by ritonavir (reduced plasma concentration)

Antiarrhythmics: serum concentrations of thyroid hormones can be affected by amiodarone — monitor thyroid function closely

Antibacterials: metabolism of levothyroxine accelerated by rifampicin (may increase requirements for levothyroxine in hypothyroidism)

Antidepressants: plasma concentration of theophylline increased by fluvoxamine (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration); plasma concentration of theophylline possibly reduced by St John’s Wort

Ulcer-healing Drugs: plasma concentration of theophylline possibly increased by fosphenytoin and phenytoin

Dairy Products: metabolism of theophylline accelerated by carbamazepine, phenobarbital and primidone (reduced plasma concentration)

Atovaquone: tetracycline reduces plasma concentration of atovaquone

Calcium Salts: absorption of tetracyclines possibly reduced by calcium salts (give at least 2 to 3 hours apart)

Caffeine and Hypnotics: theophylline possibly reduces effects of benzodiazepines

Anticoagulants: tetracyclines possibly enhance anticoagulant effect of coumarins and phenindione

Antidiabetics: tetracyclines possibly increased risk of ergotism when tetracyclines given with ergotamine

Iron Salts: absorption of tetracyclines reduced by oral iron salts, also absorption of oral iron salts reduced by tetracyclines (give at least 2 to 3 hours apart)

Lipid-regulating Drugs: absorption of tetracyclines possibly reduced by colestipol and colesteryramine

Retinoids: possible increased risk of benign intracranial hypertension when tetracyclines given with retinoids (avoid concomitant use)

Strontium Ranelate: absorption of tetracyclines reduced by Strontium Ranelate (manufacturer of strontium ranelate advises avoid concomitant use)

Ulcer-healing Drugs: absorption of tetracyclines reduced by sucralfate and Tripotassium Dicitrato Bismuthate

Vaccines: antibiotics inactivate oral typhoid vaccine — see Oral Typhoid Vaccine in BNF or BNFC

Zinc: absorption of tetracyclines possibly reduced by zinc (give at least 2 to 3 hours apart)

Theophylline

Allopurinol: plasma concentration of theophylline possibly increased by allopurinol

Anaesthetics, General: increased risk of convulsions when theophylline given with ketamine

Anti-arrhythmics: theophylline antagonises anti-arrhythmic effect of adenosine — manufacturer of adenosine advises avoid concomitant use for 24 hours before adenosine; plasma concentration of theophylline increased by propafenone

Antibacterials: plasma concentration of theophylline possibly increased by clarithromycin and isoniazid; plasma concentration of theophylline increased by erythromycin (also theophylline may reduce absorption of oral erythromycin); plasma concentration of theophylline increased by ciprofloxacin and norfloxacin; metabolism of theophylline accelerated by rifampicin (reduced plasma concentration); possible increased risk of convulsions when theophylline given with quinolones

Antidepressants: plasma concentration of tetracycline increased by fluvoxamine (concomitant use should usually be avoided, but where not possible halve tetracycline dose and monitor plasma-tetracycline concentration); plasma concentration of tetracycline possibly reduced by St John’s Wort

Antiepileptics: metabolism of theophylline accelerated by carbamazepine, phenobarbital and primidone (reduced effect)

Antidiabetics: absorption of levothyroxine possibly reduced by antacids

Antivirals: plasma concentration of theophylline possibly increased by aciclovir and valaciclovir; metabolism of theophylline accelerated by ritonavir (reduced plasma concentration)

Anticoagulants: tetracyclines possibly enhance anticoagulant effect of coumarins and phenindione

Anticholinergics: serum concentrations of thyroid hormones can be affected by amiodarone — monitor thyroid function closely

Antibacterials: metabolism of levothyroxine accelerated by rifampicin (may increase requirements for levothyroxine in hypothyroidism)

Anticoagulants: thyroid hormones enhance anticoagulant effect of coumarins and phenindione
Thyroid Hormones (continued)

- Antidepressants: thyroid hormones enhance effects of AMITRIPTYLINE and IMPRIPRAMINE; thyroid hormones possibly enhance effects of TRICYCLICS
- Antiepileptics: metabolism of thyroid hormones accelerated by CARBAMAZEPINE, PHENOBARBITAL and PRIMODONE (may increase requirements for thyroid hormones in hypothyroidism); metabolism of thyroid hormones accelerated by FOSPHENYTIOIN and PHENYTOIN (may increase requirements in hypothyroidism), also plasma concentration of fosphenytoin and phenytoin possibly increased
- Beta-blockers: levothyroxine accelerates metabolism of PROPRAVOLOL
- Calcium Salts: absorption of levothyroxine reduced by CALCIUM SALTS
- Cytotoxics: plasma concentration of levothyroxine possibly reduced by IMATINIB
- Iron Salts: absorption of levothyroxine reduced by oral IRON SALTS (give at least 2 hours apart)
- Lanthanum: absorption of levothyroxine reduced by LANTHANUM (give at least 2 hours apart)
- Lipid-regulating Drugs: absorption of levothyroxine reduced by COLESEVELAM; absorption of thyroid hormones reduced by COLESTIPOL and COLESTYRAMINE
- Oestrogens: requirements for thyroid hormones in hypothyroidism may be increased by OESTROGENS
- Orlistat: possible increased risk of hypothyroidism when levothyroxine given with ORLISTAT
- Polystyrene Sulfonate Resins: absorption of levothyroxine reduced by POLYSTYRENE SULFONATE RESINS
- Sevelamer: absorption of levothyroxine possibly reduced by SEVELAMER
- Sympathomimetics: avoidance of thyroid hormones advised by manufacturer of MIDODRINE
- Ulcer-healing Drugs: absorption of levothyroxine reduced by CIMETIDINE and SUCCINATE

Tiagabine

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: plasma concentration of tiagabine reduced by CARBAMAZEPINE, FOSPHENYTIOIN, PHENOBARBITAL, PHENYTOIN and PRIMODONE
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by MELFLOQUINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ANTIPSYCHOTICS (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ORLISTAT

Tiaprofenic Acid see NSAIDs

Tibilone

- Antibacterials: metabolism of tibolone accelerated by RIFAMPICIN (reduced plasma concentration)
- Antiepileptics: metabolism of tibolone accelerated by CARBAMAZEPINE (reduced plasma concentration); metabolism of tibolone accelerated by FOSPHENYTIOIN and PHENYTOIN

Ticagrelor (continued)

- Antivirals: plasma concentration of ticagrelor possibly increased by ATAZANAVIR and RITONAVIR—manufacturer of ticagrelor advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of ticagrelor increased by DILTIAZEM
- Cardiac Glycosides: ticagrelor increases plasma concentration of DIGOXIN
- Ciclosporin: plasma concentration of ticagrelor increased by CICLOSPORIN
- Ergot Alkaloids: ticagrelor possibly increases plasma concentration of ERGOT ALKALOIDS
- Lipid-regulating Drugs: ticagrelor increases plasma concentration of SIMVASTATIN (increased risk of toxicity); separating administration from ticagrelor by 12 hours advised by manufacturer of LOMITAPIDE

Ticarcillin see Penicillins

Tick-borne Encephalitis Vaccine see Vaccines

Tigecycline

- Anticoagulants: tigecycline possibly enhances anticoagulant effect of COUMARINS
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Timolol see Beta-blockers

Tinidazole

- Alcohol: possibility of disulfiram-like reaction when tinidazole given with ALCOHOL
- Antibacterials: plasma concentration of tinidazole possibly reduced by RIFAMPICIN
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF or BNFC

Tinzaparin see Heparins

Tioguanine

- Antipsychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)
- Cytotoxics: increased risk of hepatotoxicity when tioguanine given with BUSULFAN

Tiotropium see Antimuscarinics

Tipranavir

- Analgesics: plasma concentration of tipranavir possibly reduced by BUPRENORPHINE
- Antacids: absorption of tipranavir reduced by ANTACIDS (give at least 2 hours apart)
- Antibacterials: tipranavir increases plasma concentration of CLARITHROMYCIN (reduce dose of clarithromycin in renal impairment), also plasma concentration of tipranavir increased by clarithromycin; tipranavir increases plasma concentration of RIFABUTIN (reduce dose of rifabutin); plasma concentration of tipranavir possibly reduced by RIFAMPICIN—avoid concomitant use; avoidance of concomitant tipranavir in severe renal and hepatic impairment advised by manufacturer of TELITHROMYCIN
- Anticoagulants: avoidance of tipranavir advised by manufacturer of APIXABAN and RIVAROXABAN
- Antidepressants: plasma concentration of tipranavir possibly reduced by ST JOHN’S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of tipranavir possibly reduced by CARBAMAZEPINE
- Antifungals: plasma concentration of tipranavir increased by FLUCONAZOLE
- Antimalarials: caution with tipranavir advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; tipranavir possibly increases plasma concentration of QUININE (increased risk of toxicity)
- Antimuscarinics: avoidance of tipranavir advised by manufacturer of DARIFENACIN
- Antipsychotics: tipranavir possibly increases plasma concentration of ARIPIPRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); tipranavir possibly increases plasma concentration of QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: tipranavir reduces plasma concentration of ABACAVIR, FOSAMPRENAVIR, LOPINAVIR, SAQUINAVIR and ZIDOVUDINE; plasma concentration of tipranavir increased by ATAZANAVIR (also plasma concentration of atazanavir
Tipranavir

- Antivirals (continued); manufacturer of tipranavir advises avoid concomitant use with BOCEPREVIR and TELAPREVIR; tipranavir reduces plasma concentration of DIDANOSINE—manufacturer of tipranavir advises tipranavir and didanosine capsules should be taken at least 2 hours apart; tipranavir reduces the plasma concentration of DOLUTEGRAVIR (see under Dolutegravir, p. 992); tipranavir reduces plasma concentration of ETARIVINE, also plasma concentration of tipranavir increased (avoid concomitant use); avoidance of tipranavir advised by manufacturer of PARTAPREVIR
- Beta-blockers: manufacturer of tipranavir advises avoid concomitant use with METHOPROLOL, for heart failure
- Bosentan manufacturer of tipranavir advises avoid concomitant use with BOSENTAN
- Cobicistat: plasma concentration of both drugs reduced when tipranavir given with COBICISTAT (avoid concomitant use)
- Lipid-regulating Drugs: Tolvaptan increases plasma concentration of KETOCONAZOLE—plasma concentration of tolvaptan increased by 12 hours advised by manufacturer of Tolvaptan by 12 hours advised by manufacturer of Tolvaptan; tipranavir possibly increases plasma concentration of Tolvaptan; tipranavir increases plasma concentration of GLIBENCLAMIDE
- Antidepressants: anticovulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticovulsant effect of antiepileptics antagonised by SSRI and TRICYCLICS (convulsive threshold lowered)
- Antidiabetics: tipranavir possibly increases plasma concentration of METFORMIN; tipranavir possibly reduces plasma concentration of GLIBENCLAMIDE
- Antiepileptics: plasma concentration of tipranavir often reduced by CARBAMAZEPINE; tipranavir increases plasma concentration of PHENOBARBITAL and PRIMIDONE; hyperammonaemia and CNS toxicity reported when tipranavir given with SODIUM VALPROATE and VALPROIC ACID
- Antimalarials: anticovulsant effect of antiepileptics antagonised by MEfloQUINE
- Antipsychotics: anticovulsant effect of antiepileptics antagonised by ANTISYPHOTICS (convulsive threshold lowered)
- Diuretics: plasma concentration of tipranavir possibly increased by HYDROCHLOROTHIAZIDE
- Lithium: tipranavir possibly affects plasma concentration of LITHIUM
- Oestrogens: tipranavir accelerates metabolism of OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF or BNFC)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ORLISTAT
- Progestogens: tipranavir accelerates metabolism of PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, eutestrogel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF or BNFC)
- Antiepileptics: metabolism of toremifene possibly accelerated by CARBAMAZEPINE (reduced plasma concentration); metabolism of toremifene possibly accelerated by FOSPHENITOIN and PHENYTOIN; metabolism of toremifene accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration)
- Cytotoxics: possible increased risk of ventricular arrhythmias when toremifene given with VANDETANIB—avoid concomitant use
- Diuretics: increased risk of hypercalcaemia when toremifene given with THIAZIDES AND RELATED DIURETICS

Tolcapone

- Antidepressants: avoid concomitant use of tolcapone with MAOIs
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLODOPA
- Tolfenamic Acid
- Tolterodine see Antimuscarinics
- Tolbutamide see Antidiabetics
- Tolcapone
- Antidepressants: avoid concomitant use of tolcapone with MAOIs
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLODOPA
- Tolfenamic Acid
- Tolterodine see Antimuscarinics
- Tolbutamide see Antidiabetics
- Tolcapone
- Antidepressants: avoid concomitant use of tolcapone with MAOIs
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLODOPA
- Tolfenamic Acid
- Tolterodine see Antimuscarinics
- Tolbutamide see Antidiabetics
- Tolcapone
- Antidepressants: avoid concomitant use of tolcapone with MAOIs
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLODOPA
- Tolfenamic Acid
- Tolterodine see Antimuscarinics
- Tolbutamide see Antidiabetics
- Tolcapone
- Antidepressants: avoid concomitant use of tolcapone with MAOIs
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLODOPA
Tretinoin see Retinoids
Triamcinolone see Corticosteroids
Triamterene see Diuretics
Trimesterine for oral
Typhoid Vaccine (parenteral) see Vaccines
Typhoid Vaccine (oral) see Vaccines
Tripotassium Dicitratobismuthate
Tripotassium Dicitratobismuthate see Antimuscarnics
Triphénylédyl see Antipsychotiques
Trimipramine see Antidepressants, Tricyclic

Ulipristal
[continued]
• Increased by ERYTHROMYCIN—manufacturer of low-dose ulipristal advises avoid concomitant use; manufacturer of ulipristal advises avoid concomitant use with rifampicin (concomitant effect of ulipristal possibly reduced)
• Anticoagulants: manufacturer of ulipristal advises give DABIGATRAN at least 1.5 hours before or after ulipristal
• Antidepressants: manufacturer of ulipristal advises avoid concomitant use with ST JOHN’S WORT (concomitant effect of ulipristal possibly reduced)
• Antiepileptics: manufacturer of ulipristal advises avoid concomitant use with carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone (concomitant effect of ulipristal possibly reduced)
• Antifungals: plasma concentration of low-dose ulipristal increased by ketoconazole—manufacturer of low-dose ulipristal advises avoid concomitant use; manufacturer of ulipristal advises avoid concomitant use with itraconazole
• Antihistamines: manufacturer of ulipristal advises give fexofenadine at least 1.5 hours before or after ulipristal
• Antivirals: manufacturer of ulipristal advises avoid concomitant use with ritonavir (concomitant effect of ulipristal possibly reduced)
• Calcium-channel blockers: manufacturer of low-dose ulipristal advises avoid concomitant use with verapamil
• Carboxyhemoglobin: manufacturer of low-dose ulipristal advises avoid concomitant use with grapefruit juice
• Progestogens: ulipristal possibly reduces contraceptive effect of progestogens

Umclidinium see Antimuscarnics
Ursodeoxycholic Acid see Bile Acids

Ustekinumab
• Antipsychotics: avoid concomitant use of cytoxan with clozapine (increased risk of agranulocytosis)
• Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use

Vaccines
• Abacavir: risk of generalised infections when live vaccines given with abacavir—avoid concomitant use
• Aminophylline: influenza vaccine possibly increases plasma concentration of aminophylline
• Anakinra: risk of generalised infections when live vaccines given with anakinra—avoid concomitant use
• Antibacterials: oral typhoid vaccine inactivated by antibacterials—see under Typhoid Vaccine in BNF or BNFC
• Anticoagulants: immunoglobulin possibly enhances anticoagulant effect of warfarin
• Antidepressants: oral typhoid vaccine inactivated by antibacterials including linezolid and tedizolid—see under Typhoid Vaccine in BNF or BNFC
• Antiepileptics: influenza vaccine enhances effects of fosphenytoin and phenytoin
• Antimalarials: oral typhoid vaccine inactivated by antimalarials—see under Typhoid Vaccine in BNF or BNFC
• Azathioprine: risk of generalised infections when live vaccines given with azathioprine—avoid concomitant use
• Corticosteroids: immune response to vaccines impaired by high doses of corticosteroids—avoid concomitant use with live vaccines
• Cytotoxics: risk of generalised infections when live vaccines given with cytotoxic antibiotics, hydroxy carbamidene, monoclonal antibodies or trabectedine—avoid concomitant use
• Dexrazoxane: risk of generalised infections when live vaccines given with dexrazoxane—avoid concomitant use
• Etanercept: risk of generalised infections when live vaccines given with etanercept—avoid concomitant use
• Immunglobulins: impaired immune response to BCG vaccine, MMR vaccine, oral typhoid vaccine, rotavirus vaccine, smallpox vaccine, varicella-zoster vaccine and yellow fever vaccine might occur with anti-D immunoglobulins—give BCG vaccine, MMR vaccine, oral typhoid vaccine, rotavirus vaccine, smallpox vaccine, varicella-zoster vaccine and yellow fever vaccine as a separate injection.

Ulipristal
• Increased by erythromycin—manufacturer of low-dose ulipristal advises avoid concomitant use; manufacturer of ulipristal advises avoid concomitant use with rifampicin (concomitant effect of ulipristal possibly reduced)
• Anticoagulants: manufacturer of ulipristal advises give dabigatran at least 1.5 hours before or after ulipristal
• Antidepressants: manufacturer of ulipristal advises avoid concomitant use with St John’s Wort (concomitant effect of ulipristal possibly reduced)
• Antiepileptics: manufacturer of ulipristal advises avoid concomitant use with carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone (concomitant effect of ulipristal possibly reduced)
• Antifungals: plasma concentration of low-dose ulipristal increased by ketoconazole—manufacturer of low-dose ulipristal advises avoid concomitant use; manufacturer of ulipristal advises avoid concomitant use with itraconazole
• Antihistamines: manufacturer of ulipristal advises give fexofenadine at least 1.5 hours before or after ulipristal
• Antivirals: manufacturer of ulipristal advises avoid concomitant use with ritonavir (concomitant effect of ulipristal possibly reduced)
• Calcium-channel blockers: manufacturer of low-dose ulipristal advises avoid concomitant use with verapamil
• Carboxyhemoglobin: manufacturer of low-dose ulipristal advises avoid concomitant use with grapefruit juice
• Progestogens: ulipristal possibly reduces contraceptive effect of progestogens
Interactions

**Antiepileptics**: (continued)
- fever vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins; impaired immune response to live influenza vaccine might occur with **ANTI-D IMMUNOGLOBULINS** and **NORMAL IMMUNOGLOBULIN**—give live influenza vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; impaired immune response to oral poliomyelitis vaccine might occur with **ANTI-D IMMUNOGLOBULINS** and **NORMAL IMMUNOGLOBULIN**—give oral poliomyelitis vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; impaired immune response to oral poliomyelitis vaccine might occur with **ANTI-D IMMUNOGLOBULINS** and **NORMAL IMMUNOGLOBULIN**—give live influenza vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; impaired immune response to oral poliomyelitis vaccine might occur with **ANTI-D IMMUNOGLOBULINS** and **NORMAL IMMUNOGLOBULIN**—give oral poliomyelitis vaccine at least 3 weeks before or 3 months after normal immunoglobulin
- Interferons: avoidance of vaccines advised by manufacturer of **INTERFERON GAMMA**
  - Leflunomide: risk of generalised infections when live vaccines given with **LEFLUNOMIDE**—avoid concomitant use
  - Teriflunomide: risk of generalised infections when live vaccines given with **TERIFLUNOMIDE**—avoid concomitant use
- Theophylline: influenza vaccine possibly increases plasma concentration of **THEOPHYLLINE**

**Valaciclovir**
- Aminophylline: valaciclovir possibly increases plasma concentration of **AMINOPHYLLINE**
- Ciclosporin: increased risk of nephrotoxicity when valaciclovir given with **CICLOSPORIN**
- Mycophenolate: plasma concentration of valaciclovir increased by **MYCOPHENOLATE**, also plasma concentration of inactive metabolite of mycophenolate increased
- Tacrolimus: possible increased risk of nephrotoxicity when valaciclovir given with **TACROLIMUS**
- Theophylline: valaciclovir possibly increases plasma concentration of **THEOPHYLLINE**

**Valganciclovir**
- Antibacterials: increased risk of convulsions when valganciclovir given with **IMIPENEM WITH CILASTATIN**
- Antivirals: valganciclovir possibly increases plasma concentration of **DIDANOSINE**; profound myelosuppression when valganciclovir given with **ZIDOVUDINE** (if possible avoid concomitant administration, particularly during initial valganciclovir therapy)
- Mycophenolate: plasma concentration of valganciclovir possibly increased by **MYCOPHENOLATE**, also plasma concentration of inactive metabolite of mycophenolate possibly increased
- Tacrolimus: possible increased risk of nephrotoxicity when valganciclovir given with **TACROLIMUS**

**Valproic Acid**
- Analgesics: effects of valproic acid enhanced by **ASPIRIN**
- Antibacterials: metabolism of valproic acid possibly inhibited by **ERYTHROMYCIN** (increased plasma concentration); avoidance of valproic acid advised by manufacturer of **PIMECILLINAM**; plasma concentration of valproic acid reduced by **CARBAPENEMS**—avoid concomitant use
- Anticoagulants: valproic acid possibly enhances anticoagulant effect of **COUMARINS**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TRICYCLIC-RELATED ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIS** and **TRICYCLICS** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of valproic acid reduced by **CARBAMAZEPINE**, also plasma concentration of active metabolite of carbamazepine increased; valproic acid possibly increases plasma concentration of **ETHOSUXIMIDE**; valproic acid increases or possibly decreases plasma concentration of **FOSPHENYTOIN** and **PHENYTOIN**, also plasma concentration of valproic acid reduced; valproic acid increases plasma concentration of **LAMOTRIGINE** (increased risk of toxicity—

**Valproic Acid**
- Antiepileptics (continued)
  - reduce lamotrigin dose); valproic acid sometimes reduces plasma concentration of an active metabolite of **OXCARBAZEPINE**; valproic acid increases plasma concentration of **PHENOBARBITAL** and **PRIMIDONE** (also plasma concentration of valproic acid reduced); valproic acid possibly increases plasma concentration of **RUFINAMIDE** (reduce dose of rufinamide); hyperammonaemia and CNS toxicity reported when valproic acid given with **TOPIRAMATE**
  - Antiinflammarials: anticonvulsant effect of antiepileptics antagonised by **MEFLOQUINE**
  - Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **ANTIPSYCHOTICS** (convulsive threshold lowered); valproic acid possibly increases or decreases plasma concentration of **CLOzapine**; increased risk of side-effects including neuropenia when valproic acid given with **OLANzapine**
  - Antivirals: plasma concentration of valproic acid possibly reduced by **RITONAVIR**; valproic acid possibly increases plasma concentration of **ZIDOVUDINE** (increased risk of toxicity)
  - Antiflammatories and Hypnotics: plasma concentration of valproic acid possibly increased by **CLOBazam**; increased risk of side-effects when valproic acid given with **CLONAZAPeM**; valproic acid possibly increases plasma concentration of **DIAZAPeM** and **LORAZAPeM**
  - Bupropion: valproic acid inhibits the metabolism of **BUPROpION**
  - Cytotoxics: valproic acid increases plasma concentration of **TemozoloMIDE**
  - Guanfacine: plasma concentration of valproic acid increased by **GUANfACINE**
  - Lipid-regulating Drugs: absorption of valproic acid possibly reduced by **COLESTYRAMINE**
  - Netupitant: caution with valproic acid advised by manufacturer of **NETUPITAN**
  - Oestrogens: plasma concentration of valproic acid possibly reduced by **ETHINYLESTRADIOL**
  - Orlistat: possible increased risk of convulsions when antiepileptics given with **ORLISTAT**
  - Sodium Benzoate: valproic acid possibly reduces effects of **SODIUM BENZOATE**
  - Sodium Oxybate: valproic acid increases the plasma concentration of **SODIUM OXYBATE** (see under Sodium Oxybate, p. 455)
  - Sodium Phenylbutyrate: valproic acid possibly reduces effects of **SODIUM PHENYLButyRATE**
  - Ultra-healing Drugs: metabolism of valproic acid inhibited by **CIMETIDINE** (increased plasma concentration)

**Valsartan** see Angiotensin-Ⅱ Receptor Antagonists

**Vancomycin**
- Anaesthetics, General: hypersensitivity-like reactions can occur when **intravenous** vancomycin given with **GENERAL ANAESThETICS**
- Antibacterials: increased risk of nephrotoxicity and ototoxicity when vancomycin given with **AMINOGlyCOSIDES**, **CAPREOMYcin** or **COlSITMethate sODIum**; increased risk of nephrotoxicity when vancomycin given with **POLYMYXINS**
- Antifungals: possible increased risk of nephrotoxicity when vancomycin given with **AMPHOTERICIN**
- Ciclosporin: increased risk of nephrotoxicity when vancomycin given with **CICLOSPORIN**
- Cytotoxics: increased risk of nephrotoxicity and possibly of ototoxicity when vancomycin given with **CISPLATIN**
- Diuretics: increased risk of ototoxicity when vancomycin given with **LODIP Diuretics**
- Lipid-regulating Drugs: effects of **oral** vancomycin antagonised by **COLESTYRAMINE**
- Muscle Relaxants: vancomycin enhances effects of **SUXAMETHONIUM**
- Tacrolimus: possible increased risk of nephrotoxicity when vancomycin given with **TACROLIMUS**
- Vaccines: antibacterials inactivate **ORAL TYPhOID VACCINE**—see under Typhoid Vaccine in BNF or BNFC
Vardenafil

- Analgesics: possible increased risk of ventricular arrhythmias when vardenafil given with METHADONE—avoid concomitant use
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when vardenafil given with AMIODARONE or DISOPYRAMIDE—avoid concomitant use
- Antibacterials: possible increased risk of ventricular arrhythmias when vardenafil given with parenteral ERYTHROMYCIN—avoid concomitant use; possible increased risk of ventricular arrhythmias when vardenafil given with MOXIFLOXACIN—avoid concomitant use; plasma concentration of vardenafil reduced by Rifampicin—manufacturer of vardenafil advises avoid concomitant use; Antidepressant: manufacturer of vardenafil advises avoid concomitant use with ST JOHN’S WORT (plasma concentration of vardenafil possibly reduced)
- Anti-diabetics: vardenafil possibly increases plasma concentration of METFORMIN (consider reducing dose of metformin)
- Antiepileptics: manufacturer of vardenafil advises avoid concomitant use with CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE (plasma concentration of vardenafil possibly reduced)
- Antihistamines: possible increased risk of ventricular arrhythmias when vardenafil given with MIZOLASTINE—avoid concomitant use
- Antimalarials: possible increased risk of ventricular arrhythmias when vardenafil given with ARTEMETHER WITH LUMEFANTRINE—avoid concomitant use
- Anti-pyretics: increased risk of ventricular arrhythmias when vardenafil given with AMISULPRIDE, CHLORPROMAZINE, HALOPERIDOL, PIMOZIDE, SULPIRIDE or ZUCLOPENTHIXOL—avoid concomitant use; avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)
- Beta-blockers: possible increased risk of ventricular arrhythmias when vardenafil given with SOTALOL—avoid concomitant use
- Cardiac Glycosides: vardenafil increases plasma concentration of DIGOXIN—possible increased risk of bradycardia
- Cytotoxics: possible increased risk of ventricular arrhythmias when vardenafil given with ARSECNI TRIOXIDE—avoid concomitant use
- Hormone Antagonists: possible increased risk of ventricular arrhythmias when vardenafil given with TOREMIFENE—avoid concomitant use
- SHT-receptor Antagonists: increased risk of ventricular arrhythmias when vardenafil given with ONDANSETRON—avoid concomitant use
- Pentamidine isetionate: possible increased risk of ventricular arrhythmias when vardenafil given with PENTAMIDINE ISETIONATE—avoid concomitant use

Vardenafil (continued)

- Antivirals: caution with vardenafil advised by manufacturer of TIPRANAVIR
- Calcium-channel Blockers: enhanced hypotensive effect when vardenafil given with NIFEDIPINE
- Cobicistat: plasma concentration of vardenafil possibly increased by COBICISTAT—manufacturer of cobicistat advises reduce dose of vardenafil (consult cobicistat product literature)
- Dopoxetine: avoidance of vardenafil advised by manufacturer of DAPoxetine
- Grapefruit Juice: plasma concentration of vardenafil possibly increased when vardenafil given with GRAPFRUIT JUICE—avoid concomitant use
- Nicorandil: possible increased hypotensive effect when vardenafil given with NICORANDIL—avoid concomitant use
- Nitrates: possible increased hypotensive effect when vardenafil given with NITRATES—avoid concomitant use
- Riociguat: possible enhanced hypotensive effect when vardenafil given with RIoCIGUAT—avoid concomitant use

Varicella-zoster Vaccine see Vaccines

Vasodilator Antihypertensives

- ACE inhibitors: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ALCOHOL
- Aldesleukin: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ALDESLEUKIN
- Alpha-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ALPHA-BLOCKERS
- Analgesics: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by NSAIDS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antidepressants: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with TRICYCLIC-RELATED ANTIDEPRESSANTS
- Antipsychotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with PHENOTHIAZINES
- Anxiolytics and Hypnotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ANXIOLYTICS AND HYPNOTICS
- Beta-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with CLONIDINE
- Corticosteroids: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by CORTICOSTEROIDS
- Dihydropyridines: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with DIAZODE
- Diuretics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with DIURETICS
- Dopaminergics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with CO- BENELDPA; enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with CO-CARELDOPA
- Methylpapaverine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with METHYLPAVERINE
- Nonsteroidal Anti-Inflammatory Drugs: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with COBENEDYMPHEN
- Vasodilator Antihypertensives: See Vasodilator Antihypertensives

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Venlafaxine (continued)
- Beta-blockers: manufacturer of venlafaxine advises avoid concomitant use with **SOTALOL** (risk of ventricular arrhythmias)
- Dopamine: possible increased risk of serotonergic effects when venlafaxine given with **DAPoxetine** (manufacturer of dapoxetine advises venlafaxine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping venlafaxine)
- Dopaminergics: caution with venlafaxine advised by manufacturer of **ENTACAPONE**; increased risk of hypertension and CNS excitation when venlafaxine given with **SELEGININE** (selegiline should not be started until 1 week after stopping venlafaxine, avoid venlafaxine for 2 weeks after stopping selegiline)
- SH3-receptor Agonists: possible increased serotonergic effects when venlafaxine given with **SHT, AGONISTS**
- SH3-receptor Antagonists: possible increased serotonergic effects when SSRI-related antidepressants given with **SHT3 ANTAGONISTS**
- Lithium: possible increased serotonergic effects when venlafaxine given with **LITHIUM**
- Methylthioninium: risk of CNS toxicity when SSRI-related antidepressants given with **METHYLTHIONIUM**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Verapamil see Calcium-channel Blockers

Vigabatrin
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TRICYCLIC-RELATED ANTI DEPRESSANTS** (convulsive threshold lowered): anticonvulsant effect of antiepileptics antagonised by **SSRIS** and **TRICYCLICS** (convulsive threshold lowered)
- Antiepileptics: vigabatrin reduces plasma concentration of **FOSPHENYTOIN** and **PHENYTOIN**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **MEFLOQUINE**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **ANTIPSYCHOTICS** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **ORLISTAT**

Vilanterol see Sympathomimetics, Beta2

Vildaglaptin see Antidiabetics

Vinblastine
- Aldesleukin: avoidance of vinblastine advised by manufacturer of **ALDESLEUKIN**
- Antibacterials: toxicity of vinblastine increased by **ERYTHROMYCIN**—avoid concomitant use; possible increased risk of ventricular arrhythmias when vinblastine given with **DELAMANID**
- Antifungals: possible increased risk of vinblastine toxicity when given with **ITRACONAZOLE**; metabolism of vinblastine possibly inhibited by **POSACONAZOLE** (increased risk of neurotoxicity)
- Antimalarials: avoidance of vinblastine advised by manufacturer of **ARTEMINOL WITH PIPERAQUINE**
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOzapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of vinblastine possibly increased by **RITONAVIR**

Vincristine
- Antibacterials: possible increased risk of ventricular arrhythmias when vincristine given with **DELAMANID**
- Antifungals: increased risk of vincristine toxicity when given with **ITRACONAZOLE**; metabolism of vincristine possibly inhibited by **POSACONAZOLE** (increased risk of neurotoxicity)
- Antimalarials: avoidance of vincristine advised by manufacturer of **ARTEMINOL WITH PIPERAQUINE**
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOzapine** (increased risk of agranulocytosis)
- Calcium-channel Blockers: metabolism of vincristine possibly inhibited by **NIFEDIPINE**
- Cardiac Glycosides: vincristine possibly reduces absorption of **DIGOXIN** tablets
**Vincristine** (continued)
- Cytotoxics: increased risk of hepatotoxicity when vincristine given with **DACTINOMYCIN**

**Vindesine**
- Antibacterials: possible increased risk of ventricular arrhythmias when vindesine given with **DELAMANID**
- Antifungals: possible increased risk of vindesine toxicity when given with **ITRACONAZOLE**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOzapine** (increased risk of agranulocytosis)

**Vinflunine**
- Antibacterials: plasma concentration of vinflunine possibly reduced by **RIFAMPICIN** — manufacturer of vinflunine advises avoid concomitant use; increased risk of ventricular arrhythmias when vinflunine given with **DELAMANID**
- Antidopaminergics: plasma concentration of vinflunine possibly reduced by **ST JOHN’S WORT** — manufacturer of vinflunine advises avoid concomitant use
- Antifungals: plasma concentration of vinflunine possibly increased by **KETOCONAZOLE** — manufacturer of vinflunine advises avoid concomitant use
- Antivirals: plasma concentration of vinflunine possibly increased by **Grapefruit Juice** — manufacturer of vinflunine advises avoid concomitant use

**Vinorelbine**
- Antibacterials: possible increased risk of neutropenia when vinorelbine given with **CLARITHROMYCIN**; possible increased risk of ventricular arrhythmias when vinorelbine given with **DELAMANID**
- Antidopaminergics: avoidance of vinorelbine advised by manufacturer of **ARTEMIMOL WITH PIPERAQUINE**
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOzapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of vinorelbine possibly increased by **RITONAVIR** — manufacturer of vinflunine advises avoid concomitant use
- Antifungals: plasma concentration of vinorelbine possibly increased by **GRAPeFRUIT JUICE** — manufacturer of vinflunine advises avoid concomitant use

**Vismodegib**
- Antibacterials: manufacturer of vismodegib advises avoid concomitant use with **RIFAMPICIN** (plasma concentration of vismodegib possibly reduced)
- Antidopaminergics: manufacturer of vismodegib advises avoid concomitant use with **ST JOHN’S WORT** (plasma concentration of vismodegib possibly reduced)
- Antiepileptics: manufacturer of vismodegib advises avoid concomitant use with **CARBAMAZEPINE**, **FOSPHENYToin** and **PHENYTOIN** (plasma concentration of vismodegib possibly reduced)
- Antipsychotics: avoid concomitant use of cytotoxics with **CLOzapine** (increased risk of agranulocytosis)

**Vitamin A** see Vitamins

**Vitamin D** see Vitamins

**Vitamin E** see Vitamins

**Vitamin K (Phytonadione)** see Vitamins

**Vitamins**
- Anticoagulants: vitamin E possibly enhances anticoagulant effect of **COUMARINS**; vitamin K antagonises anticoagulant effect of **COUMARINS** and **PHENINDION**
- Antiepileptics: alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with **CARBAMAZEPINE**; alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with **PHOSPHENYToin**; alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with **PHENOBARBITAL**; alfacalcidol, calcitriol, colecalciferol,

**Vitamins**
- Antiepileptics (continued)
  - dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with **PHENYTOIN**; alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with **PRIMIDONE**
  - Antifungals: plasma concentration of paricalcitol possibly increased by **KETOCONAZOLE**; effects of alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol and vitamin D possibly reduced by **MICONAZOLE**
  - Antivirals: increased risk of bleeding when high doses of vitamin E given with **TIPRANAVIR**
  - Cisplatin: vitamin E possibly affects plasma concentration of **CICLOSPORIN**
  - Cytotoxics: effects of alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol and vitamin D possibly reduced by **DACTINOMYCIN**; avoidance of vitamin E advised by manufacturer of **IBRUTINIB**
  - Diuretics: increased risk of hypercalcaemia when alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D given with **THIAZIDES AND RELATED DIURETICS**
  - Dopaminergics: pyridoxine reduces effects of **LEVODOPA** when given without dopa-decarboxylase inhibitor
  - Lipid-regulating Drugs: absorption of calcitriol possibly reduced by **COLESTYRAMINE** (give at least 1 hour before or 4 to 6 hours after colestatramine)
  - Retinoids: risk of hypervitaminosis A when vitamin A given with **RETINoIDS** — avoid concomitant use
  - Selenium: ascorbic acid possibly reduces absorption of **SELENIum** (give at least 4 hours apart)
  - Sevelamer: absorption of calcitriol reduced by **SEVELAMER** (give at least 1 hour before or 3 hours after sevelamer)

**Voriconazole** see Antifungals, Triazole

**Vortioxetine**
- Analgesics: possible increased serotonergic effects when vortioxetine given with **TRAMADOL**
- Antibacterials: plasma concentration of vortioxetine reduced by **RIFAMPICIN** — consider increasing dose of vortioxetine
- Antidepressants: plasma concentration of vortioxetine possibly increased by **FLUOXETINE** and **PAROXETINE** (consider reducing dose of vortioxetine); increased risk of hypertension and CNS excitation when vortioxetine given with **MAOIS** (vortioxetine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 2 weeks after stopping vortioxetine); manufacturer of vortioxetine advises avoid concomitant use with **LINEZOLID** and **MOLOBEMIDE**; possible increased risk of convulsions when vortioxetine given with **SSRI-RELATED ANTIdePRESSANTS**, **SSRIS** or **TRICYCLICS**; possible increased serotonergic effects when vortioxetine given with **ST JOHN’S WORT**
- Antiepileptics: plasma concentration of vortioxetine possibly reduced by **CARBAMAZEPINE**, **FOSPHENYToin** and **PHENYTOIN** — consider increasing dose of vortioxetine
- Antimalarials: avoidance of antidepressants advised by manufacturer of **ARTEMETHER WITH LUMEFANTRIN** and **ARTEMIMOL WITH PIPERAQUINE**; possible increased risk of convulsions when vortioxetine given with **MefLOQUINE**
- Antipsychotics: possible increased risk of convulsions when vortioxetine given with **BUTYROPHENONES**, **PHENOThIAZinEs** and **THIOXANTHENES**
- Atomoxetine: possible increased risk of convulsions when antidepressants given with **ATOMOXETINE**
- Bupropion: plasma concentration of vortioxetine increased by **BUPROPION** (consider reducing dose of vortioxetine)
- Dopaminergics: risk of CNS excitation and hypertension when vortioxetine given with **RASAGLINiNE** or **SELEGLiNINE**
- 5HT2-receptor Agonists: possible increased serotonergic effects when vortioxetine given with **5HT, AGONiSTS**

**Warfarin** see Coumarins

**Wasp Venom Extracts**
- ACE Inhibitors: possible severe anaphylactoid reaction when wasp venom extracts given with **ACE inhibitors**

**Xipamide** see Diuretics

**Xylometazoline** see Sympathomimetics
Yellow Fever Vaccine  see Vaccines
Zafirlukast  see Leukotriene Receptor Antagonists
Zaleplon  see Anxiolytics and Hypnotics

Zidovudine

- **NOTE** Increased risk of toxicity with nephrotoxic and myelosuppressive drugs—for further details consult product literature
- Analgesics: increased risk of haematological toxicity when zidovudine given with **NSAIDs**; plasma concentration of zidovudine possibly increased by **METHADONE**
- Antibacterials: absorption of zidovudine reduced by **CLARITHROMYCIN** tablets (give at least 2 hours apart); manufacturer of zidovudine advises avoid concomitant use with **RIFAMPICIN**
- Antiepileptics: zidovudine increases or decreases plasma concentration of **FOSPHENYTOIN** and **PHENYTOIN**; plasma concentration of zidovudine possibly increased by **SODIUM VALPROATE** and **VALPROIC ACID** (increased risk of toxicity)
- Antifungals: plasma concentration of zidovudine increased by **FLUCONAZOLE** (increased risk of toxicity)
- Antimalarials: increased risk of haematological toxicity when zidovudine given with **PYRIMETHAMINE**
- Antivirals: profound myelosuppression when zidovudine given with **GANCICLOVIR** or **VALGANCICLOVIR** (if possible avoid concomitant administration, particularly during initial ganciclovir or valganciclovir therapy); increased risk of granulocytopenia when zidovudine given with **NEVIRAPINE**; increased risk of anaemia when zidovudine given with **RIBAVIRIN**—avoid concomitant use; zidovudine possibly inhibits effects of **STAVUDINE** (manufacturers advise avoid concomitant use); plasma concentration of zidovudine reduced by **TIPRANAVIR**
- Atovaquone: plasma concentration of zidovudine increased by **ATOVAQUONE** (increased risk of toxicity)
- Efavirenz: caution with zidovudine advised by manufacturer of **NETUPITANT**
- Orlistat: absorption of zidovudine possibly reduced by **ORLISTAT**

Zinc

- Antibacterials: zinc reduces absorption of **CIPROFLOXACIN**, **LEVOFLOXACIN**, **NORFLOXACIN** and **OFLOXACIN** (give at least 2 hours apart); zinc reduces absorption of **MOXIFLOXACIN** (give at least 6 hours apart); zinc possibly reduces absorption of **TETRACYCLINES** (give at least 2 to 3 hours apart)
- Calcium Salts: absorption of zinc reduced by **CALCIUM SALTS**
- Eltrombopag: zinc possibly reduces absorption of **ELTROMBOPAG** (give at least 4 hours apart)
- Iron Salts: absorption of zinc reduced by oral **IRON SALTS**, also absorption of oral iron salts reduced by zinc
- Penicillamine: absorption of zinc reduced by **PENICILLAMINE**, also absorption of penicillamine reduced by zinc
- Trientine: absorption of zinc reduced by **TRIENTINE**, also absorption of trientine reduced by zinc

Zoledronic Acid  see Bisphosphonates
Zolmitriptan  see 5HT₁-receptor Agonists (under HT)
Zolpidem  see Anxiolytics and Hypnotics
Zonisamide

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **TRICYCLIC-RELATED ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIS** and **TRICYCLICS** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of zonisamide reduced by **CARBAMAZEPINE**, **FOSPHENYTOIN**, **PHENOBARBITAL**, **PHENYTOIN** and **PRIMIDONE**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **MEFLOQUINE**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **ANTIPSYCHOTICS** (convulsive threshold lowered)
- Diuretics: manufacturer of zonisamide advises avoid concomitant use with **CARBONIC ANHYDRASE INHIBITORS** in children
- Orlistat: possible increased risk of convulsions when antiepileptics given with **ORLISTAT**

Zopiclone  see Anxiolytics and Hypnotics

Zuclopenthixol  see Antipsychotics
In certain conditions some foods (and toilet preparations) have characteristics of drugs and the Advisory Committee on Borderline Substances (ACBS) advises as to the circumstances in which such substances may be regarded as drugs. Prescriptions issued in accordance with the Committee's advice and endorsed 'ACBS' will normally not be investigated.

Information

General Practitioners are reminded that the ACBS recommends products on the basis that they may be regarded as drugs for the management of specified conditions. Doctors should satisfy themselves that the products can safely be prescribed, that patients are adequately monitored and that, where necessary, expert hospital supervision is available.

Foods which may be prescribed on FP10, GP10 (Scotland), or WP10 (Wales)

All the food products listed in this appendix have ACBS approval. The clinical condition for which the product has been approved is included with each entry.

Note

Foods included in this appendix may contain cariogenic sugars and patients should be advised to take appropriate oral hygiene measures.

Enteral feeds and supplements

For most enteral feeds and nutritional supplements, the main source of carbohydrate is either maltodextrin or glucose syrup; other carbohydrate sources are listed in the relevant table, below. Feeds containing residual lactose (less than 1 g lactose/100 mL formula) are described as 'clinically lactose-free' or 'lactose-free' by some manufacturers. The presence of lactose (including residual lactose) in feeds is indicated in the relevant table, below. The primary sources of protein or amino acids are included with each product entry. The fat or oil content is derived from a variety of sources such as vegetables, soya bean, corn, palm nuts, and seeds; where the fat content is derived from animal or fish sources, this information is included in the relevant table, below. The presence of medium chain triglycerides (MCT) is also noted where the quantity exceeds 30% of the fat content.

Enteral feeds and nutritional supplements can contain varying amounts of vitamins, minerals, and trace elements—the manufacturer's product literature should be consulted for more detailed information. Feeds containing vitamin K may affect the INR in patients receiving warfarin. The suitability of food products for patients requiring a vegan, kosher, halal, or other compliant diet should be consulted for more detailed information. Feeds containing medium chain triglycerides (MCT) should be avoided in children unless recommended by an appropriate specialist or dietician.

Nutritional values

Nutritional values of products vary with flavour and pack size—consult product literature.

Other conditions for which ACBS products can be prescribed

This is a list of clinical conditions for which the ACBS has approved toilet preparations.

BIRTHMARKS

Dermatitis

Eczema and Pruritus

Aveeno® Bath Oil; Aveeno® Cream; Aveeno® Lotion; E45® Emollient Bath Oil; E45® Emollient Wash Cream; E45® Lotion

Disfiguring skin lesions (birthmarks, mutilating lesions, scars, vitiligo)

Covermark® classic foundation and finishing powder; Dermablend® Ultra corrective foundation; Dermacolor® Camouflage cream and fixing powder; Keromask® masking cream and finishing powder; Veil® Cover cream and Finishing Powder. (Cleansing Creams, Cleansing Milks, and Cleansing Lotions are excluded).

Disinfectants (antiseptics)

May be prescribed on an FP10 only when ordered in such quantities and with such directions as are appropriate for
the treatment of patients, but not for general hygenic purposes.

**Dry mouth (xerostomia)**
For patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome. *AS Saliva Orthana®; Biotène Oralbalance®; BioXtra®; Glandosane®; Saliveze®.*

**Photodermatoses (skin protection in)**
*Anthelios® XL SPF 50+ Melt-in cream; Sunsense® Ultra; Uvistat® Lipscreen SPF 50, Uvistat® Suncream SPF 30 and 50*

**Standard ACBS indications:** Disease-related malnutrition, intractable malabsorption, pre-operative preparation of malnourished patients, dysphagia, proven inflammatory bowel disease, following total gastrectomy, short-bowel syndrome, bowel fistula
<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 1500 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g cows’ milk soya</td>
<td>13 g (sugars 0.9 g)</td>
<td>3.4 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years</td>
<td>Fresubin 1500 Complete liquid: 1.5 litre = £13.28</td>
</tr>
<tr>
<td>Fresubin® Original (Fresenius Kabi Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g cows’ milk soya</td>
<td>13.8 g (sugars 3.5 g)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin Feed in flexible pack contains fish oil and fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Fresubin Original drink: blackcurrant, chocolate, nut, peach, vanilla 200 ml = £2.14; Fresubin Original tube feed liquid: 1000 ml = £8.26; 500 ml = £4.17; 1500 ml = £12.39</td>
</tr>
<tr>
<td>Fresubin® Original Fibre (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g cows’ milk soya</td>
<td>13 g (sugars 0.9 g)</td>
<td>3.4 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years</td>
<td>Fresubin Original Fibre liquid: 1000 ml = £9.42; 500 ml = £4.72</td>
</tr>
<tr>
<td>Jevity® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>449 kJ (107 kcal)</td>
<td>4 g caseinates</td>
<td>14.1 g (sugars 470 mg)</td>
<td>3.47 g</td>
<td>1.76 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula. Not suitable for child under 2 years</td>
<td>Jevity liquid: 500 ml = £5.20; 1500 ml = £14.14; 1000 ml = £9.46</td>
</tr>
<tr>
<td>Nutrison® (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g cows’ milk</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Nutrison liquid: 500 ml = £4.92; 1500 ml = £12.93; 1000 ml = £8.63; 500 ml = £4.43</td>
</tr>
<tr>
<td>Nutrison® Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g cows’ milk</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula</td>
<td>Nutrison Multi Fibre liquid: 1000 ml = £9.99; 500 ml = £4.99; 500 ml = £5.31; 1500 ml = £14.97</td>
</tr>
<tr>
<td>Osmolite® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>424 kJ (100 kcal)</td>
<td>4 g caseinates soy isolate</td>
<td>13.6 g (sugars 630 mg)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Osmolite liquid: 500 ml = £4.65; 1000 ml = £8.46; 1500 ml = £12.65</td>
</tr>
</tbody>
</table>
### SOYA PROTEIN FORMULA

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (kJ)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® Soya Fibre (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 (100 kcal)</td>
<td>3.8 g soya protein</td>
<td>13.3 g (sugars 4.1 g)</td>
<td>3.6 g</td>
<td>2 g</td>
<td>Gluten-free Lactose-free Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349; also cows' milk protein intolerance, lactose intolerance</td>
<td>Fresubin Soya Fibre liquid: 500 ml = £4.88</td>
</tr>
<tr>
<td>Nutrison® Soya (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 (100 kcal)</td>
<td>4 g soy isolate</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Milk protein-free</td>
<td>Borderline substances standard ACBS indications p. 1349; also cows' milk protein and lactose intolerance</td>
<td>Nutrison Soya liquid: 500 ml = £5.30; 1000 ml = £10.62</td>
</tr>
<tr>
<td>Nutrison® Soya Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 (100 kcal)</td>
<td>4 g soy isolate</td>
<td>12.3 g (sugars 700 mg)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Milk protein-free</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula; also cows' milk protein and lactose intolerance</td>
<td>Nutrison Soya Multi Fibre liquid: 1.5 litre = £17.66</td>
</tr>
</tbody>
</table>

### PEPTIDE-BASED FORMULA

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (kJ)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrison Peptisorb® (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>425 (100 kcal)</td>
<td>4 g whey protein hydrolysate</td>
<td>17.6 g (sugars 1.7 g)</td>
<td>1.7 g (MCT 47 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Nutrison Peptisorb liquid: 1000 ml = £13.94; 500 ml = £7.73; 500 ml = £7.04</td>
</tr>
<tr>
<td>Peptamen® (Nestle Health Science)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>420 (100 kcal)</td>
<td>4 g whey peptides</td>
<td>12.7 g (sugars 480 mg)</td>
<td>3.7 g (MCT 70 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Peptamen liquid: vanilla 800 ml = £12.14; unflavoured 500 ml = £6.82; 1000 ml = £12.80</td>
</tr>
<tr>
<td>Survivem® OPD (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 (100 kcal)</td>
<td>4.5 g whey protein hydrolysate</td>
<td>14.3 g (sugars 1.1 g)</td>
<td>2.8 g (MCT 51 %)</td>
<td>0.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349; also growth failure</td>
<td>Survivem OPD: liquid 500 ml = £6.96; 800 ml = £12.84; 1000 ml = £13.92; HN liquid 500 ml = £6.70</td>
</tr>
</tbody>
</table>

### Enteral feeds: Less than 1 kcal/mL and less than 5 g protein/100 mL

#### AMINO ACID FORMULA (ESSENTIAL AND NON-ESSENTIAL AMINO ACIDS)

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (kJ)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental 028® Extra (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>360 (86 kcal)</td>
<td>2.5 g (protein equivalent)</td>
<td>11 g (sugars 4.7 g)</td>
<td>3.5 g (MCT 35 %)</td>
<td>Nil</td>
<td></td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Elemental 028 Extra liquid summer fruits: 250 ml = £3.73</td>
</tr>
<tr>
<td>Standard dilution (20 %) of powder (sip or tube feed)</td>
<td></td>
<td>374 (89 kcal)</td>
<td>2.5 g (protein equivalent)</td>
<td>11.8 g (sugars 1.8 g)</td>
<td>3.5 g (MCT 35 %)</td>
<td>Nil</td>
<td></td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Elemental 028 Extra powder: plain, orange, banana 100 gram = £7.24</td>
</tr>
</tbody>
</table>

Powder provides protein equivalent 12.5 g, carbohydrate 59 g, fat 17.45 g, energy 1871 kj (443 kcal)/100 g.
### Enteral feeds (non-disease specific): 5 g (or more) protein/100 mL

**Enteral feeds: 1.5 kcal/mL and 5 g (or more) protein/100 mL**

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fresubin® 2250 Complete</strong></td>
<td>Liquid (tube feed)</td>
<td>630 kJ</td>
<td>5.6 g</td>
<td>18.8 g</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Fresubin 2250 Complete liquid: 1.5 litre = £14.82</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>(sugars 1.5 g)</td>
<td></td>
<td></td>
<td>Contains fish oil and fish gelatin</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
<tr>
<td><strong>Fresubin® Energy</strong></td>
<td>Liquid (sip feed)</td>
<td>630 kJ</td>
<td>5.6 g</td>
<td>18.8 g</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Fresubin Energy liquid: banana, blackcurrant, cappuccino, chocolate, lemon, strawberry, tropical fruits, vanilla 200 ml = £1.40; unflavoured 200 ml = £1.40; 500 ml = £5.11</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>(sugar content varies with flavour)</td>
<td></td>
<td></td>
<td>Contains fish gelatin Strawberry flavour may contain traces of wheat starch and egg.</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
<tr>
<td><strong>Fresubin® Energy Fibre</strong></td>
<td>Liquid (tube feed)</td>
<td>630 kJ</td>
<td>5.6 g</td>
<td>18.8 g</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Fresubin Energy Fibre liquid: banana, caramel, cherry, chocolate, strawberry 200 ml = £2.05; unflavoured 500 ml = £5.60; 1000 ml = £10.68</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>(sugars 1.4 g)</td>
<td></td>
<td></td>
<td>Contains fish oil and fish gelatin</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
<tr>
<td><strong>Fresubin® HP Energy</strong></td>
<td>Liquid (tube feed)</td>
<td>630 kJ</td>
<td>7.5 g</td>
<td>17 g</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Fresubin HP Energy liquid: 500 ml = £5.20; 1000 ml = £10.40</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>(sugars 1.5 g)</td>
<td></td>
<td></td>
<td>Contains fish oil and fish gelatin</td>
<td>ACBS indications p. 1349; also CAPD and haemodialysis</td>
<td></td>
</tr>
<tr>
<td><strong>Jevity® 1.5 kcal</strong></td>
<td>Liquid (tube feed)</td>
<td>649 kJ</td>
<td>6.38 g</td>
<td>20.1 g</td>
<td>4.9 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Jevity 1.5kcal liquid: 500 ml = £6.24; 1000 ml = £11.36; 1500 ml = £16.97</td>
</tr>
<tr>
<td>(Abbott Laboratories Ltd)</td>
<td>per 100 mL</td>
<td>(154 kcal)</td>
<td>caseinates and soy isolate</td>
<td>(sugars 1.47 g)</td>
<td></td>
<td></td>
<td>Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
<tr>
<td><strong>Nutrison® Energy</strong></td>
<td>Liquid (tube feed)</td>
<td>630 kJ</td>
<td>6 g</td>
<td>18.5 g</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Nutrison Energy liquid: 1500 ml = £16.10; 500 ml = £5.72; 500 ml = £5.35; 1000 ml = £10.77</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>(sugars 1.5 g)</td>
<td></td>
<td></td>
<td>Not recommended for child 2-10 years</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
<tr>
<td><strong>Nutrison® Energy Multi Fibre</strong></td>
<td>Liquid (tube feed)</td>
<td>630 kJ</td>
<td>6 g</td>
<td>18.5 g</td>
<td>5.8 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Nutrison Energy Multi Fibre liquid: 1500 ml = £18.45; 1000 ml = £11.95; 500 ml = £6.35; 500 ml = £5.99</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>(sugars 1.5 g)</td>
<td></td>
<td></td>
<td>Not recommended for child 2-10 years</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
<tr>
<td><strong>Osmolite® 1.5 kcal</strong></td>
<td>Liquid (tube feed)</td>
<td>632 kJ</td>
<td>6.25 g</td>
<td>20 g</td>
<td>5 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard</td>
<td>Osmolite 1.5kcal tube feed liquid: 500 ml = £5.60; 1000 ml = £10.19; 1500 ml = £15.23</td>
</tr>
<tr>
<td>(Abbott Laboratories Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>cows' milk</td>
<td>soya protein isolate</td>
<td></td>
<td></td>
<td>Not recommended for child 2-10 years</td>
<td>ACBS indications p. 1349</td>
<td></td>
</tr>
</tbody>
</table>
## Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>12.5 g (sugars 1.1 g)</td>
<td>3.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Fresubin 1000 Complete liquid: 1 litre = £10.68</td>
</tr>
<tr>
<td>Fresubin® 1200 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>500 kJ (120 kcal)</td>
<td>6 g cows’ milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Fresubin 1200 Complete liquid: 1 litre = £13.60</td>
</tr>
<tr>
<td>Fresubin® 1800 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>500 kJ (120 kcal)</td>
<td>6 g cows’ milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Fresubin 1800 Complete liquid: 1.5 litre = £13.60</td>
</tr>
<tr>
<td>Jevity® Plus (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>514 kJ (122 kcal)</td>
<td>5.5 g caseinates soy isolates</td>
<td>15.1 g (sugars 890 mg)</td>
<td>3.93 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td>Jevity Plus liquid: 500 ml = £6.20; 1000 ml = £11.28; 1500 ml = £16.86</td>
</tr>
<tr>
<td>Jevity® Plus HP (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>551 kJ (131 kcal)</td>
<td>8.13 g cows’ milk soy isolates</td>
<td>14.2 g (sugars 950 mg)</td>
<td>4.33 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td>Jevity Plus HP gluten free liquid: 500 ml = £6.20</td>
</tr>
<tr>
<td>Jevity® Promote (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>434 kJ (103 kcal)</td>
<td>5.55 g caseinates soy isolates</td>
<td>12 g (sugars 670 mg)</td>
<td>3.32 g</td>
<td>1.7 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td>Jevity Promote liquid: 1 litre = £10.80</td>
</tr>
</tbody>
</table>
### Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL (product list continued)

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrison® 800 Complete Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>345 kJ (83 kcal)</td>
<td>5.5 g cows’ milk pea protein soya protein</td>
<td>8.8 g (sugars 600 mg)</td>
<td>2.5 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula Not suitable for child under 6 years; not recommended for child 6–12 years</td>
<td>Nutrison 800 Complete Multi Fibre liquid: 1 litre = £10.45</td>
</tr>
<tr>
<td>Nutrison® 1000 Complete Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>11.3 g (sugars 700 mg)</td>
<td>3.7 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Disease related malnutrition in patients with low energy and/or low fluid requirements</td>
<td>Nutrison 1000 Complete Multi Fibre liquid: 1 litre = £11.08</td>
</tr>
<tr>
<td>Nutrison® 1200 Complete Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>505 kJ (120 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>15 g (sugars 1.2 g)</td>
<td>4.3 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula</td>
<td>Nutrison 1200 Complete Multi Fibre liquid: 1000 ml = £11.73; 1500 ml = £17.61</td>
</tr>
<tr>
<td>Nutrison® MCT (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5 g cows’ milk</td>
<td>12.6 g (sugars 1 g)</td>
<td>3.3 g (MCT 61%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Nutrison MCT liquid: 1000 ml = £9.98</td>
</tr>
<tr>
<td>Nutrison® Protein Plus (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>525 kJ (125 kcal)</td>
<td>6.3 g cows’ milk</td>
<td>14.2 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Nutrison Protein Plus liquid: 1 litre = £10.25</td>
</tr>
<tr>
<td>Nutrison® Protein Plus Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>525 kJ (125 kcal)</td>
<td>6.3 g cows’ milk</td>
<td>14.1 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Disease related malnutrition</td>
<td>Nutrison Protein Plus Multifibre liquid: 1 litre = £11.42</td>
</tr>
<tr>
<td>Osmolite® Plus (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>508 kJ (121 kcal)</td>
<td>5.55 g caseinates</td>
<td>15.8 g (sugars 730 mg)</td>
<td>3.93 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 10 years</td>
<td>Osmolite Plus liquid: 1500 ml = £14.15; 1000 ml = £9.46; 500 ml = £5.20</td>
</tr>
<tr>
<td>Peptamen® HN (Nestle Health Science)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>556 kJ (133 kcal)</td>
<td>6.6 g whey protein hydrolysates</td>
<td>15.6 g (sugars 1.4 g)</td>
<td>4.9 g (MCT 70%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Hydrolysed with pork trypsin</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula Not suitable for child under 3 years</td>
<td>Peptamen HN liquid: 500 ml = £7.34</td>
</tr>
<tr>
<td>Perative® (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>552 kJ (131 kcal)</td>
<td>6.7 g caseinate whey protein hydrolysates</td>
<td>17.7 g (sugars 660 mg)</td>
<td>3.7 g (MCT 42%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 5 years</td>
<td>Perative liquid: 1000 ml = £13.66; 500 ml = £7.50</td>
</tr>
</tbody>
</table>
**Enteral feeds: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL**

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® TwoCal (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed per 100 mL)</td>
<td>838 kJ (200 kcal)</td>
<td>8.4 g cows' milk</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also haemodialysis and CAPD</td>
<td>Ensure TwoCal liquid: banana, neutral, strawberry, vanilla 200 ml = £2.22</td>
</tr>
<tr>
<td>TwoCal® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed per 100 mL)</td>
<td>837 kJ (200 kcal)</td>
<td>8.4 g cows' milk caseinates</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Adults with or at risk of disease-related malnutrition, catabolic or fluid-restricted patients, and other patients requiring a 2 kcal/mL feed</td>
<td>TwoCal liquid: 1 litre = £14.80</td>
</tr>
</tbody>
</table>

**Enteral feeds (non-disease specific): Child under 12 years see BNF for Children**

**Table 2 Nutritional supplements (non-disease specific)**

Nutritional supplements: less than 5 g protein/100 mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed per 100 mL)</td>
<td>423 kJ (100 kcal)</td>
<td>4 g caseinates soy isolate</td>
<td>13.6 g (sugars 3.93 g)</td>
<td>3.36 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Ensure liquid: vanilla, chocolate, coffee 250 ml = £2.26</td>
</tr>
</tbody>
</table>

Nutritional supplements: 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>AYMES® Shake (Aymes International Ltd)</td>
<td>Standard dilution of powder (57 g in 200 mL water) (sip feed per 100 mL)</td>
<td>530.5 kJ (126 kcal)</td>
<td>4.5 g cows' milk</td>
<td>17.5 g (sugars 8.4 g)</td>
<td>4.2 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Aymes Shake Sample Pack powder: 285 gram = £4.78; Aymes Shake powder: banana, strawberry 399 gram = £4.90; chocolate, neutral, vanilla 399 gram = £4.90</td>
</tr>
</tbody>
</table>

Powder 57 g reconstituted with 200 mL whole milk provides: protein 15.8 g, carbohydrate 44.1 g, fat 16.4 g, energy 1625 kJ (388 kcal).

**Nutritional supplements: More than 1 kcal/mL and less than 5 g protein/100 mL**

Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Juce (Abbott Laboratories Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>638 kJ (150 kcal)</td>
<td>4.8 g whey protein isolate</td>
<td>32.7 g (sugars 9.4 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Ensure Plus Juce liquid: assorted 880 ml = no price available; apple, fruit punch, lemon &amp; lime, orange, peach 220 ml = £1.97</td>
</tr>
<tr>
<td>Fortijuce® (Nutricia Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>640 kJ (150 kcal)</td>
<td>4.0 g cows' milk</td>
<td>33.5 g (sugars 13.1 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Fortijuce Starter Pack liquid: 800 ml = £8.08; Fortijuce liquid: apple, blackcurrant, lemon, orange, strawberry, tropical 200 ml = £2.02; forest fruits 200 ml = £2.02</td>
</tr>
<tr>
<td>Fresubin® Jucy Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>630 kJ (150 kcal)</td>
<td>4 g whey protein</td>
<td>33.5 g (sugars 8 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis</td>
<td>Fresubin Jucy drink: apple, blackcurrant, cherry, orange, pineapple 800 ml = £7.80</td>
</tr>
<tr>
<td>Nutritional supplements: More than 1 kcal/mL and less than 5 g protein/100 mL (product list continued)</td>
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<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
<td>ACBS Indications</td>
<td>Presentation &amp; Flavour</td>
</tr>
<tr>
<td>Resource® Dessert Energy (Nestle Health Science)</td>
<td>Semi-solid per 100 g</td>
<td>671 kJ (160 kcal)</td>
<td>4.8 g cows’ milk</td>
<td>21.2 g (sugars 9.9 g)</td>
<td>6.2 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis.</td>
<td>Resource Dessert Energy semi-solid food: caramel, chocolate, vanilla 125 gram = £1.63</td>
</tr>
<tr>
<td>Resource® Fruit (Nestle Health Science)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>520 kJ (125 kcal)</td>
<td>4 g whey protein hydrolysate</td>
<td>27 g (sugars 9.5 g)</td>
<td>less than 0.2 g</td>
<td>less than 0.2 g</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years.</td>
<td>Resource Fruit liquid: apple, orange, pear &amp; cherry, raspberry &amp; blackcurrant 800 ml = £7.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutritional supplements: 5 g (or more) protein/100 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL</td>
</tr>
<tr>
<td>Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated</td>
</tr>
</tbody>
</table>

| Product | Formulation | Energy | Protein | Carbohydrate | Fat | Fibre | Special Characteristics | ACBS Indications | Presentation & Flavour |
| Altraplen® Protein (Nualtra Ltd) | Liquid (sip feed) per 100 mL | 632 kJ (150 kcal) | 10 g cows’ milk soya protein | 15 g (sugars 4.6 g) | 5.6 g | Nil | Gluten-free Residual lactose | Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-6 years | Altraplen Protein liquid: strawberry, vanilla 800 ml = £5.80 |

| Ensure® Plus Advance (Abbott Laboratories Ltd) | Liquid (sip or tube feed) per 100 mL | 631 kJ (150 kcal) | 9.1 g cows’ milk soya protein isolate whey protein concentrate | 16.8 g (sugars 6.8 g) | 4.8 g | 0.75 g | Gluten-free Residual lactose | Frail elderly people (this is defined as older than 65 years with BMI less than or equal to 23 kg/m² where clinical assessment and nutritional screening show the individual to be at risk of undernutrition). Not suitable as the sole source of nutrition. | Ensure Plus Fibre liquid: banana, chocolate, coffee, strawberry, vanilla 200 ml = £2.02 |

| Ensure® Plus Commence (Abbott Laboratories Ltd) | Starter pack (5-10 day’s supply), contains: Ensure® Plus Milkshake Style (various flavours), 1 pack (10 x 200 mL) = £14.00 |

| Ensure® Plus Fibre (Abbott Laboratories Ltd) | Liquid (sip or tube feed) per 100 mL | 652 kJ (155 kcal) | 6.25 g cows’ milk soya protein isolate | 15 g (sugars 6.5 g) | 4.92 g | 2.5 g | Gluten-free Residual lactose | Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis. | Ensure Plus Fibre liquid: banana, chocolate, raspberry, strawberry, vanilla 200 ml = £2.02 |

<p>| Ensure® Plus Milkshake style (Abbott Laboratories Ltd) | Liquid (sip or tube feed) per 100 mL | 632 kJ (150 kcal) | 6.25 g cows’ milk soya protein isolate | 15 g (sugars 6.89 g) | 4.92 g | Nil | Gluten-free Residual lactose | Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis | Ensure Plus milkshake style liquid: banana, chocolate, coffee, fruits of the forest, neutral, orange, peach, raspberry, strawberry, vanilla 220 ml = £1.40 |</p>
<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Nutritional Components</th>
<th>Calories per 100 mL</th>
<th>Protein per 100 mL</th>
<th>Carbohydrate per 100 mL</th>
<th>Fat per 100 mL</th>
<th>Gluten-free?</th>
<th>Residual Lactose</th>
<th>Disease-related Malnutrition</th>
<th>Dysphagia or Presence of Risk</th>
<th>Indications</th>
<th>Price per 200 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Savoury</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows' milk</td>
<td>20.2 g (sugars 1.13 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis.</td>
<td>Ensure Plus savoury liquid: chicken, mushroom 220 ml = £1.40</td>
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<tr>
<td></td>
<td>(Abbott Laboratories Ltd)</td>
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<tr>
<td>Ensure® Plus Yoghurt</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows' milk</td>
<td>20.2 g (sugars 11.7 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis.</td>
<td>Ensure Plus yoghurt style liquid: orchard peach, strawberry swirl 200 ml = £1.40</td>
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<td></td>
<td>Style (Abbott Laboratories Ltd)</td>
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<tr>
<td>Fortisip® Bottle</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows' milk</td>
<td>18.4 g</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Fortisip Bottle: banana, caramel, chocolate, neutral, orange, strawberry, tropical fruit, vanilla 200 ml = £1.40</td>
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<tr>
<td></td>
<td>(Nutricia Ltd)</td>
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<tr>
<td>Fortisip® Range</td>
<td>Starter pack contains: 4 x Fortisip® Bottle, 4 x Fortijuce®, 2 x Fortisip® Yoghurt Style, 1 pack (10 x 200mL) = £20.20</td>
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<td></td>
<td>(Nutricia Ltd)</td>
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<tr>
<td>Fortisip® Yoghurt</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows' milk</td>
<td>18.7 g (sugars 10.8 g)</td>
<td>5.8 g</td>
<td>0.2 g</td>
<td>Gluten-free</td>
<td>Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years</td>
<td>Fortisip Yoghurt Style liquid vanilla &amp; lemon: 200 ml = £2.02</td>
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<tr>
<td></td>
<td>Style (Nutricia Ltd)</td>
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<tr>
<td>Fresubin® Protein</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows' milk</td>
<td>12.4 g (sugars 6.4 g)</td>
<td>6.7 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis.</td>
<td>Fresubin Protein Energy drink: cappuccino, chocolate, tropical fruits, vanilla, wild strawberry 200 ml = £2.04</td>
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<tr>
<td>Energy Drink</td>
<td>(Fresenius Kabi Ltd)</td>
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<tr>
<td>Fresubin® Thickened</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows' milk</td>
<td>12.2 g (sugars 7.1 g)</td>
<td>6.7 g</td>
<td>0.48 g</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Dysphagia or disease-related malnutrition. Not suitable for child under 3 years; use with caution in child 3-4 years.</td>
<td>Fresubin Thickened Stage 1 syrup: vanilla, wild strawberry 800 ml = £9.24; Fresubin Thickened Stage 2 custard: vanilla, wild strawberry 800 ml = £9.24</td>
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<tr>
<td></td>
<td>(Fresenius Kabi Ltd)</td>
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<tr>
<td>Fresubin® Yocrème</td>
<td>Semi-solid per 100 g</td>
<td>630 kJ (150 kcal)</td>
<td>7.5 g whey protein</td>
<td>19.5 g (sugars 16.8 g)</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Contains lactose</td>
<td>Dysphagia, or presence or risk of malnutrition Not suitable for child under 3 years</td>
<td>Fresubin Yocrème dessert: apricot-peach, biscuit, lemon, raspberry 500 gram = £8.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Nutritional supplements: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Crème (Abbott Laboratories Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>574 kJ (137 kcal)</td>
<td>5.68 g cow’s milk soya protein isolates</td>
<td>18.4 g (sugars 12.4 g)</td>
<td>4.47 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains soya</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Ensure Plus Crème: chocolate, neutral, vanilla 500 gram = £7.51</td>
</tr>
<tr>
<td>Nutilis® Fruit Stage 3 (Nutricia Ltd)</td>
<td>Semi-Solid per 100 g</td>
<td>560 kJ (133 kcal)</td>
<td>7 g whey isolate</td>
<td>16.7 g (sugars 11.3 g)</td>
<td>4 g</td>
<td>2.6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 except bowel fistula; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Nutilis Fruit Stage 3: apple, strawberry 450 gram = £7.08</td>
</tr>
<tr>
<td>Oral Impact® (Nestle Health Science)</td>
<td>Standard dilution of powder (74 g in 250 mL water) (sip feed) per 100 mL</td>
<td>425 kJ (101 kcal)</td>
<td>5.6 g cows’ milk</td>
<td>13.4 g (sugars 7.4 g)</td>
<td>2.8 g</td>
<td>1 g</td>
<td>Residual lactose Contains fish oil</td>
<td>Pre-operative nutritional supplement for malnourished patients or patients at risk of malnourishment Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Oral Impact oral powder 74g sachets: citrus, coffee, tropical 5 sachet = £16.93</td>
</tr>
</tbody>
</table>

*Powder provides: protein 16.8 g, carbohydrate 40.2 g, fat 8.3 g, fibre 3 g, energy 1276 kJ (303 kcal)/74 g.*

## Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altraplen Compact® (Nualta Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1008 kJ (240 kcal)</td>
<td>9.6 g cows’ milk soya protein</td>
<td>28.8 g (sugars 11.6 g)</td>
<td>9.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-6 years.</td>
<td>Altraplen Compact liquid: strawberry, vanilla 500 mL = £5.80</td>
</tr>
<tr>
<td>Complan® Shake (Nutricia Ltd)</td>
<td>Powder per 57 g</td>
<td>1057 kJ (251 kcal)</td>
<td>8.8 g cows’ milk</td>
<td>35.2 g (sugars 22.7 g)</td>
<td>8.4 g</td>
<td>Trace</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1349</td>
<td>Complan Shake Starter Pack sachets: 5 sachet = £4.39; Complan Shake oral powder 57 g sachets: banana, chocolate, milk, strawberry 4 sachet = £2.80; vanilla 4 sachet = £2.80</td>
</tr>
</tbody>
</table>

*Powder 57 g reconstituted with 200 mL whole milk provides: protein 15.6 g, carbohydrate 44.5 g, fat 16.4 g, energy 1621 kJ (387 kcal).*

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Compact (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>1008 kJ (240 kcal)</td>
<td>10.2 g cow’s milk</td>
<td>28.8 g (sugars 6.2 g)</td>
<td>9.35 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>As a sole source of nutrition or as a nutritional supplement for the dietary management of patient with, or at risk of developing, disease-related malnutrition.</td>
<td>Ensure Compact Liquid: banana, strawberry, vanilla 125 ml = £1.45</td>
</tr>
<tr>
<td>Product Name</td>
<td>Description</td>
<td>Serving</td>
<td>Nutritional Information</td>
<td>ADIS Code</td>
<td>Notes</td>
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<tr>
<td>Ensure® Shake</td>
<td>Oral powder</td>
<td>57 g</td>
<td>178.2 kJ (434 kcal)</td>
<td>33 g (sugars 33.7 g)</td>
<td>Gluten-free Residual lactose</td>
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<tr>
<td>Foodlink® Complete</td>
<td>Powder</td>
<td>21.3 g</td>
<td>1826 kJ (434 kcal)</td>
<td>56.7 g</td>
<td>Nil Contains lactose</td>
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<tr>
<td>Foodlink® Complete with Fibre</td>
<td>Powder</td>
<td>19.4 g</td>
<td>1683 kJ (400 kcal)</td>
<td>52.7 g</td>
<td>Contains lactose</td>
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<tr>
<td>FortiSure® Complete</td>
<td>Semi-solid</td>
<td>675 kJ (160 kcal)</td>
<td>19.2 g</td>
<td>5 g</td>
<td>Gluten-free Residual lactose</td>
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<tr>
<td>Fortisip® Compact</td>
<td>Liquid (sip feed)</td>
<td>1010 kJ (240 kcal)</td>
<td>29.7 g</td>
<td>9.3 g</td>
<td>Residual lactose</td>
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</tr>
<tr>
<td>Fortisip® Compact Fibre</td>
<td>Liquid (sip feed)</td>
<td>1000 kJ (240 kcal)</td>
<td>25.2 g</td>
<td>10.4 g</td>
<td>Gluten-free Residual lactose</td>
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<tr>
<td>Fortisip® Compact Protein</td>
<td>Liquid (sip feed)</td>
<td>1010 kJ (240 kcal)</td>
<td>24.4 g</td>
<td>9.4 g</td>
<td>Gluten-free Residual lactose</td>
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<tr>
<td>Fortisip® Extra</td>
<td>Liquid (sip feed)</td>
<td>675 kJ (160 kcal)</td>
<td>18.1 g</td>
<td>5.3 g</td>
<td>Gluten-free Contains lactose</td>
<td></td>
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</tr>
<tr>
<td>Fresubin® 2 kcal Drink</td>
<td>Liquid (sip feed)</td>
<td>840 kJ (200 kcal)</td>
<td>22.5 g</td>
<td>7.8 g</td>
<td>Gluten-free Residual lactose</td>
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</tbody>
</table>

Borderline substances: standard ACBS indications p. 1349. Not suitable for child under 3 years; use with caution in child 3-5 years.
### Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL (product list continued)

Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 2 kcal Fibre Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>10 g cows’ milk</td>
<td>22.5 g (sugars 5.8 g)</td>
<td>7.8 g</td>
<td>1.6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349; also CAPD, haemodialysis. Not suitable for use in child under 1 year; use with caution in child 1-5 years.</td>
<td>Fresubin 2 kcal Fibre drink: apricot-peach, cappuccino, chocolate, lemon, neutral 200 ml = £1.98</td>
</tr>
<tr>
<td>Fresubin® Powder Extra (Fresenius Kabi Ltd)</td>
<td>Powder per 100 g</td>
<td>1764 kJ (420 kcal)</td>
<td>17.5 g cows’ milk whey protein</td>
<td>63 g (sugars 24.7 g)</td>
<td>10.9 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 1 year; use with caution in child 1-5 years.</td>
<td>Fresubin Powder Extra oral powder 62g sachets: chocolate, neutral, strawberry, vanilla 7 sachet = £5.32</td>
</tr>
<tr>
<td>Powder reconstituted with 200 ml whole milk provides: protein 17.7 g, carbohydrate 48.5 g, fat 14.8 g, energy 1658 kJ (397 kcal).</td>
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<tr>
<td>Nutilis® Complete Stage 1 (Nutricia Ltd)</td>
<td>Liquid (pre-thickened) per 100 mL</td>
<td>1010 kJ (240 kcal)</td>
<td>9.6 g cows’ milk</td>
<td>29.1 g (sugars 5.4 g)</td>
<td>9.3 g</td>
<td>3.2 g</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Nutilis Complete Stage 1 liquid: strawberry, vanilla 500 ml = £8.84</td>
</tr>
<tr>
<td>Nutilis® Complete Stage 2 (Nutricia Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>1030 kJ (245 kcal)</td>
<td>9.6 g cows’ milk</td>
<td>29.1 g (sugars 11.8 g)</td>
<td>9.4 g</td>
<td>3.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-6 years.</td>
<td>Nutilis Complete Stage 2 custard: chocolate, strawberry, vanilla 500 gram = £8.84</td>
</tr>
<tr>
<td>Nutricrem® (Nuálntra Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>756 kJ (180 kcal)</td>
<td>10 g cows’ milk soya protein</td>
<td>18.8 g (sugars 9.7 g)</td>
<td>7.2 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-6 years.</td>
<td>Nutricrem dessert: strawberry, vanilla 500 gram = £5.60</td>
</tr>
<tr>
<td>Renilon® 7.5 (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>7.5 g cows’ milk</td>
<td>20 g (sugars 4.8 g)</td>
<td>10 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Renilon 7.5 liquid: apricot, caramel 500 ml = £8.64</td>
</tr>
<tr>
<td>Resource® 2.0 Fibre (Nestlé Health Science)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>836 kJ (200 kcal)</td>
<td>9 g cows’ milk</td>
<td>21.4 g (sugars 5.5 g)</td>
<td>8.7 g</td>
<td>2.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1349 Not suitable for child under 6 years; use with caution in child 6-10 years.</td>
<td>Resource Fibre 2.0 liquid: apricot, coffee, neutral, strawberry, summer fruit, vanilla 200 ml = £1.88</td>
</tr>
</tbody>
</table>
### Table 3 Specialised formulas

**Specialised formulas: Infant and child see BNF for Children**

**Specialised formulas for specific clinical conditions**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alicalm®</strong>&lt;sup&gt;®&lt;/sup&gt; (Nutricia Ltd)</td>
<td>Standard dilution (30%) of powder per 100 mL</td>
<td>567 kJ (135 kcal)</td>
<td>4.5 g caseinate whey</td>
<td>17.4 g (sugars 3.2 g)</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Crohn's disease Not suitable for child under 1 year; use as nutritional supplement only in children 1-6 years.</td>
<td>Alicalm oral powder: 400 gram = £21.79</td>
</tr>
<tr>
<td>Powder provides: protein 15 g, carbohydrate 58 g, fat 17.5 g, energy 1889 kJ (450 kcal)/100 g.</td>
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<tr>
<td><strong>Forticare®</strong> (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL.</td>
<td>675 kJ (160 kcal)</td>
<td>9 g cows' milk</td>
<td>19.1 g (sugars 13.6 g)</td>
<td>5.3 g</td>
<td>2.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Nutritional supplement in patients with lung cancer undergoing chemotherapy, or with pancreatic cancer Not suitable in child under 3 years</td>
<td>Forticare liquid: cappuccino, orange &amp; lemon, peach &amp; ginger 500 ml = £8.92</td>
</tr>
<tr>
<td><strong>Heparon® Junior</strong> (Nutricia Ltd)</td>
<td>Standard dilution (18%) of powder per 100 mL</td>
<td>363 kJ (86 kcal)</td>
<td>2 g cows' milk</td>
<td>11.6 g (sugars 2.9 g)</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Contains lactose Electrolytes/100 mL: Na+ 0.56 mmol K+ 1.9 mmol Ca++ 2.3 mmol P+ 1.6 mmol</td>
<td>Enteral feed or nutritional supplement for children with acute or chronic liver failure</td>
<td>Heparon Junior powder: 400 gram = £21.95</td>
</tr>
<tr>
<td>Powder provides: protein 11.1 g, carbohydrate 64.2 g, fat 19.9 g, energy 2016 kJ (480 kcal)/100 g.</td>
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<tr>
<td><strong>KetoCal®</strong> (Nutricia Ltd)</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>602 kJ (146 kcal)</td>
<td>3.1 g cows' milk with additional amino acids</td>
<td>600 mg (sugars 120 mg)</td>
<td>14.6 g (LCT 100 %)</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na+ 4.3 mmol K+ 4.1 mmol Ca++ 2.15 mmol P+ 2.77 mmol</td>
<td>Enteral feed or nutritional supplement as part of ketogenic diet in management of epilepsy resistant to drug therapy, in children over 1 year, only on the advice of secondary care physician with experience of ketogenic diet.</td>
<td>KetoCal 4:1 powder: unflavoured, vanilla 300 gram = £30.91</td>
</tr>
<tr>
<td>Powder provides: protein 15.25 g, carbohydrate 3 g, fat 73 g, energy 3011 kJ (730 kcal)/100 g.</td>
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<tr>
<td><strong>KetoCal® 3:1</strong> (Nutricia Ltd)</td>
<td>Standard dilution (5.5%) of powder per 100 mL</td>
<td>276 kJ (66 kcal)</td>
<td>1.5 g</td>
<td>680 mg (sugars 570 mg)</td>
<td>6.4 g</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na+ 1.3 mmol K+ 2.4 mmol Ca++ 2 mmol P+ 1.7 mmol</td>
<td>Enteral feed or nutritional supplement as part of ketogenic diet in management of drug resistant epilepsy or other conditions for which a ketogenic diet is indicated in children from birth to 6 years; as a nutritional supplement in children over 6 years.</td>
<td>KetoCal 3:1 powder: 300 gram = £29.91</td>
</tr>
<tr>
<td>Powder provides: protein 15.3 g, carbohydrate 7.2 g, fat 67.7 g, energy 2927 kJ (699 kcal)/100 g.</td>
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<tr>
<td><strong>KetoCal® 4:1 LQ</strong> (Nutricia Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>620 kJ (150 kcal)</td>
<td>3.09 g casein and whey with additional amino acids</td>
<td>610 mg (sugars 230 mg)</td>
<td>14.8 g (LCT 100 %)</td>
<td>1.12 g</td>
<td>Electrolytes/100 mL: Na+ 4.9 mmol K+ 4.7 mmol Ca++ 2.4 mmol P+ 3.1 mmol</td>
<td>Enteral feed or nutritional supplement as part of ketogenic diet in management of drug resistant epilepsy or other conditions for which a ketogenic diet is indicated in children 1-10 years; as a nutritional supplement in children over 10 years.</td>
<td>KetoCal 4:1 LQ liquid: unflavoured, vanilla 200 ml = £4.41</td>
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<tr>
<td>Specialised formulas for specific clinical conditions (product list continued)</td>
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<tr>
<td><strong>Product</strong></td>
<td><strong>Formulation</strong></td>
<td><strong>Energy</strong></td>
<td><strong>Protein</strong></td>
<td><strong>Carbohydrate</strong></td>
<td><strong>Fat</strong></td>
<td><strong>Fibre</strong></td>
<td><strong>Special Characteristics</strong></td>
<td><strong>ACBS indications</strong></td>
<td><strong>Presentation &amp; Flavour</strong></td>
</tr>
<tr>
<td>Kindergen®</td>
<td>Kindergen powder (Nutricia Ltd)</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>421 kJ (101 kcal)</td>
<td>1.5 g whey protein</td>
<td>11.8 g (sugars 1.2 g)</td>
<td>5.3 g Nil</td>
<td>Electrolytes/100 mL: Na⁺ 2 mmol K⁺ 0.6 mmol Ca²⁺ 2.8 mmol P⁺ 3 mmol Low Vitamin A</td>
<td>Enteral feed or nutritional supplement for children with chronic renal failure receiving peritoneal rapid overnight dialysis.</td>
<td>Kindergen powder: 400 gram = £29.47</td>
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<tr>
<td>Modulen IBD®</td>
<td>Modulen IBD powder (Nestle Health Science)</td>
<td>Standard dilution (20%) of powder (sip or tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.6 g casein</td>
<td>11 g (sugars 3.98 g)</td>
<td>4.7 g Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Crohn’s disease active phase, and in remission if malnourished</td>
<td>Modulen IBD powder: 400 gram = £15.06</td>
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<tr>
<td>ProSure®</td>
<td>ProSure liquid (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>536 kJ (127 kcal)</td>
<td>6.65 g cows’ milk</td>
<td>18.3 g (sugars 2.95 g)</td>
<td>2.56 g 2.07 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Nutritional supplement for patients with pancreatic cancer. Not suitable for child under 1 year; use with caution in child 1-4 years.</td>
<td>ProSure liquid: 220 ml = £3.34; 240 ml = £3.34</td>
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<tr>
<td>Renamil®</td>
<td>Renamil powder (Stanningley Pharma Ltd)</td>
<td>Powder (sip or tube feed when reconstituted) per 100 g</td>
<td>2003 kJ (477 kcal)</td>
<td>4.6 g cows’ milk</td>
<td>70.8 g</td>
<td>19.3 g Nil</td>
<td>Contains lactose Gluten-free Electrolytes/100 g: Na⁺ 1.04 mmol K⁺ 0.13 mmol Ca²⁺ 10.22 mmol P⁺ 1.06 mmol Contains no vitamin A or vitamin D</td>
<td>Enteral feed or nutritional supplement for adults and children over 1 year with chronic renal failure.</td>
<td>Renamil powder: 1000 gram = £25.40</td>
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<tr>
<td>Renapro®</td>
<td>Renapro powder (Stanningley Pharma Ltd)</td>
<td>Powder per 100 g</td>
<td>1580 kJ (372 kcal)</td>
<td>90 g whey protein</td>
<td>800 mg</td>
<td>1 g Nil</td>
<td>Gluten-free Residual lactose Electrolytes/100 g: Na⁺ 23 mmol K⁺ 2 mmol Ca²⁺ 4.99 mmol P⁺ 4.84 mmol</td>
<td>Nutritional supplement for biochemically proven hypoproteinaemia and patients undergoing dialysis. Not suitable for child under 1 year.</td>
<td>Renapro powder: 600 gram = £69.60</td>
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<tr>
<td>Renastart®</td>
<td>Renastart powder (Vitaflo International Ltd)</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>414 kJ (99 kcal)</td>
<td>1.5 g cows’ milk soya</td>
<td>12.5 g (sugars 1.3 g)</td>
<td>4.8 g Nil</td>
<td>Contains lactose Electrolytes/100 mL: Na⁺ 2.1 mmol K⁺ 0.6 mmol Ca²⁺ 0.6 mmol P⁺ 0.6 mmol</td>
<td>Dietary management of renal failure in child from birth to 10 years.</td>
<td>Renastart powder: 400 gram = £26.37</td>
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Specialised formulas for specific clinical conditions:

- **Kindergen**
  - Energy: 421 kJ (101 kcal)
  - Protein: 1.5 g whey protein
  - Carbohydrate: 11.8 g (sugars 1.2 g)
  - Fat: 5.3 g (LCT 93 %)
  - Fibre: Nil
  - Special Characteristics: Electrolytes/100 mL: Na⁺ 2 mmol K⁺ 0.6 mmol Ca²⁺ 2.8 mmol P⁺ 3 mmol Low Vitamin A
  - ACBS Indications: Enteral feed or nutritional supplement for children with chronic renal failure receiving peritoneal rapid overnight dialysis.
  - Presentation & Flavour: Kindergen powder: 400 gram = £29.47

- **Modulen IBD**
  - Energy: 420 kJ (100 kcal)
  - Protein: 3.6 g casein
  - Carbohydrate: 11 g (sugars 3.98 g)
  - Fat: 4.7 g
  - Fibre: Nil
  - Special Characteristics: Gluten-free Residual lactose
  - ACBS Indications: Crohn’s disease active phase, and in remission if malnourished
  - Presentation & Flavour: Modulen IBD powder: 400 gram = £15.06

- **ProSure**
  - Energy: 536 kJ (127 kcal)
  - Protein: 6.65 g cows’ milk
  - Carbohydrate: 18.3 g (sugars 2.95 g)
  - Fat: 2.56 g
  - Fibre: 2.07 g
  - Special Characteristics: Gluten-free Residual lactose Contains fish oil
  - ACBS Indications: Nutritional supplement for patients with pancreatic cancer. Not suitable for child under 1 year; use with caution in child 1-4 years.
  - Presentation & Flavour: ProSure liquid: 220 ml = £3.34; 240 ml = £3.34

- **Renamil**
  - Energy: 2003 kJ (477 kcal)
  - Protein: 4.6 g cows’ milk
  - Carbohydrate: 70.8 g
  - Fat: 19.3 g
  - Fibre: Nil
  - Special Characteristics: Contains lactose Gluten-free Electrolytes/100 g: Na⁺ 1.04 mmol K⁺ 0.13 mmol Ca²⁺ 10.22 mmol P⁺ 1.06 mmol Contains no vitamin A or vitamin D
  - ACBS Indications: Enteral feed or nutritional supplement for adults and children over 1 year with chronic renal failure.
  - Presentation & Flavour: Renamil powder: 1000 gram = £25.40

- **Renapro**
  - Energy: 1580 kJ (372 kcal)
  - Protein: 90 g whey protein
  - Carbohydrate: 800 mg
  - Fat: 1 g
  - Fibre: Nil
  - Special Characteristics: Gluten-free Residual lactose Electrolytes/100 g: Na⁺ 23 mmol K⁺ 2 mmol Ca²⁺ 4.99 mmol P⁺ 4.84 mmol
  - ACBS Indications: Nutritional supplement for biochemically proven hypoproteinaemia and patients undergoing dialysis. Not suitable for child under 1 year.
  - Presentation & Flavour: Renapro powder: 600 gram = £69.60

- **Renastart**
  - Energy: 414 kJ (99 kcal)
  - Protein: 1.5 g cows’ milk soya
  - Carbohydrate: 12.5 g (sugars 1.3 g)
  - Fat: 4.8 g
  - Fibre: Nil
  - Special Characteristics: Contains lactose Electrolytes/100 mL: Na⁺ 2.1 mmol K⁺ 0.6 mmol Ca²⁺ 0.6 mmol P⁺ 0.6 mmol
  - ACBS Indications: Dietary management of renal failure in child from birth to 10 years.
  - Presentation & Flavour: Renastart powder: 400 gram = £26.37
### Table 4 Feed supplements

#### High-energy supplements

**High-energy supplements: carbohydrate**

Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloreen® (Nestle Health Science)</td>
<td>Powder per 100 g</td>
<td>1640 kJ (390 kcal)</td>
<td>Nil</td>
<td>96 g Maltodextrin</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Caloreen powder: 500 gram = £3.69</td>
</tr>
<tr>
<td>Maxijul® Super Soluble (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1615 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g Glucose polymer (sugars 8.6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Maxijul Super Soluble powder: 200 gram = £2.64; 528 gram = £6.56; 25000 gram = £157.74</td>
</tr>
<tr>
<td>Polycal® (Nutricia Ltd)</td>
<td>Liquid per 100 mL</td>
<td>1050 kJ (247 kcal)</td>
<td>Nil</td>
<td>61.9 g Maltodextrin (sugars 12.2 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Polycal liquid: neutral, orange 200 ml = £1.72</td>
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<tr>
<td></td>
<td>Powder per 100 g</td>
<td>1630 kJ (384 kcal)</td>
<td>Nil</td>
<td>96 g Maltodextrin (sugars 6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Polycal powder: 400 gram = £4.28</td>
</tr>
<tr>
<td>S.O.S.® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>1590 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g (sugars 9 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>S.O.S. products are age-range specific - consult product literature</td>
<td>For use as an emergency regimen in the dietary management of inborn errors of metabolism in adults and children from birth.</td>
<td>S.O.S.: 20 oral powder 42g sachets 30 sachet = £14.62; 15 oral powder 31g sachets 30 sachet = £10.79; 25 oral powder 52g sachets 30 sachet = £18.09; 10 oral powder 21g sachets 30 sachet = £7.31</td>
</tr>
</tbody>
</table>
### High-energy supplements: carbohydrate (product list continued)
Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (kcal)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitajoule®</td>
<td>Powder</td>
<td>1590 (380)</td>
<td>Nil</td>
<td>95 g glucose</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Vitajoule powder: 500 gram = £4.38</td>
</tr>
<tr>
<td>(Vitaflo International Ltd)</td>
<td>per 100 g</td>
<td></td>
<td></td>
<td>syrup (sugars 9 g)</td>
<td></td>
<td></td>
<td>Lactose-free</td>
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<tr>
<td></td>
<td>Liquid</td>
<td>1570 (375)</td>
<td>Nil</td>
<td>100 g glucose</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free</td>
<td></td>
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<tr>
<td></td>
<td>per 100 mL</td>
<td></td>
<td></td>
<td>syrup (sugars 10 g)</td>
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<td></td>
<td>Lactose-free</td>
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</table>

### High-energy supplements: fat
Liquid supplements should be diluted before use in child under 5 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (kcal)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calogen® 5 kcal Shot</td>
<td>Liquid (emulsion)</td>
<td>1850 (450)</td>
<td>Nil</td>
<td>0.2 g sucrrose</td>
<td>50</td>
<td>400</td>
<td>Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.</td>
<td>Calogen emulsion: neutral, strawberry 200 ml = £4.36; 500 ml = £10.72; banana 500 ml = £10.72</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>per 100 mL</td>
<td></td>
<td></td>
<td>(sucrose)</td>
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<td></td>
<td>Lactose-free</td>
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</tr>
<tr>
<td></td>
<td>Liquid (emulsion)</td>
<td>2100 (500)</td>
<td>Nil</td>
<td>4.0 g sucrrose</td>
<td>53.8</td>
<td>400</td>
<td>Gluten-free</td>
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<tr>
<td></td>
<td>per 100 mL</td>
<td></td>
<td></td>
<td>(sucrose)</td>
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<td>Lactose-free</td>
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<tr>
<td></td>
<td>Liquid (emulsion)</td>
<td>2100 (500)</td>
<td>Nil</td>
<td>4.0 g sucrrose</td>
<td>53.8</td>
<td>400</td>
<td>Gluten-free</td>
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<tr>
<td></td>
<td>per 100 mL</td>
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<td></td>
<td>(sucrose)</td>
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<td>Lactose-free</td>
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<tr>
<td></td>
<td>Liquid (emulsion)</td>
<td>2100 (500)</td>
<td>Nil</td>
<td>4.0 g sucrrose</td>
<td>53.8</td>
<td>400</td>
<td>Gluten-free</td>
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<td></td>
<td>per 100 mL</td>
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<td></td>
<td>(sucrose)</td>
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<td>Lactose-free</td>
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<tr>
<td></td>
<td>Liquid (emulsion)</td>
<td>2100 (500)</td>
<td>Nil</td>
<td>4.0 g sucrrose</td>
<td>53.8</td>
<td>400</td>
<td>Gluten-free</td>
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<td></td>
<td>per 100 mL</td>
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<td>(sucrose)</td>
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<td>Lactose-free</td>
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<tr>
<td></td>
<td>Liquid (emulsion)</td>
<td>2100 (500)</td>
<td>Nil</td>
<td>4.0 g sucrrose</td>
<td>53.8</td>
<td>400</td>
<td>Gluten-free</td>
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<td></td>
<td>per 100 mL</td>
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<td></td>
<td>(sucrose)</td>
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<td>Lactose-free</td>
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### Medium-chain Triglyceride (MCT) Oil
Liquid per 100 mL

<table>
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<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (kcal)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium-chain</td>
<td>Liquid</td>
<td>3515 (855)</td>
<td>Nil</td>
<td>Nil</td>
<td>MCT</td>
<td>Nil</td>
<td>Lactose-free</td>
<td>Nutritional supplement for steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease and liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in epilepsy, type 1 hyperlipoproteinaemia</td>
<td>MCT oil: 500 ml = £14.89</td>
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<tr>
<td>Triglyceride (MCT) Oil</td>
<td>per 100 mL</td>
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<tr>
<td>(Nutricia Ltd)</td>
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<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
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<td>Presentation &amp; Flavour</td>
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</tr>
<tr>
<td>Duocal® Super Soluble (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>2061 kJ (492 kcal)</td>
<td>Nil</td>
<td>72.7 g (sugars 6.5 g)</td>
<td>22.3 g (MCT 35 %)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.</td>
<td>Duocal Super Soluble powder: 400 gram = £18.34</td>
</tr>
<tr>
<td>Energivit® (Nutricia Ltd)</td>
<td>Standard dilution (15%) of powder per 100 mL</td>
<td>309 kJ (74 kcal)</td>
<td>Nil</td>
<td>10 g (sugars 900 mg)</td>
<td>3.75 g</td>
<td>Nil</td>
<td>Lactose-free With vitamins, minerals, and trace elements</td>
<td>For children requiring additional energy, vitamins, minerals, and trace elements following a protein-restricted diet</td>
<td>Energivit powder: 400 gram = £22.30</td>
</tr>
<tr>
<td></td>
<td><strong>Powder provides:</strong> carbohydrate 66.7 g, fat 25 g, energy 2059 kJ (492 kcal)/100 g.</td>
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### High-energy supplements: protein

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProSource® Jelly (Nutrinovo Ltd)</td>
<td>Semi-solid per 100 mL</td>
<td>315 kJ (75 kcal)</td>
<td>16.9 g collagen protein hydrolysate whey protein isolate</td>
<td>Less than 1 g</td>
<td>Nil</td>
<td>Less than 1 g</td>
<td>Gluten-free Lactose-free Contains porcine derivatives</td>
<td>Hypoproteinaemia Not recommended for child under 3 years</td>
<td>ProSource jelly: fruit punch, orange 118 ml = £1.83</td>
</tr>
<tr>
<td>Protifar® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1580 kJ (373 kcal)</td>
<td>88.5 g cows' milk</td>
<td>less than 1.5 g</td>
<td>1.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Electrolytes/100 mL: Na+ 1.3 mmol K+ 1.28 mmol Ca2+ 33.75 mmol P+ 22.58 mmol</td>
<td>Nutritional supplement for use in biochemically proven hypoproteinaemia.</td>
<td>Protifar powder: 225 gram = £8.69</td>
</tr>
<tr>
<td></td>
<td><strong>Powder provides:</strong> protein 2.2 g per 2.5 g scoopful.</td>
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### PROTEIN AND CARBOHYDRATE

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialamine® (Nutricia Ltd)</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>264 kJ (62 kcal)</td>
<td>4.3 g protein equivalent (essential and non-essential amino acids)</td>
<td>11.2 g (sugars 10.2 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Contains vitamin C</td>
<td>Hypoproteinaemia, chronic renal failure, wound fistula leakage with excessive protein loss, conditions requiring a controlled nitrogen intake, and haemodialysis. Not suitable for child under 6 months.</td>
<td>Dialamine powder: 400 gram = £74.49</td>
</tr>
<tr>
<td></td>
<td><strong>Powder provides:</strong> protein equivalent 25 g, carbohydrate 65 g, vitamin C 125 mg, energy 1530 kJ (360 kcal)/100 g.</td>
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<tr>
<td>ProSource® Liquid (Nutrinovo Ltd)</td>
<td>Liquid per 30 mL</td>
<td>420 kJ (100 kcal)</td>
<td>10 g collagen protein whey protein isolate</td>
<td>15 g (sugars 8 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free May contain porcine derivatives</td>
<td>Biochemically proven hypoproteinaemia Not recommended for child under 3 years.</td>
<td>ProSource liquid 30ml sachets: citrus berry, lemon, orange creme, neutral 100 sachet = £98.79</td>
</tr>
<tr>
<td>High-energy supplements: protein (product list continued)</td>
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<td><strong>PROTEIN AND CARBOHYDRATE</strong></td>
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<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
<td>ACBS Indications</td>
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</tr>
<tr>
<td>ProSource® Plus (Nutrinovo Ltd)</td>
<td>Liquid per 30 mL</td>
<td>420 kJ (100 kcal)</td>
<td>15 g collagen protein whey protein isolate</td>
<td>11 g (sugars 10 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free May contain porcine derivatives</td>
<td>Hypoproteinaemia Not recommended for child under 3 years.</td>
<td>ProSource plus liquid 100 x 30ml sachets: unflavoured: £140.53</td>
</tr>
<tr>
<td>Calogen® Extra (Nutricia Ltd)</td>
<td>Liquid per 100 mL</td>
<td>1650 kJ (400 kcal)</td>
<td>5 g cows’ milk</td>
<td>4.5 g (sugars 3.5 g)</td>
<td>40.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years; use with caution in child 3-6 years. May require dilution for child 3-5 years.</td>
<td>Calogen Extra emulsion: neutral, strawberry 200 ml = £4.98</td>
</tr>
<tr>
<td>Calshake® (Fresenius Kabi Ltd)</td>
<td>Powder per 87 g</td>
<td>1841 kJ (439 kcal)</td>
<td>4.1 g cows’ milk</td>
<td>56.4 g (sugars 20 g)</td>
<td>22 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year.</td>
<td>Calshake powder: banana, neutral, strawberry 609 gram = £16.73; chocolate 630 gram = £16.73</td>
</tr>
<tr>
<td>Enshake® (Abbott Laboratories Ltd)</td>
<td>Powder per 100 g</td>
<td>1893 kJ (450 kcal)</td>
<td>8.4 g cows’ milk, soy protein isolate</td>
<td>69 g (sugars 14.5 g)</td>
<td>15.6 g</td>
<td>Nil</td>
<td>Residual lactose Contains vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-6 years.</td>
<td>Enshake oral powder 96.5g sachets: banana, chocolate, strawberry, vanilla 6 sachet = £12.93</td>
</tr>
</tbody>
</table>

**PROTEIN, FAT AND CARBOHYDRATE**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calogen® Extra Shots (Nutricia Ltd)</td>
<td>Liquid per 100 mL</td>
<td>1650 kJ (400 kcal)</td>
<td>5 g cows’ milk</td>
<td>4.5 g (sugars 3.5 g)</td>
<td>40.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose With vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years; use with caution in child 3-6 years. May require dilution for child 3-5 years.</td>
<td>Calogen Extra Shots emulsion: neutral, strawberry 240 ml = £5.75</td>
</tr>
<tr>
<td>Calshake® (Fresenius Kabi Ltd)</td>
<td>Powder per 100 g</td>
<td>1841 kJ (439 kcal)</td>
<td>4.1 g cows’ milk</td>
<td>56.4 g (sugars 20 g)</td>
<td>22 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year.</td>
<td>Calshake powder: banana, neutral, strawberry 609 gram = £16.73; chocolate 630 gram = £16.73</td>
</tr>
</tbody>
</table>

Powder: one sachet reconstituted with 240 mL whole milk provides approx. 2 kcal/mL and protein 12 g.

Powder: 96.5 g reconstituted with 240 mL whole milk provides approx. 2 kcal/mL and protein 16 g.
<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
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<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT Procal® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2742 kJ (657 kcal)</td>
<td>12.5 g cows’ milk</td>
<td>20.6 g (sugars 3.1 g)</td>
<td>63.1 g (MCT 99%)</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Dietary management of disorders of long-chain fatty acid oxidation, fat malabsorption, and other disorders requiring a low LCT, high MCT supplement. Not suitable for child under 1 year.</td>
<td>MCT procal oral powder 16 g sachets: 30 sachet = £23.76</td>
</tr>
<tr>
<td>Pro-Cal® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2787 kJ (667 kcal)</td>
<td>13.6 g cows’ milk</td>
<td>28.2 g (sugars 16 g)</td>
<td>55.5 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-5 years.</td>
</tr>
<tr>
<td>Scandishake® Mix (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>2099 kJ (500 kcal)</td>
<td>4.7 g cows’ milk</td>
<td>65 g (sugars 14.3 g)</td>
<td>24.7 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Gluten-free Contains soya</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
</tr>
<tr>
<td>Vitasavoury® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2562 kJ (619 kcal)</td>
<td>12 g cows’ milk</td>
<td>22.4 g (sugars 1.4 g)</td>
<td>52 g</td>
<td>6.4 g</td>
<td>Contains lactose Contains soya (chicken flavour)</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Vitasavoury powder: chicken, golden vegetable, leek &amp; potato, mushroom 500 g = £19.33</td>
</tr>
</tbody>
</table>

**High-fibre supplements**

**Fibre, vitamin, and mineral supplements**

- **Resource® Optifibre® (Nestle Health Science)**
  - Powder per 100 g
  - 323 kJ (76 kcal)
  - Nil
  - 19 g guar gum, partially hydrolysed
  - Nil
  - 78 g
  - Gluten-free Lactose-free
  - Borderline substances standard ACBS indications p. 1349 except dysphagia Not suitable for child under 5 years
  - Resource Optifibre powder: 250 gram = £10.28; 80 gram = £4.18
<table>
<thead>
<tr>
<th>Product</th>
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<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
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<th>Special Characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>FruitiVits® (Vitaflo International Ltd)</td>
<td>Powder</td>
<td>133 kJ (33 kcal)</td>
<td>Nil</td>
<td>8.3 g (sugars 400 mg)</td>
<td>Less than 100 mg</td>
<td>3.3 g</td>
<td></td>
<td>Vitamin, mineral, and trace element supplement in children 3–10 years with restrictive therapeutic diets</td>
<td>FruitiVits oral powder 6 g sachets: 30 sachet = £64.23</td>
</tr>
<tr>
<td>Paediatric Seravit® (Nutricia Ltd)</td>
<td>Powder</td>
<td>1275 kJ (300 kcal)</td>
<td>Nil</td>
<td>75 g (sugars 6.75 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Pineapple flavour not suitable for child under 6 months</td>
<td>Vitamin, mineral, and trace element supplement in infants and children with restrictive therapeutic diets</td>
<td>Seravit Paediatric powder: unflavoured 200 gram = £18.16; pineapple 200 gram = £19.35</td>
</tr>
<tr>
<td>Renavit® (Stanningley Pharma Ltd)</td>
<td>Tablet</td>
<td>3.15 kJ (0.75 kcal)</td>
<td>Nil</td>
<td>170 mg</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>Dietary management of water-soluble vitamin deficiency in adults with renal failure on dialysis</td>
<td>Renavit tablets: 100 tablet = £12.50</td>
</tr>
</tbody>
</table>

**Table Note:**
- **Energy:** 133 kJ (33 kcal) for FruitiVits, 1275 kJ (300 kcal) for Paediatric Seravit, 3.15 kJ (0.75 kcal) for Renavit.
- **Protein:** Nil for all products.
- **Carbohydrate:** 8.3 g (sugars 400 mg) for FruitiVits, 75 g (sugars 6.75 g) for Paediatric Seravit, 170 mg for Renavit.
- **Fat:** Less than 100 mg for FruitiVits, Nil for Paediatric Seravit, Nil for Renavit.
- **Fibre:** 3.3 g for FruitiVits, Nil for Paediatric Seravit, Nil for Renavit.
- **Special Characteristics:** Pineapple flavour, Pineapple flavour not suitable for child under 6 months, Nil for all products.
Feed additives

Special additives for conditions of intolerance

Colief®
- For the relief of symptoms associated with lactose intolerance in infants, provided that lactose intolerance is confirmed by the presence of reducing substances and/or excessive acid in stools, a low concentration of the corresponding disaccharide enzyme on intestinal biopsy or by breath hydrogen test or lactose intolerance test. For dosage and administration details, consult product literature.

Colief 50,000 units/g infant drops (Forum Health Products Ltd)
7 ml (ACBS) • NHS indicative price = £8.40

Fructose
- (Laevulose) For proven glucose/galactose intolerance

Glucose
- (Dextrose monohydrate) For use as an energy supplement in sucrose-isomaltase deficiency

VSL#3®
- Nutritional supplement for use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults. For dosage and administration details, consult product literature.

POWDER, containing 8 strains of live, freeze-dried, lactic acid bacteria. Contains traces of soya, gluten, and lactose.

VSL#3 Probiotic Food Supplement oral powder 4.4g sachets (Ferring Pharmaceuticals Ltd)
30 sachet (ACBS) • NHS indicative price = £34.36

Feed thickeners and pre-thickened drinks

Carobel, Instant®
- For thickening feeds in the treatment of vomiting.

POWDER, carob seed flour.

Instant Carobel powder (Cow & Gate Ltd)
135 gram (ACBS) • NHS indicative price = £2.84

Multi-thick®
- For thickening of liquids and foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive. POWDER, modified maize starch, gluten- and lactose-free.

POWDER, carbohydrate content varies with consistency (3 consistencies available), see product literature.

Multi-thick powder (Abbott Laboratories Ltd)
250 gram (ACBS) • NHS indicative price = £4.83

Nutilis® Clear
- For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years.

POWDER, maltodextrin, xanthan gum, guar gum, gluten- and lactose-free.

Nutilis Clear powder (Nutricia Ltd)
72 gram (ACBS) • NHS indicative price = £11.04 | 175 gram (ACBS) • NHS indicative price = £8.46

Nutilis® Powder
- For thickening of foods in dysphagia. Not suitable for children under 3 years.

POWDER, carbohydrate 86 g, energy 1520 kJ (358 kcal)/100 g, modified maize starch, gluten- and lactose-free.

Nutilis powder (Nutricia Ltd)
240 gram (ACBS) • NHS indicative price = £6.60 | 300 gram (ACBS) • NHS indicative price = £5.01

Resource® Thickened Drink
- For dysphagia. Not suitable for children under 1 year.

LIQUID, carbohydrate 22 g, energy: orange 382 kJ (90 kcal); apple 376 kJ (89 kcal)/100 mL. Gluten- and lactose-free.

Resource Thickened Drink custard apple (Nestle Health Science)
114 ml (ACBS) • NHS indicative price = £0.73

Resource Thickened Drink custard orange (Nestle Health Science)
114 ml (ACBS) • NHS indicative price = £0.73

Resource Thickened Drink syrup apple (Nestle Health Science)
114 ml (ACBS) • NHS indicative price = £0.73

Resource Thickened Drink syrup orange (Nestle Health Science)
114 ml (ACBS) • NHS indicative price = £0.73

Resource® Thickened Clear
- For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years.

POWDER, maltodextrin, xanthan gum, gluten- and lactose-free.

Resource Thickened Clear powder (Nestle Health Science)
28.8 gram (ACBS) • NHS indicative price = £5.28 | 125 gram (ACBS) • NHS indicative price = £8.46

Resource® Thickened Clear
- For thickening of foods in dysphagia. Not suitable for children under 1 year.

POWDER, modified maize starch. Gluten- and lactose-free.

Resource Thickened Clear powder (Nestle Health Science)
227 gram (ACBS) • NHS indicative price = £4.66 | 337.5 gram (ACBS) • NHS indicative price = £17.86

SLO Drinks®
- Nutritional supplement for patient hydration in the dietary management of dysphagia. Not suitable for children under 3 years.

POWDER, carbohydrate content varies with flavour and chosen consistency (3 consistencies available), see product literature.

SLO Drink 1 oral powder lemon (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 1 oral powder orange (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 1 oral powder hot chocolate (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 1 oral powder white coffee (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 2 oral powder hot chocolate (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 2 oral powder lemon (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 2 oral powder hot chocolate (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 2 oral powder white tea (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Drink 3 oral powder orange (SLO Drinks Ltd)
25 cup (ACBS) • NHS indicative price = £7.50

SLO Milkshakes+®
- Nutritional supplement in the dietary management of dysphagia. Not suitable for children under 3 years.

POWDER, carbohydrate content varies with flavour and chosen consistency (2 consistencies available), see product literature.

SLO Milkshake+ 1 oral powder chocolate (SLO Drinks Ltd)
7 x 50 gram (ACBS) • NHS indicative price = £5.88

SLO Milkshake+ 1 oral powder strawberry (SLO Drinks Ltd)
7 x 50 gram (ACBS) • NHS indicative price = £5.88

SLO Milkshake+ 2 oral powder chocolate (SLO Drinks Ltd)
7 x 50 gram (ACBS) • NHS indicative price = £5.88

SLO Milkshake+ 2 oral powder strawberry (SLO Drinks Ltd)
7 x 50 gram (ACBS) • NHS indicative price = £5.88

Thick and Easy®
- For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

POWDER, modified maize starch.

Thick & Easy powder (Fresenius Kabi Ltd)
225 gram (ACBS) • NHS indicative price = £5.12 | 900 gram (ACBS) • NHS indicative price = £31.00 | 4540 gram (ACBS) • NHS indicative price = £85.64

Thicken Aid®
- For thickening of foods in dysphagia. Not suitable for children under 1 year.

POWDER, modified maize starch, maltodextrin, gluten- and lactose-free.
**Foods for special diets**

**Gluten-free foods**

**ACBS indications**: established gluten-sensitive enteropathies including steatorrhoea due to gluten sensitivity, coeliac disease, and dermatitis herpetiformis.

**Bread**

**LOAVES**

**Barkat® Loaf**

- **Barkat gluten free brown rice bread** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) • NHS indicative price = £5.73
- **Barkat gluten free par baked white bread sliced** (Gluten Free Foods Ltd)
  - 300 gram (ACBS) • NHS indicative price = £4.13
- **Barkat gluten free home fresh country loaf** (Gluten Free Foods Ltd)
  - 250 gram (ACBS) • NHS indicative price = £4.35
- **Barkat gluten free wheat free multigrain bread** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) • NHS indicative price = £5.73

**Ener-G® Loaves**

- **Ener-G gluten free brown rice bread** (General Dietary Ltd)
  - 474 gram (ACBS) • NHS indicative price = £5.47
- **Ener-G gluten free tapioca bread** (General Dietary Ltd)
  - 480 gram (ACBS) • NHS indicative price = £5.47
- **Ener-G gluten free rice loaf** (General Dietary Ltd)
  - 612 gram (ACBS) • NHS indicative price = £5.47
- **Ener-G gluten free Seattle brown loaf** (General Dietary Ltd)
  - 454 gram (ACBS) • NHS indicative price = £6.22

**Genius Gluten Free® Loaf**

- **Genius gluten free brown bread sliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Genius gluten free brown bread unsliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.77
- **Genius gluten free brown sandwich bread sliced** (Genius Foods Ltd)
  - 553 gram (ACBS) • NHS indicative price = £3.73
- **Genius gluten free white bread sliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Genius gluten free white bread unsliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.77
- **Genius gluten free white sandwich bread sliced** (Genius Foods Ltd)
  - 553 gram (ACBS) • NHS indicative price = £3.73

**Glutafin® Loaves**

- **Glutafin gluten free wholemeal bread sliced** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) • NHS indicative price = £3.98
- **Glutafin gluten free white rice bread** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) • NHS indicative price = £5.73

**Genius Gluten Free® Loaf**

- **Genius gluten free brown bread sliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Genius gluten free brown bread unsliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.77
- **Genius gluten free brown sandwich bread sliced** (Genius Foods Ltd)
  - 553 gram (ACBS) • NHS indicative price = £3.73
- **Genius gluten free white bread sliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Genius gluten free white bread unsliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.77
- **Genius gluten free white sandwich bread sliced** (Genius Foods Ltd)
  - 553 gram (ACBS) • NHS indicative price = £3.73

**Gluten-free Flours**

- **Genius Gluten Free® White Rice Flour** (Genius Foods Ltd)
  - 125 gram (ACBS) • NHS indicative price = £3.98
- **Genius Gluten Free® Brown Rice Flour** (Genius Foods Ltd)
  - 225 gram (ACBS) • NHS indicative price = £5.73
- **Gluten Free Rice Flour** (Genius Foods Ltd)
  - 225 gram (ACBS) • NHS indicative price = £5.73

**FlavourPac oral powder 4g sachets**

- **FlavourPac oral powder 4g sachets blackcurrant** (Vitafo International Ltd)
  - 30 sachet (ACBS) • NHS indicative price = £13.79 • 120 sachet (ACBS) • No NHSindicative price available

**FlavourPac oral powder 4g sachets lemon** (Vitafo International Ltd)

- 30 sachet (ACBS) • NHS indicative price = £13.79 • 120 sachet (ACBS) • No NHSindicative price available

**FlavourPac oral powder 4g sachets orange** (Vitafo International Ltd)

- 30 sachet (ACBS) • NHS indicative price = £13.79 • 120 sachet (ACBS) • No NHSindicative price available

**FlavourPac oral powder 4g sachets raspberry** (Vitafo International Ltd)

- 30 sachet (ACBS) • NHS indicative price = £13.79 • 120 sachet (ACBS) • No NHSindicative price available

**FlavourPac oral powder 4g sachets tropical** (Vitafo International Ltd)

- 30 sachet (ACBS) • NHS indicative price = £13.79 • 120 sachet (ACBS) • No NHSindicative price available

**Genius Gluten Free® Loaf**

- **Genius gluten free brown bread sliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Genius gluten free brown bread unsliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.77
- **Genius gluten free brown sandwich bread sliced** (Genius Foods Ltd)
  - 553 gram (ACBS) • NHS indicative price = £3.73
- **Genius gluten free white bread sliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Genius gluten free white bread unsliced** (Genius Foods Ltd)
  - 400 gram (ACBS) • NHS indicative price = £2.77
- **Genius gluten free white sandwich bread sliced** (Genius Foods Ltd)
  - 553 gram (ACBS) • NHS indicative price = £3.73

**Glutafin® Loaves**

- **Glutafin gluten free fibre loaf sliced** (Dr Schar UK Ltd)
  - 500 gram (ACBS) • NHS indicative price = £2.89
- **Glutafin gluten free white loaf sliced** (Dr Schar UK Ltd)
  - 500 gram (ACBS) • NHS indicative price = £2.89

**Gluten Free Foods Ltd**

- **Gluten Free Foods Ltd**
  - 400 gram (ACBS) • NHS indicative price = £2.88
- **Gluten Free Foods Ltd**
  - 500 gram (ACBS) • NHS indicative price = £3.98
- **Gluten Free Foods Ltd**
  - 500 gram (ACBS) • NHS indicative price = £5.73
Lifestyle gluten free brown bread sliced (Ultrapharm Ltd)
400 gram (ACBS) • NHS indicative price = £2.82

Lifestyle gluten free high fibre bread sliced (Ultrapharm Ltd)
400 gram • NHS indicative price = £2.82

Lifestyle gluten free white bread sliced (Ultrapharm Ltd)
400 gram (ACBS) • NHS indicative price = £2.82

Livwell® Loaf
GLUTEN-FREE

Livwell gluten free multi grain bread sliced (Livwell Ltd)
200 gram • NHS indicative price = £2.25

Livwell gluten free white bread sliced (Livwell Ltd)
200 gram (ACBS) • NHS indicative price = £2.25

Warburtons® Loaf
GLUTEN-FREE

Warburtons gluten free brown bread sliced (Warburtons Ltd)
400 gram (ACBS) • NHS indicative price = £3.06

Warburtons gluten free white bread sliced (Warburtons Ltd)
400 gram (ACBS) • NHS indicative price = £3.06

Wellfoods® Loaf
GLUTEN-FREE

Wellfoods gluten free loaf sliced (Wellfoods Ltd)
600 gram (ACBS) • NHS indicative price = £4.95

Wellfoods gluten free loaf unsliced (Wellfoods Ltd)
600 gram (ACBS) • NHS indicative price = £4.85

BAGUETTES, BUNS AND ROLLS

Barkat® Baguettes and rolls
GLUTEN-FREE

Barkat gluten free par baked rolls (Gluten Free Foods Ltd)
200 gram (ACBS) • NHS indicative price = £3.98

Barkat gluten free par baked baguettes (Gluten Free Foods Ltd)
200 gram (ACBS) • NHS indicative price = £3.98

Ener-G® Rolls
GLUTEN-FREE

Ener-G gluten free dinner rolls (General Dietary Ltd)
280 gram (ACBS) • NHS indicative price = £3.71

Ener-G gluten free white round rolls (General Dietary Ltd)
220 gram (ACBS) • NHS indicative price = £2.98

Ener-G gluten free white long rolls (General Dietary Ltd)
220 gram (ACBS) • NHS indicative price = £2.98

Glutafin® Baguettes and rolls
GLUTEN-FREE

Glutafin gluten free baguettes (Dr Schar UK Ltd)
350 gram (ACBS) • NHS indicative price = £3.51

Glutafin gluten free 4 white rolls (Dr Schar UK Ltd)
200 gram (ACBS) • NHS indicative price = £3.68

Glutafin gluten free part baked 4 fibre rolls (Dr Schar UK Ltd)
200 gram (ACBS) • NHS indicative price = £3.68

Glutafin® Select Rolls
GLUTEN-FREE

Glutafin gluten free part baked 4 white rolls (Dr Schar UK Ltd)
200 gram (ACBS) • NHS indicative price = £3.68

Glutafin gluten free part baked 2 long white rolls (Dr Schar UK Ltd)
150 gram (ACBS) • NHS indicative price = £2.81

Juvela® Rolls
GLUTEN-FREE

Juvela gluten free fresh fibre rolls (Hero UK Ltd)
425 gram (ACBS) • NHS indicative price = £4.42

Juvela gluten free fresh white rolls (Hero UK Ltd)
425 gram (ACBS) • NHS indicative price = £4.42

Juvela gluten free fibre bread rolls (Hero UK Ltd)
425 gram (ACBS) • NHS indicative price = £4.77

Juvela gluten free bread rolls (Hero UK Ltd)
425 gram (ACBS) • NHS indicative price = £4.77

Juvela gluten free part baked fibre bread rolls (Hero UK Ltd)
375 gram (ACBS) • NHS indicative price = £4.94

Juvela gluten free part baked white bread rolls (Hero UK Ltd)
375 gram (ACBS) • NHS indicative price = £4.94

Lifestyle® Rolls
GLUTEN-FREE

Lifestyle gluten free brown bread rolls (Ultrapharm Ltd)
400 gram (ACBS) • NHS indicative price = £2.82

Lifestyle gluten free high fibre bread rolls (Ultrapharm Ltd)
400 gram (ACBS) • NHS indicative price = £2.82

Lifestyle gluten free white bread rolls (Ultrapharm Ltd)
400 gram (ACBS) • NHS indicative price = £2.82

Livwell® Baguettes, buns and rolls
GLUTEN-FREE

Livwell gluten free white baguettes (Livwell Ltd)
140 gram (ACBS) • NHS indicative price = £2.15

Livwell gluten free toasting bread buns (Livwell Ltd)
180 gram (ACBS) • NHS indicative price = £2.40

Proceli® Baguettes, buns and rolls
GLUTEN-FREE

Proceli gluten free part baked baguettes (Ambe Ltd)
250 gram (ACBS) • NHS indicative price = £3.24

Warburtons® Baguettes and rolls
GLUTEN-FREE

Warburtons gluten free baguettes (Warburtons Ltd)
150 gram (ACBS) • NHS indicative price = £2.86

Warburtons gluten free brown rolls (Warburtons Ltd)
220 gram (ACBS) • NHS indicative price = £2.55

Warburtons gluten free white rolls (Warburtons Ltd)
220 gram (ACBS) • NHS indicative price = £2.55

Wellfoods® Buns and rolls
GLUTEN-FREE

Wellfoods gluten free burger buns (Wellfoods Ltd)
380 gram (ACBS) • NHS indicative price = £3.95

Wellfoods gluten free rolls (Wellfoods Ltd)
360 gram (ACBS) • NHS indicative price = £3.65

SPECIALITY BREADS

Livwell® Flat bread
GLUTEN-FREE

Livwell gluten free flat bread (Livwell Ltd)
220 gram (ACBS) • NHS indicative price = £3.00

Livwell gluten free tear drop flat bread (Livwell Ltd)
180 gram (ACBS) • NHS indicative price = £3.00

Cereals

Juvela® Fibre flakes and oats
GLUTEN-FREE

Juvela gluten free fibre flakes (Hero UK Ltd)
300 gram (ACBS) • NHS indicative price = £2.78

Juvela gluten free flakes (Hero UK Ltd)
300 gram (ACBS) • NHS indicative price = £2.78

Juvela gluten free pure oats (Hero UK Ltd)
500 gram (ACBS) • NHS indicative price = £2.78

Nairns® Porridge
GLUTEN-FREE

Nairn’s gluten free oat porridge (Nairn’s Oatcakes Ltd)
500 gram (ACBS) • NHS indicative price = £3.05

Cookies and biscuits

Barkat® Biscuits
GLUTEN-FREE

Barkat gluten free digestive biscuits (Gluten Free Foods Ltd)
175 gram (ACBS) • NHS indicative price = £2.61

Barkat gluten free coffee biscuits (Gluten Free Foods Ltd)
200 gram (ACBS) • NHS indicative price = £3.38

Ener-G® Cookies
GLUTEN-FREE

Ener-G gluten free vanilla cookies (General Dietary Ltd)
435 gram (ACBS) • NHS indicative price = £5.23

Glutafin® Cookies and biscuits
GLUTEN-FREE
Glutafin gluten free tea biscuits (Dr Schar UK Ltd)
150 gram (ACBS) · NHS indicative price = £2.09
Glutafin gluten free digestive biscuits (Dr Schar UK Ltd)
150 gram (ACBS) · NHS indicative price = £2.13
Glutafin gluten free biscuits (Dr Schar UK Ltd)
200 gram (ACBS) · NHS indicative price = £4.14
Glutafin gluten free savoury short biscuits (Dr Schar UK Ltd)
150 gram (ACBS) · NHS indicative price = £2.80
Glutafin gluten free shortbread biscuits (Dr Schar UK Ltd)
100 gram (ACBS) · NHS indicative price = £1.73
Glutafin gluten free sweet biscuits (Dr Schar UK Ltd)
150 gram (ACBS) · NHS indicative price = £2.13
Juvela® Biscuits GLUTEN-FREE
Juvela gluten free digestive biscuits (Hero UK Ltd)
150 gram (ACBS) · NHS indicative price = £3.05
Juvela gluten free savoury biscuits (Hero UK Ltd)
150 gram (ACBS) · NHS indicative price = £3.82
Juvela gluten free sweet biscuits (Hero UK Ltd)
150 gram (ACBS) · NHS indicative price = £2.88
Juvela gluten free tea biscuits (Hero UK Ltd)
150 gram (ACBS) · NHS indicative price = £3.05
Crackers, crispsbreads, and breadsticks
Barkat® Crackers GLUTEN-FREE
Barkat gluten free matzo crackers (Gluten Free Foods Ltd)
200 gram (ACBS) · NHS indicative price = £3.52
Glutafin® Crackers GLUTEN-FREE
Glutafin gluten free high fibre crackers (Dr Schar UK Ltd)
200 gram (ACBS) · NHS indicative price = £2.90
Glutafin gluten free crackers (Dr Schar UK Ltd)
200 gram (ACBS) · NHS indicative price = £3.46
Glutafin gluten free mini crackers (Dr Schar UK Ltd)
175 gram (ACBS) · NHS indicative price = £2.96
Juvela® Crispbread GLUTEN-FREE
Juvela gluten free crispbread (Hero UK Ltd)
200 gram (ACBS) · NHS indicative price = £4.64
Warburtons® Crackers GLUTEN-FREE
Warburtons gluten free bran crackers (Warburtons Ltd)
150 gram (ACBS) · NHS indicative price = £2.34
Flour mixes and xanthan gum
FLOUR MIXES
Barkat® Flour mix GLUTEN-FREE
Barkat gluten free bread mix (Gluten Free Foods Ltd)
500 gram (ACBS) · NHS indicative price = £6.81
Barkat gluten free high fibre bread mix (Gluten Free Foods Ltd)
500 gram (ACBS) · NHS indicative price = £8.96
Barkat gluten free all purpose flour mix (Gluten Free Foods Ltd)
500 gram (ACBS) · NHS indicative price = £4.65
Finax® Flour mix GLUTEN-FREE
Finax gluten free coarse flour mix (Drossa Ltd)
900 gram (ACBS) · NHS indicative price = £8.66
Finax gluten free bread mix (Drossa Ltd)
1000 gram (ACBS) · NHS indicative price = £9.92
Finax gluten free flour mix (Drossa Ltd)
900 gram (ACBS) · NHS indicative price = £8.66
Glutafin Select® Flour mix GLUTEN-FREE
Glutafin gluten free Select bread mix (Dr Schar UK Ltd)
500 gram (ACBS) · NHS indicative price = £6.66
Glutafin gluten free Select fibre bread mix (Dr Schar UK Ltd)
500 gram (ACBS) · NHS indicative price = £6.66
Glutafin gluten free Select multipurpose fibre mix (Dr Schar UK Ltd)
500 gram (ACBS) · NHS indicative price = £6.66
Glutafin gluten free Select multipurpose white mix (Dr Schar UK Ltd)
500 gram (ACBS) · NHS indicative price = £6.66
Glutafin® Flour mix GLUTEN-FREE
Glutafin gluten free multipurpose white mix (Dr Schar UK Ltd)
500 gram (ACBS) · NHS indicative price = £6.66
Heron Foods® Flour mix GLUTEN-FREE
Heron Hi-Fibre gluten free organic bread mix (Gluten Free Foods Ltd)
500 gram (ACBS) · NHS indicative price = £6.66
Mrs Crimble’s Flour mixes GLUTEN-FREE
Mrs Crimble’s gluten free bread mix (Stiletto Foods (UK) Ltd)
275 gram (ACBS) · NHS indicative price = £1.09
Mrs Crimble’s gluten free pastry mix (Stiletto Foods (UK) Ltd)
200 gram (ACBS) · NHS indicative price = £1.09
Orgran® Flour mix GLUTEN-FREE
Orgran gluten free pizza & pastry mix (Naturally Good Food Ltd)
375 gram (ACBS) · NHS indicative price = £3.80
Orgran gluten free self-raising flour (Naturally Good Food Ltd)
500 gram (ACBS) · NHS indicative price = £3.10
Orgran gluten free all purpose plain flour (Naturally Good Food Ltd)
500 gram · NHS indicative price = £3.10
Proceli® Flour mix GLUTEN-FREE
Proceli gluten free white plain flour (Ambe Ltd)
1000 gram (ACBS) · NHS indicative price = £9.95
Pure® Flour mix GLUTEN-FREE
Innovative Solutions Pure gluten free blended flour (Innovative Solutions (UK) Ltd)
1000 gram (ACBS) · NHS indicative price = £4.35
Innovative Solutions Pure gluten free brown rice flour (Innovative Solutions (UK) Ltd)
500 gram (ACBS) · NHS indicative price = £1.63
Innovative Solutions Pure gluten free white rice flour (Innovative Solutions (UK) Ltd)
500 gram (ACBS) · NHS indicative price = £1.73
Innovative Solutions Pure gluten free potato flour (Innovative Solutions (UK) Ltd)
500 gram (ACBS) · NHS indicative price = £1.73
Innovative Solutions Pure gluten free tapioca flour (Innovative Solutions (UK) Ltd)
500 gram (ACBS) · NHS indicative price = £2.33
Innovative Solutions Pure gluten free brown teff flour (Innovative Solutions (UK) Ltd)
1000 gram (ACBS) · NHS indicative price = £4.91
Innovative Solutions Pure gluten free white teff flour (Innovative Solutions (UK) Ltd)
1000 gram (ACBS) · NHS indicative price = £4.91
Tobia® Flour mix GLUTEN-FREE
Tobia Teff gluten free brown teff flour (Tobia Teff UK Ltd)
1000 gram (ACBS) · NHS indicative price = £3.40

Tobia Teff gluten free brown teff flour (Tobia Teff UK Ltd)
1000 gram (ACBS) · NHS indicative price = £3.40
**Gluten-freepastas**

**Gluten-free xanthan gum**

- **Ener-G xanthan gum**
  - 500 gram (ACBS) · NHS indicative price = £7.65

**Innovative Solutions Pure xanthan gum**

- **Pure® Xanthan gum**
  - 100 gram (ACBS) · NHS indicative price = £6.85

**Pasta**

**Barkat® Pasta**

- **Barkat gluten free pasta animal shapes** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £5.88
- **Barkat gluten free pasta macaroni** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £5.88
- **Barkat gluten free pasta spaghetti** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £5.88
- **Barkat gluten free pasta spirals** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £5.88
- **Barkat gluten free pasta tagliatelle** (Gluten Free Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £2.93
- **Barkat gluten free pasta buckwheat penne** (Gluten Free Foods Ltd)
  - 250 gram (ACBS) · NHS indicative price = £2.93

**BiAlimento® Pasta**

- **BiAlimento gluten free pasta spirals** (Drossa Ltd)
  - 500 gram (ACBS) · NHS indicative price = £5.97

**Ener-G® Pasta**

- **General Dietary gluten free macaroni** (General Dietary Ltd)
  - 454 gram (ACBS) · NHS indicative price = £5.03
- **General Dietary gluten free spaghetti** (General Dietary Ltd)
  - 454 gram (ACBS) · NHS indicative price = £5.03
- **General Dietary gluten free vermicelli** (General Dietary Ltd)
  - 500 gram (ACBS) · NHS indicative price = £5.03

**Glutafin® Pasta**

- **Glutafin gluten free pasta lasagne** (Dr Schar UK Ltd)
  - 250 gram (ACBS) · NHS indicative price = £3.53
- **Glutafin gluten free pasta macaroni penne** (Dr Schar UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £6.73
- **Glutafin gluten free pasta shells** (Dr Schar UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £6.73
- **Glutafin gluten free pasta spirals** (Dr Schar UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £6.73
- **Glutafin gluten free pasta tagliatelle nests** (Dr Schar UK Ltd)
  - 250 gram (ACBS) · NHS indicative price = £3.53

**Glutafin gluten free pasta long-cut spaghetti** (Dr Schar UK Ltd)

- 500 gram (ACBS) · NHS indicative price = £6.73

**Glutafin gluten free pasta fibre spaghetti** (Dr Schar UK Ltd)

- 500 gram (ACBS) · NHS indicative price = £5.74

**Juvela® Pasta**

- **Juvela gluten free fibre penne** (Hero UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £6.61
- **Juvela gluten free pasta fusilli** (Hero UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £7.21
- **Juvela gluten free pasta lasagne** (Hero UK Ltd)
  - 250 gram (ACBS) · NHS indicative price = £3.68
- **Juvela gluten free pasta macaroni** (Hero UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £7.21
- **Juvela gluten free pasta spaghetti** (Hero UK Ltd)
  - 500 gram (ACBS) · NHS indicative price = £7.21
- **Juvela gluten free pasta tagliatelle** (Hero UK Ltd)
  - 250 gram (ACBS) · NHS indicative price = £3.47

**Orgran® Pasta**

- **Orgran gluten free pasta rice & corn lasagne** (Naturally Good Food Ltd)
  - 200 gram (ACBS) · NHS indicative price = £3.66
- **Orgran gluten free pasta rice & corn macaroni** (Naturally Good Food Ltd)
  - 250 gram (ACBS) · NHS indicative price = £2.42
- **Orgran gluten free pasta buckwheat spirals** (Naturally Good Food Ltd)
  - 250 gram (ACBS) · NHS indicative price = £2.42
- **Orgran gluten free pasta corn spirals** (Naturally Good Food Ltd)
  - 250 gram (ACBS) · NHS indicative price = £2.42
- **Orgran gluten free pasta brown rice spirals** (Naturally Good Food Ltd)
  - 250 gram (ACBS) · NHS indicative price = £2.42
- **Orgran gluten free pasta rice & corn spirals** (Naturally Good Food Ltd)
  - 250 gram (ACBS) · NHS indicative price = £2.42

**Rizopia® Pasta**

- **Rizopia gluten free organic brown rice pasta fusilli** (PGR Health Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £2.72
- **Rizopia gluten free organic brown rice pasta lasagne** (PGR Health Foods Ltd)
  - 375 gram (ACBS) · NHS indicative price = £2.72
- **Rizopia gluten free organic brown rice pasta penne** (PGR Health Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £2.72
- **Rizopia gluten free organic brown rice pasta spaghetti** (PGR Health Foods Ltd)
  - 500 gram (ACBS) · NHS indicative price = £2.72

**Pizza bases**

**Barkat®, Pizza crust**

- **Barkat gluten free brown rice pizza crust** (Gluten Free Foods Ltd)
  - 150 gram (ACBS) · NHS indicative price = £5.00
- **Barkat gluten free white rice pizza crust** (Gluten Free Foods Ltd)
  - 150 gram (ACBS) · NHS indicative price = £5.00

**Glutafin® Pizza base**

**Glutafin gluten free pizza base** (Dr Schar UK Ltd)

- 300 gram (ACBS) · NHS indicative price = £6.56

**Juvela® Pizza base**

- **Juvela gluten free pizza base** (Dr Schar UK Ltd)
  - 200 gram (ACBS) · NHS indicative price = £5.74
Juvela gluten free pizza base (Hero UK Ltd)
360 gram (ACBS) - NHS indicative price = £8.78

Proceli® Pizza base
GLUTEN-FREE

Proceli gluten free pizza base (Ambe Ltd)
250 gram (ACBS) - NHS indicative price = £3.90

Wellfoods® Pizza base
GLUTEN-FREE
Wellfoods gluten free pizza base (Wellfoods Ltd)
600 gram (ACBS) - NHS indicative price = £8.95

Gluten- and wheat-free foods
ACBS indications: established gluten-sensitive enteropathies with coexisting established wheat sensitivity only.

Ener-G® Bread loaves, rolls and pizza bases
GLUTEN-FREE, WHEAT-FREE

Ener-G gluten free Seattle brown hamburger rolls (General Dietary Ltd)
320 gram (ACBS) - NHS indicative price = £4.08

Ener-G gluten free Seattle brown hot dog rolls (General Dietary Ltd)
320 gram (ACBS) - NHS indicative price = £4.08

Glutafin® Flour mix, fibre and crispbread
GLUTEN-FREE, WHEAT-FREE

Glutafin gluten free crispbread (Dr Schar UK Ltd)
150 gram (ACBS) - NHS indicative price = £3.25

Glutafin gluten free bread mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66

Glutafin gluten free fibre bread mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66

Glutafin gluten free wheat free fibre mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66

Heron Foods® Flour mixes
GLUTEN-FREE, WHEAT-FREE

Heron gluten free organic bread mix (Gluten Free Foods Ltd)
500 gram (ACBS) - NHS indicative price = £8.96

Low-protein foods
ACBS indications: inherited metabolic disorders, renal or liver failure, requiring a low-protein diet.

Bread

Ener-G® Rice bread
LOW PROTEIN

Ener-G low protein rice bread (General Dietary Ltd)
600 gram (ACBS) - NHS indicative price = £5.60

Juvela® Loaf and rolls
LOW PROTEIN

Juvela gluten free loaf sliced (Hero UK Ltd)
400 gram (ACBS) - NHS indicative price = £3.54

Juvela low protein bread rolls (Hero UK Ltd)
350 gram (ACBS) - NHS indicative price = £4.52

Juvela low protein loaf sliced (Hero UK Ltd)
400 gram (ACBS) - NHS indicative price = £3.64

Loprofin® Bread
LOW-PROTEIN

Loprofin low protein part baked bread rolls (Nutricia Ltd)
260 gram (ACBS) - NHS indicative price = £4.20

Loprofin low protein part baked loaf sliced (Nutricia Ltd)
400 gram (ACBS) - NHS indicative price = £3.98

PK Foods® Loaf
LOW PROTEIN

PK Foods low protein white bread sliced (Gluten Free Foods Ltd)
550 gram (ACBS) - NHS indicative price = £4.75

Cake, biscuits, and snacks

Juvela® Cookies
LOW-PROTEIN

Juvela low protein cinnamon cookies (Hero UK Ltd)
125 gram (ACBS) - NHS indicative price = £7.62

Juvela low protein chocolate chip cookies (Hero UK Ltd)
110 gram (ACBS) - NHS indicative price = £7.62

Juvela low protein orange cookies (Hero UK Ltd)
125 gram (ACBS) - NHS indicative price = £7.62

Loprofin® Wafers
LOW-PROTEIN

Loprofin low protein crackers (Nutricia Ltd)
150 gram (ACBS) - NHS indicative price = £3.67

Loprofin low protein herb crackers (Nutricia Ltd)
150 gram (ACBS) - NHS indicative price = £3.67

Loprofin low protein vanilla cream wafers (Nutricia Ltd)
100 gram (ACBS) - NHS indicative price = £2.62

PK Foods® Biscuits
LOW-PROTEIN

PK Foods Aminex low protein biscuits (Gluten Free Foods Ltd)
200 gram (ACBS) - NHS indicative price = £5.04

PK Foods Aminex low protein cookies (Gluten Free Foods Ltd)
150 gram (ACBS) - NHS indicative price = £5.04

PK Foods Aminex low protein rusk (Gluten Free Foods Ltd)
200 gram (ACBS) - NHS indicative price = £5.04

PK Foods low protein chocolate chip cookies (Gluten Free Foods Ltd)
150 gram (ACBS) - NHS indicative price = £5.04

PK Foods low protein crispbread (Gluten Free Foods Ltd)
75 gram (ACBS) - NHS indicative price = £2.42

PK Foods low protein orange cookies (Gluten Free Foods Ltd)
150 gram (ACBS) - NHS indicative price = £5.04

Promin® Cooked and flavoured pasta snax
LOW-PROTEIN

Promin low protein Snax salt & vinegar 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available

Promin low protein Snax ready salted 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available

Promin low protein Snax cheese & onion 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available

Taranis® Cake bars
LOW-PROTEIN

Taranis low protein apricot cake (Lactalis Nutrition Sante)
240 gram (ACBS) - NHS indicative price = £6.08

Taranis low protein lemon cake (Lactalis Nutrition Sante)
240 gram (ACBS) - NHS indicative price = £6.08

Taranis low protein pear cake (Lactalis Nutrition Sante)
240 gram (ACBS) - NHS indicative price = £6.08

Vita Bite®
■ Not recommended for any child under 1 year. LOW PROTEIN.
Bar, protein 30 mg (less than 2.5 mg phenylalanine), carbohydrate 15.35 g, fat 8.4 g, energy 572 kJ (137 kcal)/25 g.

VitaBite bar (Vitalfo International Ltd)
175 gram (ACBS) - NHS indicative price = £8.61

Vitafose® Mini crackers
LOW-PROTEIN

Vitafose mini crackers (Vitalfo International Ltd)
40 gram (ACBS) - NHS indicative price = £0.85

Cereals

Loprofin® Breakfast cereal
LOW-PROTEIN

Loprofin low protein breakfast cereal flakes apple (Nutricia Ltd)
375 gram (ACBS) - NHS indicative price = £8.09
Loprofin low protein breakfast cereal flakes chocolate (Nutricia Ltd)
375 gram (ACBS) • NHS indicative price = £8.09
Loprofin low protein breakfast cereal flakes strawberry (Nutricia Ltd)
375 gram (ACBS) • NHS indicative price = £8.09
Loprofin low protein breakfast cereal loops (Nutricia Ltd)
375 gram (ACBS) • NHS indicative price = £8.39
Promin® Hot breakfast
LOW-PROTEIN
Promin low protein hot breakfast powder sachets apple & cinnamon (Firstplay Dietary Foods Ltd)
342 gram (ACBS) • NHS indicative price = £8.09
Promin low protein hot breakfast powder sachets banana (Firstplay Dietary Foods Ltd)
342 gram (ACBS) • NHS indicative price = £8.09
Promin low protein hot breakfast powder sachets chocolate (Firstplay Dietary Foods Ltd)
342 gram (ACBS) • NHS indicative price = £8.09
Promin low protein hot breakfast powder sachets original (Firstplay Dietary Foods Ltd)
336 gram (ACBS) • NHS indicative price = £8.09

Desserts
PK Foods® Jelly
LOW-PROTEIN
PK Foods low protein jelly mix dessert cherry (Gluten Free Foods Ltd)
320 gram (ACBS) • NHS indicative price = £8.03
PK Foods low protein jelly mix dessert orange (Gluten Free Foods Ltd)
320 gram (ACBS) • NHS indicative price = £8.03
Promin® Desserts
LOW-PROTEIN
Promin low protein imitation rice pudding apple (Firstplay Dietary Foods Ltd)
276 gram (ACBS) • NHS indicative price = £6.33
Promin low protein imitation rice pudding banana (Firstplay Dietary Foods Ltd)
276 gram (ACBS) • NHS indicative price = £6.33
Promin low protein imitation rice pudding original (Firstplay Dietary Foods Ltd)
276 gram (ACBS) • NHS indicative price = £6.33
Promin low protein imitation rice pudding strawberry (Firstplay Dietary Foods Ltd)
276 gram (ACBS) • NHS indicative price = £6.33

Flour mixes and egg substitutes
Ener-G® Egg replacer
LOW-PROTEIN
Ener-G low protein egg replacer (General Dietary Ltd)
454 gram (ACBS) • NHS indicative price = £5.17
Fate® Flour mix
LOW PROTEIN
Fate low protein all purpose mix (Fate Special Foods)
500 gram (ACBS) • NHS indicative price = £6.97
Fate low protein chocolate cake mix (Fate Special Foods)
500 gram (ACBS) • NHS indicative price = £6.97
Fate low protein plain cake mix (Fate Special Foods)
500 gram (ACBS) • NHS indicative price = £6.97
Juvela® Mix
LOW-PROTEIN
Juvela low protein mix (Hero UK Ltd)
500 gram (ACBS) • NHS indicative price = £7.79
Loprofin® Flour mixes and egg substitutes
LOW-PROTEIN
Loprofin low protein egg replacer (Nutricia Ltd)
500 gram (ACBS) • NHS indicative price = £15.72
Loprofin low protein egg white replacer (Nutricia Ltd)
100 gram (ACBS) • NHS indicative price = £10.12
Loprofin low protein cake mix chocolate (Nutricia Ltd)
500 gram (ACBS) • NHS indicative price = £9.06
Loprofin low protein mix (Nutricia Ltd)
500 gram (ACBS) • NHS indicative price = £8.43
PK Foods® Flour mix and egg substitute
LOW-PROTEIN
PK Foods low protein egg replacer (Gluten Free Foods Ltd)
200 gram (ACBS) • NHS indicative price = £4.08
PK Foods low protein flour mix (Gluten Free Foods Ltd)
750 gram (ACBS) • NHS indicative price = £10.71

Pasta
Promin® Pasta
LOW-PROTEIN
Loprofin low protein pasta animal shapes (Nutricia Ltd)
500 gram (ACBS) • NHS indicative price = £8.61
Loprofin low protein pasta lasagne (Nutricia Ltd)
250 gram (ACBS) • NHS indicative price = £4.35
Loprofin low protein pasta penne (Nutricia Ltd)
500 gram (ACBS) • NHS indicative price = £8.94
Loprofin low protein pasta tagliatelle (Nutricia Ltd)
250 gram (ACBS) • NHS indicative price = £4.30
Loprofin low protein pasta macaroni elbows (Nutricia Ltd)
250 gram (ACBS) • NHS indicative price = £4.30
Loprofin low protein pasta long cut spaghetti (Nutricia Ltd)
500 gram (ACBS) • NHS indicative price = £8.94
Promin® Pasta
LOW-PROTEIN
Promin low protein pasta alphabets (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin Plus low protein pasta macaroni (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin Plus low protein pasta flat noodles (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin low protein pasta shells (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin low protein pasta short cut spaghetti (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin low protein tricolour pasta spirals (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin low protein tricolour pasta alphabets (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin low protein tricolour pasta shells (Firstplay Dietary Foods Ltd)
500 gram (ACBS) • NHS indicative price = £6.99
Promin low protein lasagne sheets (Firstplay Dietary Foods Ltd)
200 gram (ACBS) • NHS indicative price = £3.03

Pizza bases
Promin® Pizza base
LOW-PROTEIN
Promin low protein pizza base (Hero UK Ltd)
360 gram (ACBS) • NHS indicative price = £8.61

Savoury meals and mixes
Promin® Savoury meals and mixes
LOW-PROTEIN
Promin low protein burger mix (Firstplay Dietary Foods Ltd)
124 gram (ACBS) • NHS indicative price = £6.36
Nutritional supplements for metabolic diseases

Glutaric aciduria (type 1)

**GA Gel®**
- Nutritional supplement for dietary management of type 1 glutaric aciduria in children 6 months–10 years.
  - GEL, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**GA Anamix® Infant**
- Nutritional supplement for the dietary management of type 1 glutaric aciduria.
  - POWDER, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Anamix products are generally intended for use in children 1–8 years.

**GAI Maxamaid**
- Nutritional supplement for the dietary management of type 1 glutaric aciduria.
  - POWDER, protein equivalent (essential and non-essential amino acids except lysine and tryptophan) 79 g, carbohydrate 4 g, energy 1411 kJ (332 kcal)/100 g.

**XLYS, TRY Glutaridon®**
- Nutritional supplement for the dietary management of type 1 glutaric aciduria in children and adults; requires additional source of vitamins, minerals, and trace elements.
  - POWDER, protein equivalent (essential and non-essential amino acids except lysine and tryptophan) 79 g, carbohydrate 4 g, energy 1411 kJ (332 kcal)/100 g.

**Glycogen storage disease**

**Corn flour and corn starch**
- For glycogen storage disease

**Glycosade®**
- A nutritional supplement for use in the dietary management of glycogen storage disease and other metabolic conditions where a constant supply of glucose is essential. Not suitable for use in children under 2 years.
  - POWDER, protein 200 mg, carbohydrate (maize starch) 47.6 g, fat 100 mg, fibre less than 600 mg, energy 803 kJ (192 kcal)/60 g.

**Glycosade oral powder 60g sachets** (Vitaflor International Ltd)
- 30 sachet (ACBS) • NHS indicative price = £111.65

**Homocystinuria or hypermethioninaemia**

**HCU Anamix® Infant**
- Nutritional supplement for the dietary management of proven vitamin B6 non-responsive homocystinuria or hypermethioninaemia in children from birth to 3 years.
  - POWDER, protein equivalent (essential and non-essential amino acids except methionine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**HCU Anamix Infant powder** (Nutricia Ltd)
- 400 gram (ACBS) • NHS indicative price = £39.45

**HCU cooler® 15**
- A methionine-free protein substitute for use as a nutritional supplement in children over 3 years with homocystinuria.
  - LIQUID, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 7 g, fat 500 mg, energy 393 kJ (92 kcal)/150 mL, with vitamins, minerals, and trace elements.

**HCU orange cooler 15 liquid** (Vitaflor International Ltd)
- 150 ml (ACBS) • NHS indicative price = £11.21

**HCU Express® 15**
- A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria.
POWDER, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 3.8 g, fat 30 mg, energy 315 kJ (75.5 kcal)/25 g with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.

**HCU express 15 oral powder 25g sachets** (Vitalfo International Ltd) 30 sachet (ACBS) - NHS indicative price = £329.89

**HCU Express® 20**
- A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria.
- POWDER, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 4.7 g, fat 70 mg, energy 416 kJ (99 kcal)/34 g with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.

**HCU express 20 oral powder 34g sachets** (Vitalfo International Ltd) 30 sachet (ACBS) - NHS indicative price = £426.21

**HCU gel®**
- A methionine-free protein substitute for use as a nutritional supplement for the dietary management of children 1–10 years with homocystinuria.
- POWDER, protein (essential and non-essential amino acids except methionine) 10 g, carbohydrate 10.3 g, fat 20 mg, energy 339 kJ (81 kcal)/24 g with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.

**HCU gel oral powder 24g sachets** (Vitalfo International Ltd) 30 sachet (ACBS) - NHS indicative price = £212.38

**HCU Lophlex® LQ 20**
- Nutritional supplement for the dietary management of homocystinuria in children over 5 years.
- LIQUID, protein equivalent (essential and non-essential amino acids except methionine) 20 g, carbohydrate 8.8 g, fat 440 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.

**HCU Lophlex LQ 20 liquid** (Nutricia Ltd) 125 mL (ACBS) - NHS indicative price = £16.27

**HCU LV®**
- Nutritional supplement for the dietary management of hypermethioninaemia or vitamin B6 non-responsive homocystinuria in children over 8 years.
- POWDER, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 2.5 g, fat 190 mg, energy 390 kJ (92 kcal)/27.8 g sachet, with vitamins, minerals, and trace elements.

**HCU-LV oral powder 27.8g sachets tropical** (Nutricia Ltd) 30 sachet (ACBS) - NHS indicative price = £50.10

**HCU-LV oral powder 27.8g sachets unflavoured** (Nutricia Ltd) 30 sachet (ACBS) - NHS indicative price = £50.10

**XMET Homidon®**
- Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children and adults.
- POWDER, protein equivalent (essential and non-essential amino acids, except methionine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

**XMET Homidon powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £188.69

**HCU Maxamaid®**
- Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements. Maxamaid products are generally intended for use in children 1–8 years.

**HCU Maxamaid powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £159.66

**Hyperlysinaemia**

**HYPER LYS Anamix® Infant**
- Nutritional supplement for the dietary management of proven hyperlysinaemia in children from birth to 3 years.
- POWDER, protein equivalent (essential and non-essential amino acids except lysine) 15.1 g, carbohydrate 49.5 g, fat 25 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kcal (69 kcal)/100 mL.

**HYPER LYS Anamix Infant powder** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £29.45

**HYPER LYS Maxamaid®**
- Nutritional supplement for the dietary management of hyperlysinaemia.
- POWDER, protein equivalent (essential and non-essential amino acids except lysine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements. Maxamaid products are generally intended for use in children 1–8 years.

**HYPER LYS Maxamaid powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £99.61

**Isovaleric acidemia**

**IVA Anamix® infant**
- Nutritional supplement for the dietary management of proven isovaleric acidemia or other proven disorders of leucine metabolism in children from birth to 3 years.
- POWDER, protein equivalent (essential and non-essential amino acids except leucine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kcal (69 kcal)/100 mL.

**IVA Anamix Infant powder** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £39.45

**IVA Maxamaid®**
- Nutritional supplement for the dietary management of isovaleric acidemia.
- POWDER, protein equivalent (essential and non-essential amino acids except leucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements. Maxamaid products are generally intended for use in children 1–8 years.

**IVA Maxamaid powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £99.61

**Maple syrup urine disease**

**MSUD Aid III®**
- Nutritional supplement for the dietary management of maple syrup urine disease and related conditions in children and adults where it is necessary to limit the intake of branched chain amino acids.
- POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

**MSUD Aid 111 powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £188.69
**Nutritional supplement for the dietary management of maple syrup urine disease in children from birth to 3 years.**

**Powder**, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 15.1 g, carbohydrate 49.9 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**MSUD Anamix Infant Powder** (Nutricia Ltd)

400 gram (ACBS) • NHS indicative price = £39.45

**MSUD Anamix Infant**

Nutritional supplement for the dietary management of proven maple syrup urine disease in children 1–10 years.

**Powder**, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.

**MSUD Anamix Infant Powder liquid** (Nutricia Ltd)

125 ml (ACBS) • NHS indicative price = £9.15

**MSUD cooler 15**

Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years. **Liquid**, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 7 g, fat 500 mg, energy 595 kJ (92 kcal)/130-mL pouch, with vitamins, minerals, and trace elements.

**MSUD orange cooler 15 Liquid** (Vitafluo International Ltd)

130 ml (ACBS) • NHS indicative price = £11.21

**MSUD red cooler 15 Liquid** (Vitafluo International Ltd)

130 ml (ACBS) • NHS indicative price = £11.21

**MSUD express 15**

Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults. **Powder**, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 3.8 g, fat less than 100 mg, energy 315 kJ (75 kcal)/25 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1570.

**MSUD express 15 Oral Powder 25g Sachet** (Vitafluo International Ltd)

30 sachet (ACBS) • NHS indicative price = £329.89

**MSUD express 20**

Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults. **Powder**, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1570.

**MSUD express 20 Oral Powder 34g Sachets** (Vitafluo International Ltd)

30 sachet (ACBS) • NHS indicative price = £426.21

**MSUD Gel**

Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years. **Powder**, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 10 g, carbohydrate 10.5 g, fat less than 100 mg, energy 539 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1570.

**MSUD gel 24g Sachets** (Vitafluo International Ltd)

30 sachet (ACBS) • NHS indicative price = £214.88

**MSUD Lophex LQ 20**

Nutritional supplement for the dietary management of maple syrup urine disease in children over 5 years. **Liquid**, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.

**MSUD Lophex LQ 20 Liquid** (Nutricia Ltd)

125 ml (ACBS) • NHS indicative price = £16.27

**MSUD Maxamaid**

Nutritional supplement for the dietary management of maple syrup urine disease. **Powder**, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1511 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Maxamaid products are generally intended for use in children 1–8 years.

**MSUD Maxamaid Powder** (Nutricia Ltd)

500 gram (ACBS) • NHS indicative price = £99.61

**MSUD Maxaxum**

Nutritional supplement for the dietary management of maple syrup urine disease. **Powder**, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Maxaxum products are generally intended for use in children over 8 years.

**MSUD Maxaxum Powder Orange** (Nutricia Ltd)

500 gram (ACBS) • NHS indicative price = £159.66

**MSUD Maxaxum Powder Unflavoured** (Nutricia Ltd)

500 gram (ACBS) • NHS indicative price = £159.66

**Methylmalonic or propionic acidaemia**

**MMA/PA Anamix Infant**

Nutritional supplement for the dietary management of proven methylmalonic acidemia or propionic acidemia in children from birth to 3 years.

**Powder**, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**MMA/PA Anamix Infant Powder** (Nutricia Ltd)

400 gram (ACBS) • NHS indicative price = £39.45

**XMTVI Asadon**

Nutritional supplement for the dietary management of methylmalonic acidemia or propionic acidemia in children and adults.

**Powder**, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

**XMTVI Asadon Powder** (Nutricia Ltd)

200 gram (ACBS) • NHS indicative price = £75.47

**MMA/PA Maxamaid**

Nutritional supplement for the dietary management of methylmalonic acidemia or propionic acidemia.

**Powder**, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1511 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Maxamaid products are generally intended for use in children 1–8 years.

**MMA/PA Maxamaid Powder** (Nutricia Ltd)

500 gram (ACBS) • NHS indicative price = £99.61

**MMA/PA Maxaxum**

Nutritional supplement for the dietary management of methylmalonic acidemia or propionic acidemia.
Nutritional supplements for metabolic diseases

POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 39 g, carbohydrate 54 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Maxamum powders are generally intended for use in children over 8 years.

MMA/PA Maxamum powder® (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £159.66

Other inborn errors of metabolism

Cystine500® • Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
POWDER, cystine 500 mg, carbohydrate 3.5 g, fat nil, energy 63 kJ (15 kcal)/4 g
Cystine500 oral powder 4 g sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £55.00

DocOmega® • Nutritional supplement for the dietary management of inborn errors of metabolism for adults from birth.
POWDER, protein (cows milk, soya) 100 mg, carbohydrate 3.2 g, fat 500 mg (of which docosahexaenoic acid 200 mg), fibre nil, energy 74 kJ (18 kcal)/4 g, with minerals
DocOmega oral powder 4 g sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £29.06

EAA® Supplement • Nutritional supplement for the dietary management of disorders of protein metabolism including urea cycle disorders in children over 3 years.
POWDER, protein equivalent (essential amino acids) 5 g, carbohydrate 4 g, fat nil, energy 151 kJ (36 kcal)/12.5 g, with vitamins, minerals, and trace elements.
EAA Supplement oral powder 12.5 g sachets® (Vitafo International Ltd) 50 sachet (ACBS) - NHS indicative price = £203.64

Isolucine50® • Nutritional supplement for use in the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
POWDER, isoleucine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g
Isolucine50 oral powder 4 g sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £53.97

KeyOmega® • Nutritional supplement for the dietary management of inborn errors of metabolism.
POWDER, protein (cows’ milk, soya) 170 mg, carbohydrate 2.8 g, fat 800 mg (of which arachidonic acid 200 mg, docosahexaenoic acid 100 mg), energy 80 kJ (19 kcal)/4 g.
KeyOmega oral powder 4 g sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £39.94

Leucine100® • Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
POWDER, leucine 100 mg, carbohydrate 3.7 g, fat nil, energy 63 kJ (15 kcal)/4 g
Leucine100 oral powder sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £53.97

Low protein drink • Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children over 1 year.
POWDER, protein (cows’ milk) 4.5 g (phenylalanine 100 mg), carbohydrate 59.5 g, fat 29.9 g, fibre nil, energy 2194 kJ (528 kcal)/100 g, with vitamins, minerals, and trace elements. Contains lactose. Termed Milupa® lp-drink by manufacturer.
Milupa LP drink® (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £9.36

Phenylalanine50® • Nutritional supplement for use in the dietary management of inborn errors of metabolism in adults and children from birth.
POWDER, phenylalanine 50 mg, carbohydrate 5.8 g, fat nil, energy 63 kJ (15 kcal)/4 g
Phenylalanine50 oral powder sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £52.40

ProZero® • A protein-free nutritional supplement for the dietary management of inborn errors of metabolism in children over 6 months and adults.
LIQUID, carbohydrate 8.1 g (of which sugars 3.5 g), fat 3.8 g, energy 278 kJ (66 kcal)/100 mL. Contains lactose.
ProZero liquid® (Vitafo International Ltd) 250 ml (ACBS) - NHS indicative price = £1.44 | 1000 ml (ACBS) - NHS indicative price = £5.75

Tyrosine1000® • Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
POWDER, tyrosine 1 g, carbohydrate 2.9 g, fat nil, energy 63 kJ (15 kcal)/4 g sachet.
Tyrosine1000 oral powder 4 g sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £4.95

Valine50® • Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
POWDER, valine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g
Valine50 oral powder 4 g sachets® (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £53.97

Phenylketonuria

Add Ins® • Nutritional supplement for the dietary management of proven phenylketonuria in children over 4 years.
POWDER, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate nil, fat 5.1 g, energy 359 kJ (86 kcal)/18.2-g sachet, with vitamins, minerals, and trace elements.
Add Ins oral powder 18.2 g sachets® (Nutricia Ltd) 60 sachet (ACBS) - NHS indicative price = £381.00

Easiphen® • Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years.
LIQUID, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 6.7 g, carbohydrate 5.1 g, fat 2 g, energy 275 kJ (65 kcal)/100 mL with vitamins, minerals, and trace elements.
Easiphen liquid® (Nutricia Ltd) 250 ml (ACBS) - NHS indicative price = £9.79

L-Tyrosine • Nutritional supplement for the dietary management of phenylketonuria in pregnant women with low plasma tyrosine concentrations.
POWDER, L-tyrosine 20 g, carbohydrate 76.8 g, fat nil, energy 1612 kJ (379 kcal)/100 g.
L-Tyrosine powder® (Nutricia Ltd) 100 gram (ACBS) - NHS indicative price = £22.22

Lophlex® • Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years and adults including pregnant women.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 2.5 g, fat 60 mg, fibre 220 mg, energy 385 kJ (91 kcal)/27.8-g sachet, with vitamins, minerals, and trace elements.
Lophlex powder 27.8 g sachets® (Nutricia Ltd) 30 sachet (ACBS) - NHS indicative price = £294.00
Nutritional supplements for metabolic diseases

Lophex powder 27.8g sachets orange (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £294.00
Lophex powder 27.8g sachets unflavoured (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £294.00
Lofrophen® PKU Drink
Nutritional supplement for the dietary management of phenylketonuria in children over 1 year and adults.
LIQUID, protein (cows' milk) 400 mg (phenylalanine 10 mg), lactose 9.4 g, fat 2 g, energy 165 kJ (40 kcal)/100 mL.
Lofrophen PKU drink (Nutricia Ltd)
200 ml (ACBS) - NHS indicative price = £0.76
Lofrophen® Sno-Pro
Nutritional supplement for the dietary management of phenylketonuria and similar amino acid abnormalities.
LIQUID, protein (cows' milk) 220 mg (phenylalanine 12.5 mg), carbohydrate 8 g, fat 3.8 g, energy 273 kJ (65 kcal)/100 mL.
Lofrophen Sno-Pro drink (Nutricia Ltd)
200 ml (ACBS) - NHS indicative price = £1.27
Phlexy-10® Exchange System
Nutritional supplement for the dietary management of phenylketonuria.
CAPSULES, protein equivalent (essential and non-essential amino acids except phenylalanine) 416.5 mg/capsule.
Phlexy-10 500mg capsules (Nutricia Ltd)
200 capsule (ACBS) - NHS indicative price = £44.00
TABLETS, protein equivalent (essential and non-essential amino acids except phenylalanine) 833 mg tablet.
Phlexy-10 tablets (Nutricia Ltd)
75 tablet (ACBS) - NHS indicative price = £28.50
DRINK MIX, powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.35 g, carbohydrate 8.8 g/20-g sachet.
Phlexy-10 drink mix apple & blackcurrant (Nutricia Ltd)
600 gram (ACBS) - NHS indicative price = £130.20
Phlexy-10 drink mix citrus burst (Nutricia Ltd)
600 gram (ACBS) - NHS indicative price = £130.20
Phlexy-10 drink mix tropical surprise (Nutricia Ltd)
600 gram (ACBS) - NHS indicative price = £130.20
Phlexy-Vits
For use as a vitamin and mineral component of restricted therapeutic diets in children over 11 years and adults with phenylketonuria and similar amino acid abnormalities.
POWDER, vitamins, minerals, and trace elements
Phlexy-Vits powder (Nutricia Ltd)
210 gram (ACBS) - NHS indicative price = £72.30
TABLETS, vitamins, minerals, and trace elements
Phlexy-Vits tablets (Nutricia Ltd)
180 tablet (ACBS) - NHS indicative price = £82.80
PK Aid 4®
Nutritional supplement for the dietary management of phenylketonuria in children and adults.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 79 g, carbohydrate 4.5 g, fat nil, energy 1420 kJ (354 kcal)/100 g.
PK Aid 4 powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £145.04
PKU Anamix Junior LQ®
LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.
PKU Anamix Junior LQ liquid berry (Nutricia Ltd)
125 ml (ACBS) - NHS indicative price = £5.69
PKU Anamix® Infant
Nutritional supplement for the dietary management of proven phenylketonuria in children from birth to 3 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.
PKU Anamix® Infant powder (Nutricia Ltd)
400 gram (ACBS) - NHS indicative price = £35.86
PKU Anamix® Junior
Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.4 g, carbohydrate 9.9 g, fat 3.9 g, energy 455 kJ (108 kcal)/29-g sachet, with vitamins, minerals, and trace elements.
PKU Anamix Junior powder chocolate (Nutricia Ltd)
1080 gram (ACBS) - NHS indicative price = £128.10
PKU Anamix Junior powder neutral (Nutricia Ltd)
1080 gram (ACBS) - NHS indicative price = £128.10
PKU Anamix® Junior LQ
Nutritional supplement for the dietary supplement of phenylketonuria in children 1–10 years.
LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.
PKU Anamix Junior LQ liquid berry (Nutricia Ltd)
125 ml (ACBS) - NHS indicative price = £5.69
PKU Anamix Junior LQ liquid orange (Nutricia Ltd)
125 ml (ACBS) - NHS indicative price = £5.69
PKU cooler®
Nutritional supplement for the dietary management of phenylketonuria in children over 3 years.
LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 5.1 g, energy 258 kJ (62 kcal)/87-mL pouch, with vitamins, minerals, and trace elements.
PKU orange cooler 10 liquid (Vitaflora International Ltd)
87 ml (ACBS) - NHS indicative price = £4.56
PKU purple cooler 10 liquid (Vitaflora International Ltd)
87 ml (ACBS) - NHS indicative price = £4.56
PKU red cooler 10 liquid (Vitaflora International Ltd)
87 ml (ACBS) - NHS indicative price = £4.56
PKU white cooler 10 liquid (Vitaflora International Ltd)
87 ml (ACBS) - NHS indicative price = £4.56
PKU cooler®
Nutritional supplement for the dietary management of phenylketonuria in children over 3 years.
LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 7.8 g, energy 586 kJ (92 kcal)/130-mL pouch, with vitamins, minerals, and trace elements.
PKU orange cooler 15 liquid (Vitaflora International Ltd)
130 ml (ACBS) - NHS indicative price = £6.80
PKU purple cooler 15 liquid (Vitaflora International Ltd)
130 ml (ACBS) - NHS indicative price = £6.80
PKU red cooler 15 liquid (Vitaflora International Ltd)
130 ml (ACBS) - NHS indicative price = £6.80
PKU white cooler 15 liquid (Vitaflora International Ltd)
130 ml (ACBS) - NHS indicative price = £6.80
PKU cooler®
Nutritional supplement for the dietary management of phenylketonuria in children over 3 years.
LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 10.2 g, energy 517 kJ (124 kcal)/174-mL pouch, with vitamins, minerals, and trace elements.
PKU orange cooler 20 liquid (Vitaflora International Ltd)
174 ml (ACBS) - NHS indicative price = £9.12
PKU purple cooler 20 liquid (Vitaflo International Ltd) 174 ml (ACBS) · NHS indicative price = £9.12
PKU red cooler 20 liquid (Vitaflo International Ltd) 174 ml (ACBS) · NHS indicative price = £9.12
PKU white cooler 20 liquid (Vitaflo International Ltd) 174 ml (ACBS) · NHS indicative price = £9.12
PKU express®
- Nutritional supplement for the dietary management of phenylketonuria. Not recommended for children under 3 years. POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 2.4 g, energy 295 kJ (70 kcal)/25 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.
PKU express 15 powder lemon (Vitaflo International Ltd) 750 gram (ACBS) · NHS indicative price = £200.00
PKU express 15 powder orange (Vitaflo International Ltd) 750 gram (ACBS) · NHS indicative price = £200.00
PKU express 15 powder tropical (Vitaflo International Ltd) 750 gram (ACBS) · NHS indicative price = £200.00
PKU express 15 powder unflavoured (Vitaflo International Ltd) 750 gram (ACBS) · NHS indicative price = £200.00
PKU express®
- Nutritional supplement for the dietary management of phenylketonuria. Not recommended for children under 3 years. POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 3.3 g, energy 389 kJ (93 kcal)/34 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.
PKU express 20 powder lemon (Vitaflo International Ltd) 1020 gram (ACBS) · NHS indicative price = £258.39
PKU express 20 powder orange (Vitaflo International Ltd) 1020 gram (ACBS) · NHS indicative price = £258.39
PKU express 20 powder tropical (Vitaflo International Ltd) 1020 gram (ACBS) · NHS indicative price = £258.39
PKU express 20 powder unflavoured (Vitaflo International Ltd) 1020 gram (ACBS) · NHS indicative price = £258.39
PKU gel®
- For use as part of the low-protein dietary management of phenylketonuria in children 1–10 years POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.9 g, fat less than 100 mg, energy 318 kJ (76 kcal)/24 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.
PKU gel powder lemon (Vitaflo International Ltd) 720 gram (ACBS) · NHS indicative price = £138.36
PKU gel powder orange (Vitaflo International Ltd) 720 gram (ACBS) · NHS indicative price = £138.36
PKU gel powder raspberry (Vitaflo International Ltd) 720 gram (ACBS) · NHS indicative price = £138.36
PKU gel powder unflavoured (Vitaflo International Ltd) 720 gram (ACBS) · NHS indicative price = £138.36
PKU Lophlex® LQ 20
- Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women. LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 8.8 g, fibre 340 mg, energy 490 kJ (115 kcal)/125 mL, with vitamins, minerals, and trace elements.
PKU Lophlex LQ 20 liquid berry (Nutricia Ltd) 125 ml (ACBS) · NHS indicative price = £10.47
PKU Lophlex LQ 20 liquid juicy berries (Nutricia Ltd) 125 ml (ACBS) · NHS indicative price = £10.47
PKU Lophlex LQ 20 liquid orange (Nutricia Ltd) 125 ml (ACBS) · NHS indicative price = £10.47
PKU Lophlex® Sensation 20
- Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women. SEMI-SOLID, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 20.2 g, fibre 1 g, energy 706 kJ (166 kcal)/109 g, with vitamins, minerals, and trace elements.
PKU Sensation 20 berries (Nutricia Ltd) 327 gram (ACBS) · NHS indicative price = £33.45
PKU Sensation 20 orange (Nutricia Ltd) 327 gram (ACBS) · NHS indicative price = £33.45
PKU squeeze®
- Nutritional supplement for the dietary management of phenylketonuria in children from 6 months to 10 years. LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 22.5 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements.
PKU squeeze liquid (Vitaflo International Ltd) 2550 gram (ACBS) · NHS indicative price = £132.27
PKU Maxamaid®
- Nutritional supplement for the dietary management of phenylketonuria in children 1–8 years. POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements.
PKU Maxamaid powder orange (Nutricia Ltd) 500 gram (ACBS) · NHS indicative price = £58.92
PKU Maxamaid powder unflavoured (Nutricia Ltd) 500 gram (ACBS) · NHS indicative price = £58.92
PKU Maxamum®
- Nutritional supplement for the dietary management of phenylketonuria in children over 8 years and adults. POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements.
PKU Maxamum oral powder 50g sachets orange (Nutricia Ltd) 30 sachet (ACBS) · NHS indicative price = £273.30
PKU Maxamum oral powder 50g sachets unflavoured (Nutricia Ltd) 30 sachet (ACBS) · NHS indicative price = £273.30
PKU Maxamum powder orange (Nutricia Ltd) 500 gram (ACBS) · NHS indicative price = £91.14
PKU Maxamum powder unflavoured (Nutricia Ltd) 500 gram (ACBS) · NHS indicative price = £91.14
Tyrosinaemia

Methionine-free TYR Anamix® Infant
- Nutritional supplement for the dietary management of proven tyrosinaemia type 1 in children from birth to 3 years.
POWDER, protein equivalent (essential and non-essential amino acids except methionine, phenylalanine, and tyrosine) 13.1 g, carbohydrate 49.5 g, fat 25 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.
TYR Anamix Infant methionine free powder (Nutricia Ltd)
- Nutritional supplement for the dietary management of proven tyrosinaemia where plasma-methionine concentrations are normal in children from birth to 3 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 13.1 g, carbohydrate 49.5 g, fat 25 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.
TYR Anamix Infant methionine free powder (Nutricia Ltd)
- Nutritional supplement for the dietary management of proven tyrosinaemia in children 1–10 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 8.4 g, carbohydrate 11 g, fat 3.9 g, energy 475 kJ (113 kcal)/29-g sachet, with vitamins, minerals, and trace elements.
TYR Anamix Junior oral powder 29g sachets (Nutricia Ltd)
- Nutritional supplement for the management of tyrosinaemia in children over 3 years and adults.
XPTM Tyrosidon powder (Vitaflo International Ltd)
- Nutritional supplement for the management of tyrosinaemia in children over 3 years and adults.
XPHEN TYR Tyrosidon Free AA Mix powder
- Nutritional supplement for the dietary management of tyrosinaemia in children 1–8 years.
TYR Maxamaid powder (Nutricia Ltd)
- Nutritional supplement for the dietary management of tyrosinaemia in children over 3 years and adults.
POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements.
TYR express20®
- Nutritional supplement for the dietary management of tyrosinaemia in children over 8 years.
POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.
TYR express 20 oral powder 34g sachets (Vitaflo International Ltd)
- Nutritional supplement for the dietary management of proven tyrosinaemia in children from birth to 3 years.
POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 10 g, carbohydrate 10.5 g, fat less than 100 mg, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements.
TYR Gel®
- Nutritional supplement for the dietary management of tyrosinaemia in children over 3 years and adults.
XPTM Tyrosidon
- Nutritional supplement for the dietary management of tyrosinaemia in children over 3 years and adults.
LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, fibre 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.
TYR Lophlex LQ 20 liquid (Nutricia Ltd)
- Nutritional supplement for the management of tyrosinaemia in children 1–8 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 509 kJ (119 kcal)/125 mL, with vitamins, minerals, and trace elements.
TYR Maxamaid®
- Nutritional supplement for the dietary management of tyrosinaemia in children 1–8 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 15 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.
XPHEN TYR Tyrosidon Free AA Mix powder
- Nutritional supplement for the dietary management of tyrosinaemia in children and adults where plasma-methionine concentrations are normal.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 10 g, carbohydrate 7 g, fat 500 mg, energy 395 kJ (92 kcal)/130 mL, with vitamins, minerals, and trace elements.
TYR express 15 oral powder 25g sachets (Vitaflo International Ltd)
- Nutritional supplement for the dietary management of proven tyrosinaemia in children 1–10 years.
POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 10 g, carbohydrate 10.5 g, fat less than 100 mg, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements.
TYR Lophlex LQ 20 oral powder (Nutricia Ltd)
- Nutritional supplement for the dietary management of tyrosinaemia in children 1–10 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, fibre 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.
TYR Maxamaid Powder (Nutricia Ltd)
- Nutritional supplement for the dietary management of proven tyrosinaemia in children 1–10 years.
POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 15 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.
TYR Maxamaid powder (Nutricia Ltd)
- Nutritional supplement for the dietary management of tyrosinaemia in children 1–10 years.
POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements.
TYR express 20 oral powder 34g sachets (Vitaflo International Ltd)
- Nutritional supplement for the dietary management of tyrosinaemia in children over 8 years.
POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1370.
TYR express 20 oral powder 34g sachets (Vitaflo International Ltd)
Appendix 3
Cautionary and advisory labels for dispensed medicines

Guidance for cautionary and advisory labels

Medicinal forms within BNF publications include code numbers of the cautionary labels that pharmacists are recommended to add when dispensing. It is also expected that pharmacists will counsel patients and carers when necessary.

Counselling needs to be related to the age, experience, background, and understanding of the individual patient or carer. The pharmacist should ensure understanding of how to take or use the medicine and how to follow the correct dosage schedule. Any effects of the medicine on co-ordination, performance of skilled tasks (e.g. driving or work), any foods or medicines to be avoided, and what to do if a dose is missed should also be explained. Other matters, such as the possibility of staining of the clothes or skin, or discolouration of urine or stools by a medicine should also be mentioned.

For some medicines there is a special need for counselling, such as an unusual method or time of administration or a potential interaction with a common food or domestic remedy, and this should be mentioned where necessary.

Original packs

Most preparations are dispensed in unbroken original packs that include further advice for the patient in the form of patient information leaflets. Label 10 may be of value where appropriate. More general leaflets advising on the administration of preparations such as eye drops, eye ointments, inhalers, and suppositories are also available.

Scope of labels

In general no label recommendations have been made for injections on the assumption that they will be administered by a healthcare professional or a well-instructed patient. The labelling is not exhaustive and pharmacists are recommended to use their professional discretion in labelling new preparations and those for which no labels are shown.

Individual labelling advice is not given on the administration of the large variety of antacids. In the absence of instructions from the prescriber, and if enquired the patient has had no verbal instructions, the directions given under ‘Dose’ should be used on the label.

It is recognised that there may be occasions when pharmacists will use their knowledge and professional discretion and decide to omit one or more of the recommended labels for a particular patient. In this case counselling is of the utmost importance. There may also be an occasion when a prescriber does not wish additional cautionary labels to be used, in which case the prescription should be endorsed ‘NCL’ (no cautionary labels). The exact wording that is required instead should then be specified on the prescription.

Pharmacists label medicines with various wordings in addition to those directions specified on the prescription. Such labels include ‘Shake the bottle’, ‘For external use only’, and ‘Store in a cool place’, as well as ‘Discard…. days after opening’ and ‘Do not use after….’, which apply particularly to antibiotic mixtures, diluted liquid and topical preparations, and to eye-drops. Although not listed in the BNF these labels should continue to be used when appropriate; indeed, ‘For external use only’ is a legal requirement on external liquid preparations, while ‘Keep out of the reach of children’ is a legal requirement on all dispensed medicines. Care should be taken not to obscure other relevant information with adhesive labelling.

It is the usual practice for patients to take standard tablets with water or other liquid and for this reason no separate label has been recommended.

The label wordings recommended by the BNF apply to medicines dispensed against a prescription. Patients should be aware that a dispensed medicine should never be taken by, or shared with, anyone other than for whom the prescriber intended it. Therefore, the BNF does not include warnings against the use of a dispensed medicine by persons other than for whom it was specifically prescribed.

The label or labels for each preparation are recommended after careful consideration of the information available. However, it is recognised that in some cases this information may be either incomplete or open to a different interpretation. The BNF will therefore be grateful to receive any constructive comments on the labelling suggested for any preparation.

Recommended label wordings

For BNF 61 (March 2011), a revised set of cautionary and advisory labels were introduced. All of the existing labels were user-tested, and the revised wording selected reflects terminology that is better understood by patients.

Wordings which can be given as separate warnings are labels 1-19, 29–30, and 32. Wordings which can be incorporated in an appropriate position in the directions for dosage or administration are labels 21–28. A label has been omitted for number 20; labels 31 and 33 no longer apply to any medicines in the BNF and have therefore been deleted.

If separate labels are used it is recommended that the wordings be used without modification. If changes are made to suit computer requirements, care should be taken to retain the sense of the original.

Welsh labels

Comprehensive Welsh translations are available for each cautionary and advisory label. These appear directly under the English label.

Labels

1 Warning: This medicine may make you sleepy

Rhybudd: Gall y feddyginiaeth hon eich gwneud yn gysglyd
To be used on preparations for children containing antihistamines, or other preparations given to children where the warnings of label 2 on driving or alcohol would not be appropriate.

2 Warning: This medicine may make you sleepy, if this happens, do not drive or use tools or machines. Do not drink alcohol

Rhybudd: Gall y feddyginiaeth hon eich gwneud yn gysglyd. Peidiwch â gyrru, defnyddio offer llaw neu beiriannau os yw hyn yn digwydd. Peidiwch ag yfed alcool
To be used on preparations for adults that can cause drowsiness, thereby affecting coordination and the ability to drive and operate hazardous machinery; label 1 is more appropriate for children. It is an offence to drive while under the influence of drink or drugs.

Some of these preparations only cause drowsiness in the first few days of treatment and some only cause drowsiness in higher doses.

In such cases the patient should be told that the advice applies until the effects have worn off. However many of these preparations can produce a slowing of reaction time and a loss of mental concentration that can have the same effects as drowsiness.

Avoidance of alcoholic drink is recommended because the effects of CNS depressants are enhanced by alcohol. Strict prohibition however could lead to some patients not taking...
the medicine. Pharmacists should therefore explain the risk and encourage compliance, particularly in patients who may think they already tolerate the effects of alcohol (see also label 5). Queries from patients with epilepsy regarding fitness to drive should be referred back to the patient’s doctor.

Side-effects unrelated to drowsiness that may affect a patient’s ability to drive or operate machinery safely include blurred vision, dizziness, or nausea. In general, no label has been recommended to cover these cases, but the patient should be suitably counselled.

3 Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines

Rhybudd: Gall y feddygyniaeth hon eich gwneud yn gysglyd. Peidiwch à gyrru, defnyddio offer llaw newi beirianuau os wv hyn yn digwyd

To be used on preparations containing monoamine-oxidase inhibitors; the warning to avoid alcohol and dealkoholised (low alcohol) drink is covered by the patient information leaflet.

Also to be used as for label 2 but where alcohol is not an issue.

4 Warning: Do not drink alcohol

Rhybudd: Peidiwch ag yfed alcohol

To be used on preparations where a reaction such as flushing may occur if alcohol is taken (e.g. metronidazole). Alcohol may also enhance the hypoglycaemia produced by some oral antidiabetic drugs but routine application of a warning label is not considered necessary.

Patients should be advised not to drink alcohol for as long as they are receiving/using a course of medication, and in some cases for a period of time after the course is finished.

5 Do not take indigestion remedies 2 hours before or after you take this medicine

Peidiwch à chymryd meddygyniaethau camdreffiai 2 awr neu ar ôl y feddygyniaeth hon

To be used with label 25 on preparations coated to resist gastric acid (e.g. enteric-coated tablets). This is to avoid the possibility of premature dissolution of the coating in the presence of an alkaline pH.

Label 5 also applies to drugs such as gabapentin where the absorption is significantly affected by antacids. Pharmacists will be aware (from a knowledge of physiology) that the usual time during which indigestion remedies should be avoided is at least 2 hours before and after the majority of medicines have been taken; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

6 Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine

Peidiwch à chymryd meddygyniaethau camdreffiai neu feddygyniaethau sy’n cynwys haearn neu sinc, 2 awr cyn neu ar ôl y feddygyniaeth hon

To be used on preparations containing ofoxacin and some other quinolones, doxycycline, lymecycline, minocycline, and penicillamine. These drugs chelate calcium, iron, and zinc and are less well absorbed when taken with calcium-containing antacids or preparations containing iron or zinc. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

7 Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine

Peidiwch à chymryd llæth, meddygyniaethau camdreffiai, neu feddygyniaeth sy’n cynwys haearn neu sinc, 2 awr cyn neu ar ôl cymryd y feddygyniaeth hon

To be used on preparations containing ciprofloxacin, norfloxacin, or tetracyclines that chelate calcium, iron, magnesium, and zinc, and are thus less available for absorption. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

Doxycycline, lymecycline, and minocycline are less liable to form chelates and therefore only require label 6 (see above).

8 Warning: Do not stop taking this medicine unless your doctor tells you to stop

Rhybudd: Peidiwch â stopio cymryd y feddygyniaeth hon, oni bai fod eich meddyg yn dweud wrthych am stopio

To be used on preparations that contain a drug which is required to be taken over long periods without the patient necessarily perceiving any benefit (e.g. antituberculous drugs). Also to be used on preparations that contain a drug whose withdrawal is likely to be a particular hazard (e.g. clonidine for hypertension). Label 10 (see below) is more appropriate for corticosteroids.

9 Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop

Gadewch yr un faint o amser rhwng pob dôs yn ystod y dydd. Parhewch i gyrru y feddygyniaeth hon bos b y cyfan wedi’i offen, oni bai eich bod yn cael cyngor i stopio

To be used on preparations where a course of treatment should be completed to reduce the incidence of relapse or failure of treatment.

The preparations are antimicrobial drugs given by mouth. Very occasionally, some may have severe side-effects (e.g. diarrhoea in patients receiving cindamycin) and in such cases the patient may need to be advised of reasons for stopping treatment quickly and returning to the doctor.

10 Warning: Read the additional information given with this medicine

Rhybudd: Darllenwch y wybodaeth ychwanegol gyda’r feddygyniaeth hon

To be used particularly on preparations containing anticoagulants, lithium, and oral corticosteroids. The appropriate treatment card should be given to the patient and any necessary explanations given.

This label may also be used on other preparations to remind the patient of the instructions that have been given.

11 Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds

Diogelwch eich croen rhag golau’r haul, hyd yn oed ar ddiwrnod braf ond cymylog. Peidiwch à defnyddio gwely haul

To be used on preparations that may cause photosxic or phototaergic reactions if the patient is exposed to ultraviolet radiation. Many drugs other than those listed in Appendix 3 (e.g. phenothiazines and sulphonamides) may, on rare occasions, cause reactions in susceptible patients. Exposure to high intensity ultraviolet radiation from sunray lamps and sunbeds is particularly likely to cause reactions.

12 Do not take anything containing aspirin while taking this medicine

Peidiwch â chymryd un rhwyb eth sy’n cynwys aspirin gyda’r feddygyniaeth hon

To be used on preparations containing sulfinpyrazone whose activity is reduced by aspirin.

Label 12 should not be used for anticoagulants since label 10 is more appropriate.

13 Dissolve or mix with water before taking

Gadewch i doddi mewn dwr cyn ei gymryd

To be used on preparations that are intended to be dissolved in water (e.g. soluble tablets) or mixed with water (e.g. powders, granules) before use. In a few cases other liquids such as fruit juice or milk may be used.
14 This medicine may cause irritation to your urine. This is harmless.

Gal y feddyginiæth hon liwio eich dŵr. Nid yw hyn yn arwydd o ddŵr.

To be used on preparations that may cause the patient’s urine to turn an unusual colour. These include triamterene (blue under some lights), levodopa (dark reddish), and rifampicin (red).

15 Caution: flammable. Keep your body away from fire or flames.

Rhybudd: Fflamadwy. Ar ôl rhoi’r feddyginiæth ymlaen, cadwch yn glir o dân neu fflamau.

To be used on preparations containing sufficient flammable solvent to render them flammable if exposed to a naked flame.

16 Dissolve the tablet under your tongue–do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening.

Rhowch y dabled i doddi dan eich tafod - peidiwch â i lyncu. Cadwch y tablidi yn y botel yma gyda’r caead wedi’i gau yn dynn. Gofynnwch am dabledi newydd 8 wythnos ar ôl el hagor.

To be used on glyceryl trinitrate tablets to remind the patient not to transfer the tablets to the plastic or less suitable containers.

17 Do not take more than... in 24 hours

Peidiwch â chymryd mwy na... mewn 24 awr

To be used on preparations for the treatment of acute migraine except those containing ergotamine, for which label 18 is used. The dose form should be specified, e.g. tablets or capsules.

It may also be used on preparations for which no dose has been specified by the prescriber.

18 Do not take more than... in 24 hours. Also, do not take more than... in any one week

Peidiwch â chymryd mwy na... mewn 24 awr. Hefyd, peidiwch â chymryd mwy na... mewn wythnos.

To be used on preparations containing ergotamine. The dose form should be specified, e.g. tablets or suppositories.

19 Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol.

Rhybudd: Bydd y feddyginiæth hon yn eich gwneud yn gysglyd. Os ydych yn da i dei’m o gysglyd drannoeith, peidiwch â gyrru, defnyddio offer llaw neu bei’ranau. Peidiwch agh yfed alcohol

To be used on preparations containing hypnotics (or some other drugs with sedative effects) prescribed to be taken at night. On the rare occasions when hypnotics are prescribed for daytime administration (e.g. nitrazepam in epilepsy), this label would clearly not be appropriate. Also to be used as an alternative to the label 2 wording (the choice being at the discretion of the pharmacist) for anxiolytics prescribed to be taken at night.

It is hoped that this wording will convey adequately the problem of residual morning sedation after taking ‘sleeping tablets’.

20 Take with or just after food, or a meal

Cymerwch gyda neu ar ôl bwyd

To be used on preparations that are liable to cause gastric irritation, or those that are better absorbed with food.

Patients should be advised that a small amount of food is sufficient.

21 Take 30 to 60 minutes before food

Cymerwch 30 i 60 munud cyn bwyd

To be used on some preparations whose absorption is thereby improved.

Most oral antibacterials require label 23 instead (see below).

22 Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food

Cymerwch y feddyginiæth hon ar stumog wag. Mae hyn yn golygu awr cyn, neu 2 awr ar ôl bwyd

To be used on oral antibacterials whose absorption may be reduced by the presence of food and acid in the stomach.

24 Suck or chew this medicine

Bydd angen cooi neu sugno’r feddyginiæth hon

To be used on preparations that should be sucked or chewed.

The pharmacist should use discretion as to which of these words is appropriate.

25 Swallow this medicine whole. Do not chew or crush

Llynchwch yn gyfan. Peidiwch â choi neu fal’u fân.

To be used on preparations that are enteric-coated or designed for modified-release.

Also to be used on preparations that taste very unpleasant or may damage the mouth if not swallowed whole.

Patients should be advised (where relevant) that some modified-release preparations can be broken in half, but that the halved tablet should still be swallowed whole, and not chewed or crushed.

26 Dissolve this medicine under your tongue

Gadewch i’r feddyginiæth hon doddi o dan y tafod

To be used on preparations designed for sublingual use.

Patients should be advised to hold under the tongue and avoid swallowing until dissolved. The buccal mucosa between the gum and cheek is occasionally specified by the prescriber.

27 Take with a full glass of water

Cymerwch gyda llond gwydr o ddŵr

To be used on preparations that should be well diluted (e.g. chloral hydrate), where a high fluid intake is required (e.g. sulfonamides), or where water is required to aid the action (e.g. methylcellulose). The patient should be advised that ‘a full glass’ means at least 150 mL. In most cases fruit juice, tea, or coffee may be used.

28 Spread thinly on the affected skin only

Taenwch yn demau ar y croen sydd wedi’i efethio yn unig

To be used on external preparations that should be applied sparingly (e.g. corticosteroids, dithranol).

29 Do not take more than 2 at any one time. Do not take more than 8 in 24 hours

Peidiwch â chymryd mwy na 2 ar unrhyw un adeg. Peidiwch â chymryd mwy nag 8 mewn 24 awr

To be used on containers of dispensed solid dose preparations containing paracetamol for adults when the instruction on the label indicates that the dose can be taken on an ‘as required’ basis. The dose form should be specified, e.g. tablets or capsules.

This label has been introduced because of the serious consequences of overdosage with paracetamol.

30 Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well

Yn cynnwys paracetamol. Peidiwch â chymryd unrhyw beth arall sy’n cynnwys paracetamol tra’n cymryd y feddyginiæth hon. Siaradwch gyda’ch meddyg ar unwaith os ydych yn cymryd gormod, hyd yn oed os ydych yn teimlo’n iawn

To be used on all containers of dispensed preparations containing paracetamol.

32 Contains aspirin. Do not take anything else containing aspirin while taking this medicine

Yn cynnwys aspirin. Peidiwch â chymryd unrhyw beth arall sy’n cynnwys aspirin tra’n cymryd y feddyginiæth hon

To be used on all containers of dispensed preparations containing aspirin when the name on the label does not include the word ‘aspirin’.
Appendix 4
Wound management products and elasticated garments

The correct dressing for wound management depends not only on the type of wound but also on the stage of the healing process. The principal stages of healing are: cleansing, removal of debris; granulation, vascularisation; epithelialisation. The ideal dressing for moist wound healing needs to ensure that the wound remains: moist with exudate, but not macerated; free of clinical infection and excessive slough; free of toxic chemicals, particles or fibres; at the optimum temperature for healing; undisturbed by the need for frequent changes; at the optimum pH value. As wound healing passes through its different stages, different types of dressings may be required to satisfy better one or other of these requirements. Under normal circumstances, a moist environment is a necessary part of the wound healing process; exudate provides a moist environment and promotes healing, but excessive exudate can cause maceration of the wound and surrounding healthy tissue. The volume and viscosity of exudate changes as the wound heals. There are certain circumstances where moist wound healing is not appropriate (e.g. gangrenous toes associated with vascular disease).

Advanced wound dressings are designed to control the environment for wound healing, for example to donate fluid (hydrogels), maintain hydration (hydrocolloids), or to absorb wound exudate (alginates, foams).

Practices such as the use of irritant cleansers and desloughing agents may be harmful and are largely obsolete; removal of debris and dressing remnants should need minimal irrigation with lukewarm sterile sodium chloride 0.9% solution or water.

Hydrogel, hydrocolloid, and medical grade honey dressings can be used to deslough wounds by promoting autolytic debridement; there is insufficient evidence to support any particular method of debridement for difficult-to-heal surgical wounds. Sterile larvae (maggots) are also available for biosurgical removal of wound debris. There have been few clinical trials able to establish a clear advantage for any particular product. The choice between different dressings depends not only on the type and stage of the wound, but also on patient preference or tolerance, site of the wound, and cost. For further information, see Buyers' Guide: Advanced wound dressings (October 2008); NHS Purchasing and Supply Agency, Centre for Evidence-based Purchasing.

Prices quoted in Appendix 4 are basic NHS net prices; for further information see Prices in the BNF under How to use the BNF.

The table below gives suggestions for choices of primary dressing depending on the type of wound (a secondary dressing may be needed in some cases).

### Basic wound contact dressings

#### Low adherence dressing

Low adherence dressings are used as interface layers under secondary absorbent dressings. Placed directly on the wound bed, non-absorbent, low adherence dressings are suitable for clean, granulating, lightly exuding wounds without necrosis, and protect the wound bed from direct contact with secondary dressings. Care must be taken to avoid granulation tissue growing into the weave of these dressings.
Wound contact material for different types of wounds

### Wound PINK (epithelasing)

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence p. 1386</td>
<td>Soft polymer p. 1392</td>
</tr>
<tr>
<td>Vapour-permeable film p. 1390</td>
<td>Foam, low absorbent p. 1394</td>
</tr>
<tr>
<td>Soft polymer p. 1392</td>
<td>Alginate p. 1396</td>
</tr>
<tr>
<td>Hydrocolloid p. 1393</td>
<td></td>
</tr>
</tbody>
</table>

### Wound RED (granulating)

Symptoms or signs of infection, see Wounds with signs of infection

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence p. 1386</td>
<td>Hydrocolloid-fibrous p. 1393</td>
<td>Foam with extra absorbency p. 1394</td>
</tr>
<tr>
<td>Soft polymer p. 1392</td>
<td>Foam p. 1394</td>
<td>Hydrocolloid-fibrous p. 1393</td>
</tr>
<tr>
<td>Hydrocolloid p. 1393</td>
<td>Alginate p. 1396</td>
<td>Alginate p. 1396</td>
</tr>
<tr>
<td>Foam, low absorbent p. 1394</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Wound YELLOW (Sloughy) (granulating)

Symptoms or signs of infection, see Wounds with signs of infection

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel p. 1389</td>
<td>Hydrocolloid-fibrous p. 1393</td>
<td>Hydrocolloid-fibrous p. 1393</td>
</tr>
<tr>
<td>Hydrocolloid p. 1393</td>
<td>Alginate p. 1396</td>
<td>Alginate p. 1396</td>
</tr>
<tr>
<td></td>
<td>Foam p. 1394</td>
<td>Capillary-action p. 1397</td>
</tr>
</tbody>
</table>

### Wound BLACK (Necrotic/ Eschar)

Consider mechanical debridement alongside autolytic debridement

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel p. 1389</td>
<td>Hydrocolloid p. 1393</td>
<td>Seek advice from wound care specialist</td>
</tr>
<tr>
<td>Hydrocolloid p. 1393</td>
<td>Hydrocolloid-fibrous p. 1393</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foam p. 1394</td>
<td></td>
</tr>
</tbody>
</table>

### Wounds with signs of infection

Consider systemic antibacterials if appropriate; also consider odour-absorbent dressings. For malodourous wounds with slough or necrotic tissue, consider mechanical or autolytic debridement

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence with honey p. 1397</td>
<td>Hydrocolloid-fibrous with silver p. 1400</td>
<td>Hydrocolloid-fibrous with silver p. 1400</td>
</tr>
<tr>
<td>Low adherence with iodine p. 1398</td>
<td>Foam with silver p. 1399</td>
<td>Foam extra absorbent, with silver p. 1399</td>
</tr>
<tr>
<td>Low adherence with silver p. 1399</td>
<td>Alginate with silver p. 1399</td>
<td>Alginate with honey p. 1398</td>
</tr>
<tr>
<td>Hydrocolloid with silver p.1400</td>
<td>Honey-topical p. 1397</td>
<td>Alginate with silver p. 1399</td>
</tr>
<tr>
<td>Honey-topical p. 1397</td>
<td>Cadexomer-iodine p. 1398</td>
<td></td>
</tr>
</tbody>
</table>

Note: In each section of this table the dressings are listed in order of increasing absorbency. Some wound contact (primary) dressings require a secondary dressing.

Tulle dressings are manufactured from cotton or viscose fibres which are impregnated with white or yellow soft paraffin to prevent the fibres from sticking, but this is only partly successful and it may be necessary to change the dressings frequently. The paraffin reduces absorbency of the dressing. Dressings with a reduced content (light loading) of soft paraffin are less liable to interfere with absorption; dressings with ‘normal loading’ (such as Jelonet®) have been used for skin graft transfer. Knitted viscose primary dressing is an alternative to tulle dressings for exuding wounds; it can be used as the initial layer of multi-layer compression bandaging in the treatment of venous leg ulcers.

**Knitted polyester primary dressing**

**Atrauman**

Non-adherent knitted polyester primary dressing impregnated with neutral triglycerides

**Atrauman dressing** (Paul Hartmann Ltd) 10cm × 20cm = £0.63, 20cm × 30cm = £1.74, 5cm × 5cm = £0.27, 7.5cm × 10cm = £0.28

**Knitted viscose primary dressing**

**N-A Dressing**

Warp knitted fabric manufactured from a bright viscose monofilament.

**N-A dressing** (Systagenix Wound Management Ltd) 19cm × 9.5cm = £0.67, 9.5cm × 9.5cm = £0.35

**N-A Ultra**

Warp knitted fabric manufactured from a bright viscose monofilament.

**N-A Ultra dressing** (Systagenix Wound Management Ltd) 19cm × 9.5cm = £0.63, 9.5cm × 9.5cm = £0.33

**Profore**

Warp knitted fabric manufactured from a bright viscose monofilament.

**Profore** (Smith & Nephew Healthcare Ltd) wound contact layer 14cm × 20cm = £0.32

**Tricotex**

Warp knitted fabric manufactured from a bright viscose monofilament.

**Tricotex dressing** (Smith & Nephew Healthcare Ltd) 9.5cm × 9.5cm = £0.34

**Paraffin Gauze Dressing**

**Cuticell**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading

**Cuticell** (BSN medical Ltd) classic dressing 10cm × 10cm = £0.29

**Jelonet**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading

**Jelonet dressing** (Smith & Nephew Healthcare Ltd) 10cm × 10cm = £0.41
Neotulle
(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading

Paragauze
(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading

Paranet
(C D Medical Ltd) dressing 10cm × 10cm= £0.28

Absorbent dressings
Perforated film absorbent dressings are suitable only for wounds with mild to moderate amounts of exudate; they are not appropriate for leg ulcers or for other lesions that produce large quantities of viscous exudate. Dressings with an absorbent cellulose or polymer wadding layer are suitable for use on moderately to heavily exuding wounds.

Absorbent cellulose dressing

CelluDress
Absorbent Cellulose Dressing with Fluid Repellent Backing

CelluDress dressing (Medicareplus International Ltd) 10cm × 10cm = £0.19, 10cm × 15cm = £0.20, 10cm × 20cm = £0.22, 15cm × 20cm = £0.30, 20cm × 25cm = £0.40, 20cm × 30cm = £0.85

Eclipse
Absorbent Cellulose Dressing with Fluid Repellent Backing

Eclipse dressing (Advanced Medical) Boot dressing 60cm × 70cm= £13.78, dressing 15cm × 15cm = £0.97, 20cm × 30cm = £2.14, 60cm × 40cm= £8.15

Exu-Dry
Absorbent Cellulose Dressing with Fluid Repellent Backing

Exu-Dry dressing (Smith & Nephew Healthcare Ltd) 10cm × 15cm= £1.14, 15cm × 23cm= £2.32, 23cm × 38cm= £5.40

Mesorb
Cellulose wadding pad with gauze wound contact layer and non-woven repellent backing

Mesorb dressing (Möhlycke Health Care Ltd) 10cm × 10cm= £0.62, 10cm × 15cm= £0.81, 10cm × 20cm= £1.00, 15cm × 20cm= £1.43, 20cm × 25cm= £2.25, 20cm × 30cm= £2.55

Telfa Max
Absorbent Cellulose Dressing with Fluid Repellent Backing

Zetuv E
Absorbent Cellulose Dressing with Fluid Repellent Backing; sterile or non-sterile

Zetuv E (Paul Hartmann Ltd) non-sterile dressing 10cm × 10cm= £0.07, 10cm × 20cm= £0.09, 20cm × 20cm= £0.14, 20cm × 40cm= £0.28, sterile dressing 10cm × 10cm= £0.21, 10cm × 20cm= £0.25, 20cm × 20cm= £0.39, 20cm × 40cm= £1.11

Absorbent perforated dressing

Adpore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Adpore dressing (Medicareplus International Ltd) 10cm × 10cm= £0.10, 10cm × 15cm= £0.16, 10cm × 20cm= £0.30, 10cm × 25cm= £0.34, 10cm × 30cm= £0.42, 10cm × 35cm= £0.50, 7cm × 8cm= £0.08

Cosmopore E
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border

Cosmopore E dressing (Paul Hartmann Ltd) 10cm × 20cm= £0.46, 10cm × 25cm= £0.56, 10cm × 35cm= £0.78, 5cm × 7.2cm = £0.08, 8cm × 10cm= £0.18, 8cm × 15cm= £0.28

Cutiplast Steril
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Cutiplast Steril dressing (Smith & Nephew Healthcare Ltd) 10cm × 20cm= £0.31, 10cm × 25cm= £0.32, 10cm × 30cm= £0.43, 8cm × 10cm= £0.11, 8cm × 15cm= £0.25

Leukomed
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Leukomed dressing (BSH medical Ltd) 10cm × 20cm= £0.43, 10cm × 25cm= £0.49, 10cm × 30cm= £0.63, 10cm × 35cm= £0.72, 5cm × 7.2cm= £0.09, 8cm × 10cm= £0.18, 8cm × 15cm= £0.32

Medipore + Pad
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Medipore + Pads dressing (3M Health Care Ltd) 10cm × 10cm= £0.15, 10cm × 15cm= £0.25, 10cm × 20cm= £0.37, 10cm × 25cm= £0.46, 10cm × 35cm= £0.64, 5cm × 7.2cm= £0.07

Medisafe
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Medisafe dressing (Neomedic Ltd) 6cm × 8cm= £0.08, 8cm × 10cm= £0.13, 8cm × 12cm= £0.23, 9cm × 15cm= £0.29, 9cm × 20cm= £0.34, 9cm × 25cm= £0.36

Mepore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Mepore dressing (Mohlycke Health Care Ltd) 10cm × 11cm= £0.22, 11cm × 15cm= £0.38, 7cm × 8cm= £0.11, 8cm × 20cm= £0.44, 9cm × 25cm= £0.61, 9cm × 30cm= £0.70, 9cm × 35cm= £0.76

PremierPore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

PremierPore dressing (Sherwood) 10cm × 10cm= £0.12, 10cm × 15cm= £0.18, 10cm × 20cm= £0.32, 10cm × 25cm= £0.36, 10cm × 30cm= £0.45, 10cm × 35cm= £0.52, 5cm × 7cm= £0.05

Primapore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Primapore dressing (Smith & Nephew Healthcare Ltd) 10cm × 20cm= £0.44, 10cm × 25cm= £0.50, 10cm × 30cm= £0.63, 10cm × 35cm= £0.97, 6cm × 8.3cm= £0.18, 8cm × 10cm= £0.19, 8cm × 15cm= £0.34

Softpore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Softpore dressing (Richardson Healthcare Ltd) 10cm × 10cm= £0.13, 10cm × 15cm= £0.20, 10cm × 20cm= £0.35, 10cm × 25cm= £0.40, 10cm × 30cm= £0.49, 10cm × 35cm= £0.56, 6cm × 7cm= £0.06

Sterifix
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Telfa Island
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border.

Telfa Island dressing (Aria Medical Ltd) 10cm × 12.5cm= £0.27, 10cm × 20cm= £0.35, 10cm × 25cm= £0.45, 10cm × 35cm= £0.62, 5cm × 10cm= £0.08

Absorbent perforated plastic film faced dressing

Absopad
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Absopad dressing (Medicareplus International Ltd) 10cm × 10cm= £0.13, 20cm × 10cm= £0.28

Askina Pad
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Askina (B.Braun Medical Ltd) Pad dressing 10cm × 10cm= £0.21
Cutisorb LA
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Interpose
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Melolin
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Melolin dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm = £0.28, 20cm × 10cm = £0.54, 5cm × 5cm = £0.17

Skintact
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Skintact dressing (Robinson Healthcare) 10cm × 10cm = £0.17, 20cm × 10cm = £0.34, 5cm × 5cm = £0.10

Solvaline N
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Solvaline N dressing (Lohmann & Rauscher (UK) Ltd) 10cm × 10cm = £0.18, 20cm × 10cm = £0.36, 5cm × 5cm = £0.10

Telfa
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing.

Telfa dressing (Aria Medical Ltd) 10cm × 7.5cm = £0.16, 15cm × 7.5cm = £0.18, 20cm × 7.5cm = £0.29, 7.5cm × 5cm = £0.12

Super absorbent cellulose and polymer primary dressing

Curea P1
Super absorbent cellulose and polymer primary dressing.

Curea P1 dressing (Charles S. Bullen Stomacare Ltd) 10cm × 10cm square= £2.15, 10cm × 20cm rectangular= £3.64, 10cm × 30cm rectangular= £5.20, 12cm × 12cm square= £2.65, 20cm × 20cm square= £6.89, 20cm × 30cm rectangular= £10.03, 7.5cm × 7.5cm square= £1.72

Curea P2
Super absorbent cellulose and polymer primary dressing (non-adherent)

Curea P2 dressing (Charles S. Bullen Stomacare Ltd) 10cm × 20cm rectangular= £4.49, 11cm × 11cm square= £2.47, 20cm × 20cm square= £7.82, 20cm × 30cm rectangular= £10.60

Cutisorb Ultra
Super absorbent cellulose and polymer primary dressing

Cutisorb Ultra dressing (BSN medical Ltd) 10cm × 10cm square= £2.13, 10cm × 20cm rectangular= £3.56, 20cm × 20cm square= £6.68, 20cm × 30cm rectangular= £10.06

DryMax Extra
Super absorbent cellulose and polymer primary dressing

DryMax Extra dressing (Aspen Medical Europe Ltd) 10cm × 10cm square= £0.67, 20cm × 20cm rectangular= £1.04, 20cm × 30cm rectangular= £1.84, 20cm × 30cm rectangular= £2.33

ELECT Superabsorber
Super absorbent cellulose and polymer primary dressing

ELECT Superabsorber dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square= £0.96, 10cm × 20cm rectangular= £1.13, 20cm × 20cm square= £2.01, 20cm × 30cm rectangular= £2.54

Zetuvit Plus
Super absorbent cellulose primary dressing

Zetuvit Plus dressing (Paul Hartmann Ltd) 10cm × 10cm= £0.64, 10cm × 20cm= £0.88, 15cm × 20cm= £1.01, 20cm × 25cm= £1.38, 20cm × 40cm= £2.13

Super absorbent hydroconductive dressing

Drawtex
Super absorbent hydroconductive dressing with absorbent, cross-action structures of viscose, polyester and cotton

Drawtex dressing (Martindale Pharmaceuticals Ltd) 10cm × 1.3m= £16.00, 10cm × 10cm= £22.24, 10cm × 1m= £16.00, 15cm × 20cm= £6.00, 20cm × 20cm × 1m= £25.00, 20cm × 20cm= £6.98, 5cm × 5cm= £0.95, 7.5cm × 1m= £15.50, 7.5cm × 7.5cm= £1.77

Advanced wound dressings

Advanced wound dressings can be used for both acute and chronic wounds. Categories for dressings in this section start with the least absorptive, moisture-donating hydrogel dressings, followed by increasingly more absorptive dressings. These dressings are classified according to their primary component; some dressings are comprised of several components.

Hydrogel dressings

Hydrogel dressings are most commonly supplied as an amorphous, cohesive topical application that can take up the shape of a wound. A secondary, non-absorbent dressing is needed. These dressings are generally used to donate liquid to dry sluggly wounds and facilitate autolytic debridement of necrotic tissue; some also have the ability to absorb very small amounts of exudate. Hydrogel products that do not contain propylene glycol should be used if the wound is to be treated with larval therapy. Hydrogel sheets have a fixed structure and limited fluid-handling capacity; hydrogel sheet dressings are best avoided in the presence of infection, and are unsuitable for heavily exuding wounds.

Hydrogel application (amorphous)

ActivHeal Hydrgel
Hydrogel containing guar gum and propylene glycol

ActivHeal (Advanced Medical Solutions Ltd) Hydrogel dressing= £1.41

Aquaform
Hydrogel containing modified starch copolymer

AquaForm (Aspen Medical Europe Ltd) Hydrogel dressing= £2.02

Askina Gel
Hydrogel containing modified starch and glycerol

Askina (B.Braun Medical Ltd) Gel dressing= £2.01

Cutimed
Hydrogel

Cutimed (BSN medical Ltd) Gel dressing= £3.02

Flexigran
Hydrogel containing modified starch and glycerol

Flexigran (A1 Pharmaceuticals) Gel dressing= £1.90

GranuGel
Hydrogel containing carboxymethylcellulose, pectin and propylene glycol

GranuGel (Convatec Ltd) Hydrocolloid Gel dressing= £2.35

Intrasite Gel
Hydrogel containing modified carmellose polymer and propylene glycol

IntraSite (Smith & Nephew Healthcare Ltd) Gel dressing= £3.63

Nu-Gel
Hydrogel containing alginate and propylene glycol

Nu-Gel (Systagenix Wound Management Ltd) Gel dressing= £2.09

Purilon Gel
Hydrogel containing carboxymethylcellulose and calcium alginate

Purilon (Coloplast Ltd) Gel dressing= £2.30

Hydrogel sheet dressings

ActiFormCool
Hydrogel dressing

ActiFormCool sheet (Activa Healthcare Ltd) 10cm × 10cm square= £2.66, 10cm × 15cm rectangular= £3.83, 20cm × 20cm square= £8.01, 5cm × 6.5cm rectangular= £1.81

Aquaflo
Hydrogel dressing

Aquaflo (Covidien (UK) Commercial Ltd) sheet 7.5cm discs= £2.60

Coolie
Hydrogel dressing (without adhesive border)

Coolie (Zeroderma Ltd) sheet 7cm discs= £1.96
Gel FX
Hydrogel dressing (without adhesive border)
Gel FX sheet (Synergy Health Plc) 10cm × 10cm square= £1.60, 5cm × 15cm square= £3.20

Geliperm
Hydrogel sheets
Geliperm (Geistlich Sons Ltd) sheet 10cm × 10cm square= £2.53

Hydrosorb
Absorbs, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film
Hydrosorb sheet (Paul Hartmann Ltd) 10cm × 10cm square= £2.26, 20cm × 20cm square= £6.77, 5cm × 7.5cm rectangular= £1.58

Hydrosorb Comfort
Absorbs, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film (with adhesive, waterproof)
Hydrosorb Comfort sheet (Paul Hartmann Ltd) 12.5cm × 12.5cm square= £3.61, 4.5cm × 6.5cm rectangular= £1.87, 7.5cm × 10cm rectangular= £2.48

Intrasite Conformable
Soft non-woven dressing impregnated with Intrasite® gel
IntraSite Conformable dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square= £1.82, 10cm × 20cm rectangular= £2.46, 40cm × 40cm rectangular= £4.40

Novogel
Glycerol-based hydrogel sheets (standard or thin)
Novogel sheet (Ford Medical Associates Ltd) 10cm × 10cm square= £3.18, 15cm × 20cm rectangular= £6.07, 20cm × 40cm rectangular= £11.56, 30cm × 30cm (0.15cm thickness) square= £12.71, (0.30cm thickness) square= £13.47, 5cm × 7.5cm rectangular= £1.99, 7.5cm diameter circular= £2.89

SanoSkin NET
Hydrogel sheet (without adhesive border)
SanoSkin (Ideal Medical Solutions Ltd) NET sheet 8.5cm × 12cm rectangular= £2.28

Vacunet
Non-adherent, hydrogel coated polyester net dressing
Vacunet dressing (Protex Healthcare Ltd) 10cm × 10cm square= £1.93, 10cm × 15cm rectangular= £2.86

Sodium hyaluronate dressings
The hydrating properties of sodium hyaluronate promote wound healing, and dressings can be applied directly to the wound, or to a primary dressing (a secondary dressing should also be applied). The iodine and potassium iodide in these dressings prevent the bacterial decay of sodium hyaluronate in the wound. Hyiodine® should be used with caution in thyroid disorders.

Hyiodine
Sodium hyaluronate 1.5%, potassium iodide 0.15%, iodine 0.1%, in a viscous solution
Hyiodine (H & R Healthcare Ltd) dressing= £35.00

Vapour-permeable films and membranes
Vapour-permeable films and membranes allow the passage of water vapour and oxygen but are impermeable to water and micro-organisms, and are suitable for lightly exuding wounds. They are highly conformable, provide protection, and moisten healing environments; transparent film dressings permit constant observation of the wound. Water vapour loss can occur at a slower rate than exudate is generated, so that fluid accumulates under the dressing, which can lead to tissue maceration and to wrinkling at the adhesive contact site (with risk of bacterial entry). Newer versions of these dressings have increased moisture vapour permeability. Despite these advances, vapour-permeable films and membranes are unsuitable for infected, large heavily exuding wounds, and chronic leg ulcers. Vapour-permeable films and membranes are suitable for partial-thickness wounds with minimal exudate, or wounds with eschar. Most commonly, they are used as a secondary dressing over alginates or hydrogels; film dressings can also be used to protect the fragile skin of patients at risk of developing minor skin damage caused by friction or pressure.

Non-woven fabric dressing with viscose-rayon pad.

Niko Fix
For intravascular and subcutaneous catheter sites
Niko (Unomedical Ltd) Fix dressing 7cm × 8.5cm= £0.19

Vapour-permeable Adhesive Film Dressing (Semi-permeable Adhesive Dressing)
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

Askina Derm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Askina Derm dressing (B.Braun Medical Ltd) 10cm × 12cm= £1.08, 10cm × 20cm= £2.06, 15cm × 20cm= £2.50, 20cm × 30cm= £4.46, 6cm × 7cm= £0.37

C-View
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
C-View dressing (Aspen Medical Europe Ltd) 10cm × 12cm= £1.02, 12cm × 12cm= £1.09, 15cm × 20cm= £2.36, 6cm × 7cm= £0.38

Dressfilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Dressfilm (St Georges Medical Ltd) dressing 15cm × 20cm= £1.90

Hydrofilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Hydrofilm dressing (Paul Hartmann Ltd) 10cm × 12.5cm= £0.42, 10cm × 15cm= £0.53, 10cm × 25cm= £0.82, 12cm × 25cm= £0.87, 15cm × 20cm= £0.97, 20cm × 30cm= £1.61, 6cm × 7cm= £0.23

Hyfapix Transparent
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Hyfapix Transparent (BSN medical Ltd) dressing 10cm × 2m= £8.79

Leukomed T
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Leukomed T dressing (BSN medical Ltd) 10cm × 12.5cm= £1.02, 11cm × 14cm= £1.24, 15cm × 20cm= £2.37, 15cm × 25cm= £2.53, 7.2cm × 5cm= £0.38, 8cm × 10cm= £0.70

Mepitel Film
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Mepitel Film dressing (Mohlycke Health Care Ltd) 10.5cm × 12cm= £1.31, 10.5cm × 25cm= £2.55, 15.5cm × 20cm= £3.24, 6.5cm × 7cm= £0.49

Mepore Film
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Mepore Film dressing (Mohlycke Health Care Ltd) 10cm × 12cm= £1.23, 10cm × 25cm= £2.39, 15cm × 20cm= £3.04, 6cm × 7cm= £0.46

OpSite Flexifix
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
OpSite Flexifix dressing (Smith & Nephew Healthcare Ltd) 10cm × 1m= £6.67, 5cm × 1m= £3.95
OpSite Flexgrid
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

OpSite Flexgrid dressing (Smith & Nephew Healthcare Ltd) 12cm x 12cm = £1.14, 15cm x 20cm = £2.88, 6cm x 7cm = £0.40

Polyskin II
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Kendall Film dressing (Aria Medical Ltd) 10cm x 12cm = £1.03, 10cm x 20cm = £2.04, 15cm x 20cm = £2.35, 20cm x 25cm = £4.11, 4cm x 4cm = £0.36, 5cm x 7cm = £0.40

ProtectFilm
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

ProtectFilm dressing (Wallace, Cameron & Company Ltd) 10cm x 12cm = £0.20, 15cm x 20cm = £0.40, 6cm x 7cm = £0.11

Suprasorb F
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Suprasorb F dressing (Lohmann & Rauscher (UK) Ltd) 10cm x 12cm = £0.81, 15cm x 20cm = £2.52, 5cm x 7cm = £0.34

Tegaderm
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Tegaderm Film dressing (3M Health Care Ltd) 12cm x 12cm = £1.11, 15cm x 20cm = £2.41, 6cm x 7cm = £0.39

Tegaderm Diamond
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Tegaderm Diamond dressing (3M Health Care Ltd) 10cm x 12cm = £1.21, 6cm x 7cm = £0.45

Vellafilm
Exttensible, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Vellafilm dressing (Advancis Medical) 12cm x 12cm = £1.10, 12cm x 35cm = £2.75, 15cm x 20cm = £2.10

Vapour-permeable Adhesive Film Dressing with absorbent pad

Adpore Ultra
Film dressing with absorbent pad
Adpore Ultra dressing (Medicareplus International Ltd) 10cm x 10cm = £0.14, 10cm x 15cm = £0.22, 10cm x 20cm = £0.33, 10cm x 25cm = £0.35, 10cm x 30cm = £0.52, 7cm x 8cm = £0.12

Vapour-permeable Adhesive Film Dressing with absorbent pad

Alldress
Film dressing with absorbent pad
Alldress dressing (Molynlycke Health Care Ltd) 10cm x 10cm = £0.96, 15cm x 15cm = £2.10, 15cm x 20cm = £2.59

C-View Post-Op
Film dressing with absorbent pad
C-View Post-Op dressing (Aspen Medical Europe Ltd) 10cm x 12cm = £1.10, 10cm x 25cm = £1.60, 10cm x 35cm = £2.60, 6cm x 7cm = £0.40

Clearpore
Film dressing with absorbent pad
Clearpore dressing (Richardson Healthcare Ltd) 10cm x 10cm = £0.20, 10cm x 15cm = £0.24, 10cm x 20cm = £0.36, 10cm x 25cm = £0.40, 10cm x 30cm = £0.65, 6cm x 10cm = £0.15, 6cm x 7cm = £0.12

Hydrofilm Plus
Film dressing with absorbent pad
Hydrofilm Plus dressing (Paul Hartmann Ltd) 10cm x 20cm = £0.46, 10cm x 25cm = £0.61, 10cm x 30cm = £0.69, 7.2cm x 5cm = £0.18, 9cm x 10cm = £0.27, 9cm x 15cm = £0.30

Leukomed T Plus
Film dressing with absorbent pad
Leukomed T Plus dressing (BSN medical Ltd) 10cm x 20cm = £1.35, 10cm x 25cm = £1.51, 10cm x 30cm = £2.53, 10cm x 35cm = £3.07, 7.2cm x 5cm = £0.27, 8cm x 10cm = £0.54, 8cm x 15cm = £0.81

Mepore Film & Pad
Film dressing with absorbent pad
Mepore Film & Pad dressing (Molynlycke Health Care Ltd) 4cm x 5cm = £0.24, 5cm x 7cm = £0.24, 9cm x 10cm = £0.62, 9cm x 15cm = £0.92, 9cm x 20cm = £1.36, 9cm x 25cm = £1.50, 9cm x 30cm = £2.01, 9cm x 35cm = £2.50

Mepore Ultra
Film dressing with absorbent pad
Mepore Ultra dressing (Molynlycke Health Care Ltd) 10cm x 11cm = £0.80, 11cm x 15cm = £1.18, 7cm x 8cm = £0.40, 9cm x 20cm = £1.51, 9cm x 25cm = £1.67, 9cm x 30cm = £2.75

OpSite Plus
Film dressing with absorbent pad
OpSite Plus dressing (Smith & Nephew Healthcare Ltd) 10cm x 12cm = £1.21, 10cm x 20cm = £2.04, 10cm x 35cm = £3.38, 6.5cm x 5cm = £0.32, 8.5cm x 9.5cm = £0.89

OpSite Post-op
Film dressing with absorbent pad
OpSite Post-Op dressing (Smith & Nephew Healthcare Ltd) 10cm x 12cm = £1.19, 10cm x 20cm = £2.00, 10cm x 25cm = £2.52, 10cm x 30cm = £2.98, 10cm x 35cm = £3.32, 8.5cm x 15.5cm = £1.21, 8.5cm x 9.5cm = £0.87

Pharmapore-PU
Film dressing with absorbent pad
Pharmapore-PU dressing (Wallace, Cameron & Company Ltd) 10cm x 25cm = £0.38, 10cm x 30cm = £0.58, 8.5cm x 15.5cm = £0.20

PremierPore VP
Film dressing with absorbent pad
PremierPore VP dressing (Shermod) 10cm x 10cm = £0.16, 10cm x 15cm = £0.24, 10cm x 20cm = £0.36, 10cm x 25cm = £0.38, 10cm x 30cm = £0.57, 10cm x 35cm = £0.69, 5cm x 7cm = £0.13

Tegaderm
Film dressing with absorbent pad
Tegaderm + Pad dressing (3M Health Care Ltd) 5cm x 7cm = £0.26, 9cm x 10cm = £0.65, 9cm x 15cm = £0.95, 9cm x 20cm = £1.40, 9cm x 25cm = £1.57, 9cm x 35cm = £2.60

Tegaderm Absorbent Clear
Film dressing with clear acrylic polymer oval-shaped pad or rectangular-shaped pad
Tegaderm Absorbent Clear Acrylic dressing (3M Health Care Ltd) 11.1cm x 12.7cm oval= £4.11, 14.2cm x 15.8cm oval= £5.78, 14.9cm x 15.2cm rectangular= £8.66, 16.8cm x 19cm sacral= £10.37, 20cm x 20.3cm rectangular= £13.91, 7.6cm x 9.5cm oval= £3.17

Vapour-permeable transparent film dressing with adhesive foam border.

Central Gard
For intravenous and subcutaneous catheter sites
Central Gard dressing (Unomedical Ltd) 16cm x 7cm = £0.95, 16cm x 8.8cm = £1.04

Easi-V
For intravenous and subcutaneous catheter sites
Easi-V (ConvTec Ltd) dressing 7cm x 7.5cm = £0.38

Vapour-permeable transparent, adhesive film dressing.

Hydrofilm I.V. Control
For intravenous and subcutaneous catheter sites
Hydrofilm (Paul Hartmann Ltd) I.V. Control dressing 7cm x 9cm = £0.31

Vapour-permeable, transparent, adhesive film dressing.

IV3000
For intravenous and subcutaneous catheter sites
IV3000 dressing (Smith & Nephew Healthcare Ltd) 10cm x 12cm = £1.41, 5cm x 6cm = £0.43, 6cm x 7cm = £0.56, 7cm x 9cm = £0.74, 9cm x 12cm = £1.47
Mepore IV
For intravenous and subcutaneous catheter sites
Mepore IV dressing (Molynex Health Care Ltd) 10cm × 11cm = £1.07, 5cm × 5.5cm = £0.31, 8cm × 9cm = £0.40

Pharmapore-PU IV
For intravenous and subcutaneous catheter sites
Pharmapore-PU-LV dressing (Wallace, Cameron & Company Ltd) 6cm × 7cm = £0.08, 7cm × 8.5cm = £0.07, 7cm × 9cm = £0.17

Tegaderm IV
For intravenous and subcutaneous catheter sites
Tegaderm IV dressing with securing tapes (3M Health Care Ltd) 10cm × 15.5cm = £1.67, 7cm × 8.5cm = £0.59, 8.5cm × 10.5cm = £1.16

Soft polyfoam dressings
Dressings with soft polyfoam, often a soft silicone polymer, in a non-adherent or gently adherent layer are suitable for use on lightly to moderately exuding wounds. For moderately to heavily exuding wounds, an absorbent secondary dressing can be added, or a soft polyfoam dressing with an absorbent pad can be used. Wound contact dressings coated with soft silicone have gentle adhesive properties and can be used on fragile skin areas or where it is beneficial to reduce the frequency of primary dressing changes. Soft polyfoam dressings should not be used on heavily bleeding wounds; blood clots can cause the dressing to adhere to the wound surface. For silicone keloid dressings see under Specialised dressings.

Cellulose dressings
Sorbiton Sachet Border
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope, with adhesive border
Cutimed Sorbiton Sachet Border dressing (BSN medical Ltd) 10cm × 10cm = £2.95, 15cm × 15cm = £4.49, 25cm × 15cm rectangular = £6.99

Sorbiton Sachet EXTRA
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope
Cutimed Sorbiton Sachet Extra dressing (BSN medical Ltd) 10cm × 10cm = £2.25, 20cm × 10cm = £3.73, 20cm × 20cm = £7.00, 30cm × 20cm = £9.99, 5cm × 5cm = £1.45, 7.5cm × 7.5cm = £1.78

Sorbiton Sachet Multi Star
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope
Cutimed Sorbiton Sachet Multi Star dressing (BSN medical Ltd) 14cm × 14cm = £4.89, 8cm × 8cm = £2.99

Sorbiton Sachet S Drainage
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope (‘V’ shaped dressing)
Cutimed (BSN medical Ltd) Sorbion Sachet S dressing 10cm × 10cm = £2.64

Suprasorb X
Biosynthetic cellulose fibre dressing
Suprasorb X dressing (Lohmann & Rauscher (UK) Ltd) 14cm × 20cm rectangular = £8.46, 2cm × 21cm rope = £6.58, 5cm × 5cm square = £2.05, 5cm × 5cm square = £4.27

With absorbent pad
Advazorb Border
Soft silicone wound contact dressing with polyurethane foam film backing and adhesive border
Advazorb Border dressing (Advancis Medical) 10cm × 10cm = £2.10, 10cm × 20cm = £2.50, 10cm × 30cm = £4.25, 12.5cm × 12.5cm = £2.58, 15cm × 15cm = £3.15, 20cm × 20cm = £5.46, 7.5cm × 7.5cm = £1.19

Advazorb Border Lite
Soft silicone wound contact dressing with polyurethane foam film backing and adhesive border
Advazorb Border Lite dressing (Advancis Medical) 10cm × 10cm = £1.89, 10cm × 20cm = £2.61, 10cm × 30cm = £3.83, 12.5cm × 12.5cm = £2.32, 15cm × 15cm = £2.84, 20cm × 20cm = £4.91, 7.5cm × 7.5cm = £1.07

Advazorb Silfix
Soft silicone wound contact dressing with polyurethane foam film backing
Advazorb Silfix dressing (Advancis Medical) 10cm × 10cm = £1.85, 10cm × 20cm = £3.18, 12.5cm × 12.5cm = £2.59, 15cm × 15cm = £3.36, 20cm × 20cm = £4.98, 7.5cm × 7.5cm = £0.99

Advazorb Silfix Lite
Soft silicone wound contact dressing with polyurethane foam film backing
Advazorb Silfix Lite dressing (Advancis Medical) 10cm × 10cm = £1.67, 10cm × 20cm = £2.86, 12.5cm × 12.5cm = £2.33, 15cm × 15cm = £3.02, 20cm × 20cm = £4.48, 7.5cm × 7.5cm = £0.89

Allevyn Gentle
Soft gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm = £2.53, 10cm × 20cm = £4.07, 15cm × 15cm = £4.25, 20cm × 20cm = £6.78, 5cm × 5cm = £1.27

Allevyn Gentle Border
Soft silicone wound contact dressing, with polyurethane foam film backing
Allevyn Gentle Border dressing (Smith & Nephew Healthcare Ltd) Heel dressing 23cm × 23.2cm = £9.74, dressing 10cm × 10cm = £2.21, 12.5cm × 12.5cm = £2.71, 17.5cm × 17.5cm = £5.34, 7.5cm × 7.5cm = £1.51

Allevyn Gentle Border Lite
Soft silicone gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle Border Lite dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm = £2.18, 15cm × 15cm = £3.85, 5.5cm × 12cm = £1.86, 5cm × 5cm = £0.91, 8cm × 15cm = £3.47

Allevyn Life
Soft silicone wound contact dressing, with central mesh screen, polyurethane foam film backing and adhesive border
Allevyn Life dressing (Smith & Nephew Healthcare Ltd) 10.3cm × 10.3cm = £1.71, 12.9cm × 12.9cm = £2.51, 15.4cm × 15.4cm = £3.06, 21cm × 21cm = £6.04

Cutimed Siltec
Soft silicone wound contact dressing, with polyurethane foam film backing
Cutimed Siltec (BSN medical Ltd) Heel dressing 16cm × 24cm = £7.72, Sacrum dressing 17.5cm × 17.5cm = £4.60, 23cm × 23cm = £7.36, dressing 10cm × 10cm = £2.48, 10cm × 20cm = £4.10, 15cm × 15cm = £4.64, 20cm × 20cm = £7.03, 5cm × 6cm = £1.33

Cutimed Siltec B
Soft silicone wound contact dressing, with polyurethane foam film backing, with adhesive border, for lightly to moderately exuding wounds
Cutimed Siltec B dressing (BSN medical Ltd) 12.5cm × 12.5cm = £3.27, 15cm × 15cm = £5.03, 17.5cm × 17.5cm = £5.29, 22.5cm × 22.5cm = £8.55, 7.5cm × 7.5cm = £1.54

Cutimed Siltec L
Soft silicone wound contact dressing, with polyurethane foam film backing, for lightly to moderately exuding wounds
Cutimed Siltec L dressing (BSN medical Ltd) 10cm × 10cm = £2.14, 15cm × 15cm = £3.52, 5cm × 6cm = £1.06

Eclypsy Adherent
Soft silicone wound contact layer with absorbent pad and film backing
Eclypsy Adherent dressing (Advancis Medical) 10cm × 10cm = £2.99, 10cm × 20cm = £3.75, 15cm × 15cm = £4.99, 20cm × 30cm = £9.99, 17cm × 19cm sacral = £3.76, 22cm × 23cm sacral = £6.23

Flivasorb
Absorbent polymer dressing with non-adherent wound contact layer
Flivasorb dressing (Lohmann & Rauscher (UK) Ltd) 10cm × 10cm square = £0.88, 10cm × 20cm rectangular = £1.05, 20cm × 20cm square = £1.86, 20cm × 30cm rectangular = £2.35
**Flivasorb Adhesive**
Absorbent polymer dressing with non-adherent wound contact layer and adhesive border

**Flivasorb Adhesive dressing** (Lohmann & Rauscher (UK) Ltd) 12cm × 12cm square= £3.35, 15cm × 15cm square= £4.58

**Mepilex**
Absorbent soft silicone dressing with polyurethane foam film backing

**Mepilex** (Molynex Health Care Ltd) Heel dressing 13cm × 20cm= £5.41, 15cm × 22cm= £6.22, XT dressing 10cm × 11cm= £2.66, 11cm × 20cm= £4.39, 15cm × 16cm= £4.82, 20cm × 21cm= £7.28, dressing 5cm × 5cm= £1.21

**Mepilex Border**
Absorbent soft silicone dressing with polyurethane foam film backing and adhesive border

**Mepilex Border** (Molynex Health Care Ltd) Heel dressing 18.5cm × 24cm= £6.63, Sacrum dressing 18cm × 18cm= £4.85, 23cm × 23cm= £7.91, dressing 10cm × 12.5cm= £2.72, 10cm × 20cm= £3.69, 10cm × 30cm= £5.55, 15cm × 17.5cm= £4.18, 17cm × 20cm= £6.07

**Mepilex Border Lite**
Thin absorbent soft silicone dressing with polyurethane foam film backing and adhesive border

**Mepilex Border Lite dressing** (Molynex Health Care Ltd) 10cm × 10cm= £1.87, 15cm × 15cm= £3.94, 4cm × 5cm= £0.92, 5cm × 12.5cm= £2.01, 7.5cm × 7.5cm= £1.35

**Mepilex Lite**
Thin absorbent soft silicone dressing with polyurethane foam film backing

**Mepilex Lite dressing** (Molynex Health Care Ltd) 10cm × 10cm= £2.17, 15cm × 15cm= £4.22, 20cm × 50cm= £26.66, 6cm × 8.5cm= £1.82

**Mepilex Transfer**
Soft silicone exudate transfer dressing

**Mepilex Transfer dressing** (Molynex Health Care Ltd) 10cm × 12cm= £3.51, 15cm × 20cm= £10.64, 20cm × 50cm= £27.20, 7.5cm × 8.5cm= £2.23

**Sorbion Sana**
Non-adherent polyethylene wound contact dressing with absorbent core

**Cutimed Sorbion Sana Gentle dressing** (BSN medical Ltd) 12cm × 12cm= £2.49, 12cm × 22cm= £4.49, 22cm × 22cm= £7.99, 8.5cm × 8.5cm= £1.99

**Urgotul Duo**
Non-adherent soft polymer wound contact dressing with absorbent pad

**Urgotul Duo dressing** (Urgo Ltd) 10cm × 12cm= £3.87, 15cm × 20cm= £8.98, 5cm × 10cm= £2.50

**Urgotul Duo Border**
Non-adherent soft polymer wound contact dressing with absorbent pad and adhesive polyurethane film backing

**Without absorbant pad**

**Adaptic Touch**
Non-adherent soft silicone wound contact dressing

**Adaptic Touch dressing** (SyStagenix Wound Management Ltd) 12.7cm × 15cm= £4.65, 20cm × 32cm= £12.50, 5cm × 7.6cm= £1.13, 7.6cm × 11cm= £2.25

**Askina SilNet**
Soft silicone-coated wound contact dressing

**Askina SilNet dressing** (B.Braun Medical Ltd) 10cm × 18cm= £4.98, 20cm × 30cm= £12.20, 5cm × 7.5cm= £1.13, 7.5cm × 10cm= £2.28

**Mepitel**
Soft silicone, semi-transparent wound contact dressing

**Mepitel dressing** (Molynex Health Care Ltd) 12cm × 15cm= £5.60, 5cm × 7cm= £1.40, 8cm × 10cm= £2.80

**Mepitel One**
Soft silicone, thin, transparent wound contact dressing

**Mepitel One dressing** (Molynex Health Care Ltd) 13cm × 15cm= £4.98, 24cm × 27.5cm= £14.25, 6cm × 7cm= £1.22, 9cm × 10cm= £2.41

**Physiotulle**
Non-adherent soft polymer wound contact dressing

**Physiotulle dressing** (Coloplast Ltd) 10cm × 10cm= £2.28, 15cm × 20cm= £6.96

**Silflex**
Soft silicone-coated polyester wound contact dressing

**Silflex dressing** (Advantis Medical) 12cm × 30cm= £11.79, 35cm × 60cm= £39.54, 5cm × 7cm= £1.11, 8cm × 10cm= £2.27

**Silon-TSR**
Soft silicone polymer wound contact dressing

**Silon-TSR dressing** (Bio Med Sciences) 13cm × 13cm= £3.52, 13cm × 25cm= £5.47, 28cm × 30cm= £7.37

**Sobion Contact**
Non-adherent soft polymer wound contact dressing

**Cutimed Sorbion Contact dressing** (BSN medical Ltd) 10cm × 10cm= £1.99, 10cm × 20cm= £3.99, 20cm × 20cm= £6.99, 20cm × 30cm= £9.99, 7.5cm × 7.5cm= £1.49

**Tegaderm Contact**
Non-adherent soft polymer wound contact dressing

**Tegaderm Contact dressing** (3M Health Care Ltd) 20cm × 25cm= £10.86, 7.5cm × 10cm= £2.27

**Urgotul**
Non-adherent soft polymer wound contact dressing

**Urgotul dressing** (Urgo Ltd) 10cm × 10cm= £3.11, 10cm × 40cm= £10.44, 15cm × 15cm= £6.60, 15cm × 20cm= £8.79, 20cm × 30cm= £14.13, 5cm × 5cm= £1.55

**Hydrocolloid dressings**
Hydrocolloid dressings are usually presented as a hydrocolloid layer on a vapour-permeable film or foam pad. Semi-permeable to water vapour and oxygen, these dressings form a gel in the presence of exudate to facilitate rehydration in lightly to moderately exuding wounds and promote autolytic debridement of dry, sloughy, or necrotic wounds; they are also suitable for promoting granulation. Hydrocolloid-fibrous dressings made from modified carmelllose fibres resemble alginate dressings; hydrocolloid-fibrous dressings are more absorptive and suitable for moderately to heavily exuding wounds.

**Hydrocolloid-fibrous dressings**

**Aquacel**
Soft non-woven pad containing hydrocolloid-fibres

**Aquacel** (ConvaTec Ltd) Ribbon dressing 1cm × 45cm= £1.84, 2cm × 45cm= £2.48, dressing 10cm × 10cm square= £2.45, 15cm × 15cm square= £4.60, 4cm × 10cm rectangular= £1.32, 4cm × 20cm rectangular= £1.94, 4cm × 30cm rectangular= £2.92, 5cm × 5cm square= £1.03

**Aquacel Foam**
Soft non-woven pad containing hydrocolloid-fibres with foam layer; with or without adhesive border

**Aquacel Foam dressing** (ConvaTec Ltd) (adhesive) 10cm × 10cm= £2.16, 12.5cm × 12.5cm= £2.68, 17.5cm × 17.5cm= £5.36, 19.8cm × 14cm heel= £5.48, 20cm × 16.9cm sacral= £4.92, 21cm × 21cm= £7.84, 25cm × 30cm= £10.15, 8cm × 8cm= £1.39, non-adhesive) 10cm × 10cm= £2.56, 15cm × 15cm= £4.30, 15cm × 20cm= £5.88, 20cm × 20cm= £7.01

**UrgoClean Pad**
Pad, hydrocolloid fibres coated with soft-adherent lipo-colloidal wound contact layer

**UrgoClean Pad dressing** (Urgo Ltd) 10cm × 10cm square= £2.14, 20cm × 15cm rectangular= £4.02, 6cm × 6cm square= £0.96

**UrgoClean Rope**
Rope, non-woven rope containing hydrocolloid fibres

**UrgoClean rope dressing** (Urgo Ltd) 2.5cm × 40cm= £2.41, 5cm × 40cm= £3.18

**Polyurethane matrix dressing**

**Cutinova Hydro**
Polyurethane matrix with absorbent particles and waterproof polyurethane film
Comfeel Plus Transparent
Hydrocolloid dressings containing carmellose sodium and calcium alginate

Comfeel Plus Transparent dressing (Coloplast Ltd) 10cm × 10cm square= £1.28, 15cm × 15cm square= £3.35, 15cm × 20cm rectangular= £3.40, 20cm × 20cm square= £3.42, 5cm × 15cm rectangular= £1.59, 5cm × 25cm rectangular= £2.59, 5cm × 7cm rectangular= £0.67, 9cm × 14cm rectangular= £2.44, 9cm × 25cm rectangular= £3.47

Comfeel Plus Ulcer
Hydrocolloid dressings containing carmellose sodium and calcium alginate

Comfeel Plus Ulcer (bevelled edge) dressing (Coloplast Ltd) 10cm × 10cm square= £2.46, 18cm × 20cm triangular= £5.73, 20cm × 20cm square= £7.59, 4cm × 6cm rectangular= £0.96

DuoDERM Extra Thin
Semi-permeable hydrocolloid dressing

DuoDERM Extra Thin dressing (Convatec Ltd) 10cm × 10cm square= £1.33, 15cm × 15cm square= £2.88, 5cm × 10cm rectangular= £0.76, 7.5cm × 7.5cm square= £0.81, 9cm × 15cm rectangular= £1.78, 9cm × 25cm rectangular= £2.85, 9cm × 35cm rectangular= £3.98

DuoDERM Signal
Semi-permeable hydrocolloid dressing with 'Time to change' indicator

DuoDERM Signal dressing (Convatec Ltd) 10cm × 10cm square= £2.14, 11cm × 19cm oval= £3.25, 14cm × 14cm square= £3.75, 18.5cm × 19.5cm heel= £5.25, 20cm × 20cm square= £7.46, 22.5cm × 20cm sacral= £6.13

Flexigran
Semi-permeable hydrocolloid dressing without adhesive border; normal or thin

Flexigran (A1 Pharmaceuticals) Thin dressing 10cm × 10cm square= £1.08, dressing 10cm × 10cm square= £2.19

Granuflex
Hydrocolloid wound contact layer bonded to plastic foam layer, with outer semi-permeable polyurethane film

Granuflex (modified) dressing (Convatec Ltd) 10cm × 10cm square= £2.83, 15cm × 15cm square= £3.56, 15cm × 20cm rectangular= £5.81, 20cm × 20cm square= £8.07

Hydrocoll Basic
Hydrocolloid dressing with absorbent wound contact pad

Hydrocoll (Paul Hartmann Ltd) Basic dressing 10cm × 10cm square= £2.47

Hydrocol Thin Film
Thin hydrocolloid dressing with absorbent wound contact pad

Hydrocol Thin Film dressing (Paul Hartmann Ltd) 10cm × 10cm square= £1.16, 15cm × 15cm square= £2.61, 7.5cm × 7.5cm square= £0.70

Nu-Derm
Semi-permeable hydrocolloid dressing (normal and thin)

Nu-Derm dressing (Systagenix Wound Management Ltd) 10cm × 10cm square= £1.56, 15cm × 15cm square= £3.18, 15cm × 18cm sacral= £4.45, 20cm × 20cm square= £6.36, 5cm × 5cm square= £0.85, 8cm × 12cm heel/elbow= £3.18, thin 10cm × 10cm square= £1.06

Tegaderm Hydrocolloid
Hydrocolloid dressing without adhesive border; normal and thin

Tegaderm Hydrocolloid (3M Health Care Ltd) Thin dressing 10cm × 10cm square= £1.55, dressing 10cm × 10cm square= £2.37

Ultex Pro
Semi-permeable hydrocolloid dressing; without adhesive border

Ultex Pro dressing (Covidien (UK) Commercial Ltd) 10cm × 10cm square= £2.28, 15cm × 15cm square= £4.44, 20cm × 20cm square= £6.69

Foam dressings
Dressings containing hydrophilic polyurethane foam (adhesive or non-adhesive), with or without plastic film-

Cutinova Hydro dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square= £2.57, 15cm × 20cm rectangular= £5.44, 5cm × 6cm rectangular= £1.28

With adhesive border

Biatain Super
Semi-permeable hydrocolloid dressing; without adhesive border

Biatain Super dressing (adhesive) (Coloplast Ltd) 10cm × 10cm square= £2.12, 12.5cm × 12.5cm square= £3.60, 12cm × 20cm rectangular= £3.61, 15cm × 15cm square= £4.35, 20cm × 20cm square= £6.78

Granuflex Bordered
Hydrocolloid wound contact layer bonded to plastic foam layer, with outer semi-permeable polyurethane film

Granuflex Bordered dressing (Convatec Ltd) 10cm × 10cm square= £3.37, 10cm × 13cm triangular= £3.97, 15cm × 15cm square= £6.43, 15cm × 18cm triangular= £6.19, 6cm × 6cm square= £1.78

Hydrocoll Border
Hydrocolloid dressing with adhesive border and absorbent wound contact pad

Hydrocoll Border (bevelled edge) dressing (Paul Hartmann Ltd) 10cm × 10cm square= £2.43, 12cm × 18cm sacral= £3.64, 15cm × 15cm square= £4.57, 5cm × 5cm square= £1.01, 7.5cm × 7.5cm square= £1.67, 8cm × 12cm concave= £2.14

Tegaderm Hydrocolloid
Hydrocolloid dressing with adhesive border; normal or thin

Tegaderm Hydrocolloid (3M Health Care Ltd) Thin dressing 10cm × 12cm oval= £1.55, 13cm × 15cm oval= £2.89, dressing 10cm × 12cm oval= £2.33, 13cm × 15cm oval= £4.34, 17.1cm × 16.1cm sacral= £4.85

Ultex Pro
Semi-permeable hydrocolloid dressing with adhesive border

Ultex Pro dressing (adhesive) (Covidien (UK) Commercial Ltd) 15cm × 18cm sacral= £3.30, 19.5cm × 23cm sacral= £4.98, 21cm × 21cm square= £4.67

Without adhesive border

ActivHeal Hydrocolloid
Semi-permeable polyurethane film backing, hydrocolloid wound contact layer, with or without polyurethane foam later

ActivHeal Hydrocolloid (Advanced Medical Solutions Ltd) dressing 10cm × 10cm square= £1.58, 15cm × 15cm square= £3.43, 15cm × 18cm sacral= £3.98, 5cm × 7.5cm rectangular= £0.78, 6cm rectangular= £3.12, 10cm × 10cm square= £1.94, 15cm × 15cm square= £2.91, 15cm × 18cm sacral= £3.36, 5cm × 7.5cm rectangular= £0.97

Askina Biofilm Transparent
Semi-permeable, polyurethane film dressing with hydrocolloid adhesive

Askina Biofilm Transparent dressing (B.Braun Medical Ltd) 10cm × 10cm square= £1.07, 20cm × 20cm square= £3.17

Biatain Super
Semi-permeable, hydrocolloid film dressing without adhesive border

Biatain Super dressing (non-adhesive) (Coloplast Ltd) 10cm × 10cm square= £2.18, 12.5cm × 12.5cm square= £3.60, 12cm × 20cm rectangular= £3.61, 15cm × 15cm square= £4.35, 20cm × 20cm square= £6.78

Comfeel Plus Contour
Hydrocolloid dressings containing carmellose sodium and calcium alginate

Comfeel Plus Contour dressing (Coloplast Ltd) 6cm × 8cm= £2.23, 9cm × 11cm= £3.87

Comfeel Plus Pressure Relieving
Hydrocolloid dressings containing carmellose sodium and calcium alginate

Comfeel Plus Pressure Relieving dressing (Coloplast Ltd) 10cm diameter circular= £4.66, 15cm diameter circular= £7.01, 7cm diameter circular= £3.48
backing, are suitable for all types of exuding wounds, but not for dry wounds; some foam dressings have a moisture-sensitive film backing with variable permeability dependant on the level of exudate Foam dressings vary in their ability to absorb exudate; some are suitable only for lightly to moderately exuding wounds, others have greater fluid-handling capacity and are suitable for heavily exuding wounds. Saturated foam dressings can cause maceration of healthy skin if left in contact with the wound. Foam dressings can be used in combination with other primary wound contact dressings. If used under compression bandaging or compression garments, the fluid-handling capacity of the foam dressing may be reduced. Foam dressings can also be used to provide a protective cushion for fragile skin. A foam dressing containing I扑酚現 is available and may be useful for treating painful exuding wounds.

Cavi-Care
Soft, conforming cavity wound dressing prepared by mixing thoroughly for 15 seconds immediately before use and allowing to expand its volume within the cavity

Polyurethane Foam Dressing

Cutimed Cavity

Cutimed Cavity dressing (BSN medical Ltd) 10cm × 10cm= £3.12, 15cm × 15cm= £4.68, 5cm × 6cm= £1.88

Kendall

Kendall Foam dressing (Aria Medical Ltd) 10cm × 10cm square= £2.05, 12.5cm × 12.5cm square= £1.80, 15cm × 15cm square= £2.60, 20cm × 20cm square= £3.01, 5cm × 5cm square= £0.71, 7.5cm × 7.5cm square= £1.21, 8.5cm × 7.5cm rectangular (fenestrated)= £0.91

Polyurethane Foam Dressing with Adhesive Border

ActivHeal Foam Adhesive

ActivHeal Foam Adhesive dressing (Advanced Medical Solutions Ltd) 10cm × 10cm square= £1.63, 12.5cm × 12.5cm square= £1.68, 15cm × 15cm square= £2.15, 20cm × 20cm square= £4.50, 7.5cm × 7.5cm square= £1.18

Allevyn Adhesive

Allevyn Adhesive dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square= £2.21, 12.5cm × 12.5cm square= £2.70, 12.5cm × 22.5cm rectangular= £4.20, 17.5cm × 17.5cm square= £5.32, 17cm × 17cm anatomically shaped sacrals= £4.00, 22.5cm × 22.5cm square= £7.75, 22cm × 22cm anatomically shaped sacrals= £5.76, 7.5cm × 7.5cm square= £1.50

Biatain Adhesive

Biatain Adhesive dressing (Coloplast Ltd) 10cm × 10cm square= £1.77, 12.5cm × 12.5cm square= £2.58, 17cm diameter contour= £5.01, 18cm × 18cm square= £5.21, 15cm × 28cm rectangular= £7.71, 19cm × 20cm heel= £5.21, 23cm × 23cm sacrals= £4.46

Biatain Silicone

Biatain Silicone dressing (Coloplast Ltd) 7.5cm × 7.5cm= £1.46, 10cm × 10cm square= £2.15, 12.5cm × 12.5cm square= £2.63, 15cm × 15cm square= £3.90, 17.5cm × 17.5cm square= £5.18

Kendall Island

Kendall Foam Island dressing (Aria Medical Ltd) 10cm × 10cm square= £1.54, 15cm × 15cm square= £2.90, 20cm × 20cm square= £5.46

PermaFoam

PermaFoam dressing (adhesive) (Paul Hartmann Ltd) 16.5cm × 18cm concave= £4.06, 18cm × 18cm sacrals= £3.34, 22cm × 22cm sacrals= £3.84

PermaFoam Comfort

PermaFoam Comfort dressing (Paul Hartmann Ltd) 10cm × 20cm rectangular= £3.38, 11cm × 11cm square= £2.14, 15cm × 15cm square= £3.50, 20cm × 20cm square= £5.08, 8cm × 8cm square= £1.13

PolyMem

PolyMem dressing (Aspen Medical Europe Ltd) (adhesive) 10cm × 10cm rectangular= £2.18, 15cm × 15cm square= £2.93, 16.5cm × 20.9cm oval= £6.74, 18.4cm × 20cm sacrals= £4.53, 5cm × 7.6cm oval= £1.15, 8.8cm × 12.7cm oval= £2.05

Polymem

PolyMem (Aspen Medical Europe Ltd) dressing (adhesive) 5cm × 5cm square= £0.52

Tegaderm Foam Adhesive

Tegaderm Foam dressing (adhesive) (3M Health Care Ltd) 10cm × 11cm oval= £2.39, 13.9cm × 13.9cm circular (heel)= £4.22, 14.3cm × 14.3cm square= £3.54, 14.3cm × 15.6cm oval= £4.24, 19cm × 22.2cm oval= £6.96, 6.9cm × 6.9cm soft cloth border= £1.71, 6.9cm × 7.6cm oval= £1.46

Tiele

Tiele (Systagenix Wound Management Ltd) Lite dressing 11cm × 11cm square= £2.28, dressing 15cm × 15cm square= £3.89, 15cm × 20cm rectangular= £4.87, 18cm × 18cm square= £4.95, 7cm × 9cm rectangular= £1.28

Tiele Lite

Tiele Lite dressing (Systagenix Wound Management Ltd) 11cm × 11cm square= £2.28, 7cm × 9cm rectangular= £1.21, 8cm × 15cm rectangular= £2.81, 8cm × 20cm rectangular= £2.97

Tiele Plus

Tiele Plus dressing (Systagenix Wound Management Ltd) 11cm × 11cm square= £2.63, 15cm × 15cm sacrams= £3.13, square= £4.30, 15cm × 20cm rectangular= £5.39, 20cm × 26.5cm heel= £4.45

Trufloam

Trufloam Border dressing (Aspen Medical Europe Ltd) 11cm × 11cm square= £1.70, 15cm × 15cm square= £2.23, 15cm × 20cm rectangular= £4.94, 7cm × 9cm rectangular= £1.16

Polyurethane Foam Film Dressing without Adhesive Border

ActivHeal Foam Non-Adhesive

ActivHeal Non-Adhesive Foam polypurathene dressing (Advanced Medical Solutions Ltd) 10cm × 10cm square= £3.13, 10cm × 20cm rectangular= £2.34, 20cm × 20cm square= £3.92, 5cm × 5cm square= £0.75

Advazorb

Advazorb (Advancis Medical) Heel dressing 17cm × 21cm= £4.75, dressing 10cm × 10cm square= £1.08, 10cm × 20cm rectangular= £3.35, 12.5cm × 12.5cm square= £1.59, 15cm × 15cm square= £2.10, 20cm × 20cm square= £3.75, 5cm × 5cm square= £0.65, 7.5cm × 7.5cm square= £0.78

Advazorb Lite

Advazorb Lite dressing (Advancis Medical) 10cm × 10cm square= £0.97, 10cm × 20cm rectangular= £3.02, 12.5cm × 12.5cm square= £1.43, 15cm × 15cm square= £1.89, 20cm × 20cm square= £3.38, 7.5cm × 7.5cm square= £0.70

Allevyn Non-Adhesive

Allevyn dressing (non-adhesive) (Smith & Nephew Healthcare Ltd) 10.5cm × 13.5cm heel (cup shaped)= £5.16, 10cm × 10cm square= £2.52, 10cm × 20cm rectangular= £4.05, 20cm × 20cm square= £6.76, 5cm × 5cm square= £1.27

Askina Foam

Askina (B.Braun Medical Ltd) Foam Cavity dressing 2.4cm × 4cm= £2.44, Foam dressing 10cm × 10cm square= £2.19, 10cm × 20cm rectangular= £3.45, 20cm × 20cm square= £5.77, Heel dressing 12cm × 20cm= £4.68

Biatain -ibu Non-Adhesive

Biatain-ibu Non-Adhesive dressing (Coloplast Ltd) 10cm × 12cm rectangular= £3.34, 10cm × 22.5cm rectangular= £5.26, 15cm × 15cm square= £3.26, 20cm × 20cm square= £8.95, 5cm × 7cm rectangular= £1.73

Biatain -ibu Soft-Hold

Biatain-ibu Soft-Hold dressing (Coloplast Ltd) 10cm × 12cm rectangular= £3.34, 10cm × 22.5cm rectangular= £5.26, 15cm × 15cm square= £5.26

Biatain Non-Adhesive

Biatain Non-Adhesive dressing (Coloplast Ltd) 10cm × 10cm square= £2.40, 10cm × 20cm rectangular= £3.96, 15cm × 15cm square= £4.43, 20cm × 20cm square= £6.57, 5cm × 7cm rectangular= £1.32

Biatain Soft-Hold

Biatain Soft-Hold dressing (Coloplast Ltd) 10cm × 10cm square= £2.61, 10cm × 20cm rectangular= £3.96, 15cm × 15cm square= £4.34, 5cm × 7cm rectangular= £1.32
**Kendall**

**Kendall Foam Plus dressing** (Aria Medical Ltd) 10cm × 10cm square= £1.47, 10cm × 20cm rectangular= £2.69, 15cm × 15cm square= £3.28, 20cm × 20cm square= £6.04, 5cm × 5cm square= £0.82, 7.5cm × 7.5cm square= £1.42, 8.5cm × 7.5cm rectangular (fenestrated)= £1.24

**Kerrahel**

Kerrahel (Crawford Healthcare Ltd) dressing 12cm × 20cm heel= £4.65

**Lyfoam Max**

Lyfoam Max dressing (Molyncke Health Care Ltd) 10cm × 10cm square= £1.14, 10cm × 20cm rectangular= £2.01, 15cm × 15cm square= £2.15, 15cm × 20cm rectangular= £2.71, 20cm × 20cm square= £3.99, 7.5cm × 8.5cm rectangular= £1.09

**PermaFoam**

PermaFoam (Paul Hartmann Ltd) Cavity dressing 10cm × 10cm= £2.03, dressing (non-adhesive) 10cm × 10cm square= £2.14, 10cm × 20cm rectangular= £3.67, 15cm × 15cm square= £4.06, 20cm × 20cm square= £6.20, 6cm diameter circular= £1.11, 8cm × 8cm (fenestrated)= £1.26

**PolyMem**

PolyMem dressing (Aspen Medical Europe Ltd) 7cm × 7cm tube= £1.72, 9cm × 9cm tube= £2.17, finger/toe size 1= £2.50, 2= £2.50, 3= £2.50

**PolyMem dressing (non-adhesive)** (Aspen Medical Europe Ltd) 10cm × 10cm square= £2.47, 10cm × 61cm rectangular= £13.10, 13cm × 13cm square= £4.12, 17cm × 19cm rectangular= £6.08, 20cm × 60cm rectangular= £30.90, 8cm × 8cm (fenestrated)= £2.23

**PolyMem Max**

PolyMem Max dressing (Aspen Medical Europe Ltd) 11cm × 11cm square= £2.97, 20cm × 20cm square= £11.68

**PolyMem WIC**

PolyMem (Aspen Medical Europe Ltd) WIC dressing 8cm × 8cm= £3.69

**Tegaderm Foam**

Tegaderm Foam dressing (3M Health Care Ltd) 10cm × 10cm square= £2.19, 10cm × 20cm rectangular= £3.71, 10cm × 60cm rectangular= £12.54, 20cm × 20cm square= £5.92, 8.8cm × 8.8cm square (fenestrated)= £2.23

**Tielle Xtra**

Tielle Xtra dressing (Systagenix Wound Management Ltd) 11cm × 11cm square= £2.24, 15cm × 15cm square= £3.37, 15cm × 20cm rectangular= £5.91

**Transorbent**

Transorbent dressing (adhesive) (B.Braun Medical Ltd) 10cm × 10cm square= £1.98, 15cm × 15cm square= £3.65, 20cm × 20cm square= £5.83, 5cm × 5cm rectangular= £1.07

**Trufoam NA**

Trufoam Non Adhesive dressing (Aspen Medical Europe Ltd) 10cm × 10cm square= £1.34, 15cm × 15cm square= £2.63, 5cm × 5cm square= £0.71

**UrgoCell TLC**

UrgoTul Absorb dressing (Urgo Ltd) 10cm × 10cm= £2.38, 15cm × 20cm= £4.20, 6cm × 6cm= £1.21, 12cm × 19cm heel= £4.80

**Alginate dressings**

Non-woven or fibrous, non-occlusive, alginate dressings, made from calcium alginate, or calcium sodium alginate, derived from brown seaweed, form a soft gel in contact with wound exudate. Alginate dressings are highly absorbent and suitable for use on exuding wounds, and for the promotion of autolytic debridement of debris in very moist wounds. Alginate dressings also act as a haemostatic, but caution is needed because blood clots can cause the dressing to adhere to the wound surface. Alginate dressings should not be used if bleeding is heavy and extreme caution is needed if used for tumours with friable tissue. Alginate sheets are suitable for use as a wound contact dressing for moderately to heavily exuding wounds and can be layered into deep wounds; alginate rope can be used in sinus and cavity wounds to improve absorption of exudate and prevent maceration. If the dressing does not have an adhesive border or integral adhesive plastic film backing, a secondary dressing will be required.

**ActivHeal Alginate**

Calcium sodium alginate dressing

**ActivHeal Alginate dressing** (Advanced Medical Solutions Ltd) 10cm × 10cm= £1.15, 10cm × 20cm= £2.83, 5cm × 5cm= £0.59

**ActivHeal Aquafiber**

Non-woven, calcium sodium alginate dressing

**ActivHeal Aquafiber** (Advanced Medical Solutions Ltd) Rope dressing 2cm × 42cm= £1.81, dressing 10cm × 10cm= £1.80, 15cm × 15cm= £3.40, 5cm × 5cm= £0.76

**Algise M**

Calcium alginate fibre, non-woven dressing

**Algise M** (Smith & Nephew Healthcare Ltd) Rope dressing 2cm × 30cm= £3.50, dressing 10cm × 10cm= £1.93, 15cm × 20cm= £5.19, 5cm × 5cm= £0.93

**Algosteril**

Calcium alginate dressing

**Algosteril** (Smith & Nephew Healthcare Ltd) Rope dressing 2g= £3.83, dressing 10cm × 10cm= £2.12, 10cm × 20cm= £3.58, 5cm × 5cm= £0.93

**Biatain Alginate**

Alginate and carboxymethylcellulose dressing, highly absorbent, gelling dressing

**Biatain Alginate dressing** (Coloplast Ltd) 10cm × 10cm= £2.33, 15cm × 15cm= £4.43, 44cm= £2.75, 5cm × 5cm= £0.98

**Cutimed Alginate**

Calcium sodium alginate dressing

**Cutimed Alginate dressing** (BSN medical Ltd) 10cm × 10cm= £1.56, 10cm × 20cm= £2.94, 5cm × 5cm= £0.75

**Kaltostat**

Calcium alginate fibre, non-woven

**Kaltostat dressing** (ConvaTec Ltd) 10cm × 20cm= £4.12, 15cm × 25cm= £7.08, 2g= £3.86, 5cm × 5cm= £0.96, 7.5cm × 12cm= £2.10

**Kendall**

Calcium alginate dressing

**Kendall Calcium Alginate** (Aria Medical Ltd) Rope dressing 30cm= £2.89, 61cm= £5.07, 91cm= £5.46, dressing 10cm × 10cm= £1.52, 10cm × 14cm= £2.45, 10cm × 20cm= £2.98, 15cm × 25cm= £5.25, 30cm × 61cm= £27.56, 5cm × 5cm= £0.72

**Kendall Plus**

Calcium alginate dressing

**Kendall** (Aria Medical Ltd) Foam Plus dressing 10cm × 10cm square= £1.47

**Melgisorb**

Calcium sodium alginate fibre, highly absorbent, gelling dressing, non-woven

**Melgisorb** (Molyncke Health Care Ltd) Cavity dressing 2.2cm × 32cm= £3.55, dressing 10cm × 10cm= £1.88, 10cm × 20cm= £3.52, 5cm × 5cm= £0.90

**Sorbalgon**

Calcium alginate dressing

**Sorbalgon** (Paul Hartmann Ltd) T dressing 2g= £3.51, dressing 10cm × 10cm= £1.72, 5cm × 5cm= £0.82

**Sorbstan Flat**

Calcium alginate fibre, highly absorbent, flat non-woven pads

**Sorbstan Flat dressing** (Aspen Medical Europe Ltd) 10cm × 10cm= £1.71, 10cm × 20cm= £3.20, 5cm × 5cm= £0.81

**Sorbstan Plus**

Alginate dressing bonded to a secondary absorbent viscose pad

**Sorbstan Plus dressing** (Aspen Medical Europe Ltd) 10cm × 15cm= £3.10, 10cm × 20cm= £3.96, 15cm × 20cm= £5.49, 7.5cm × 10cm= £1.76

**Sorbstan Ribbon**

Alginate dressing bonded to a secondary absorbent viscose pad

**Sorbstan** (Aspen Medical Europe Ltd) Ribbon dressing 40cm= £2.04
Sorbans Surgical Packing
Alginate dressing bonded to a secondary absorbent viscose pad
Sorbans (Aspen Medical Europe Ltd) Packing dressing 2g = £3.47

Suprasorb A
Calcium alginate dressing

Suprasorb A (Lohmann & Rauscher (UK) Ltd) alginate dressing 10cm x 10cm = £1.23, 5cm x 5cm = £0.63, cavity dressing 2g = £2.28

Tegaderm Alginate
Calcium alginate dressing

Tegaderm Alginate dressing (3M Health Care Ltd) 10cm x 10cm = £1.72, 2cm x 30.4cm = £2.87, 5cm x 5cm = £0.81

Urgosorb
Alginate and carboxymethylcellulose dressing without adhesive border

Urgosorb (Urgo Ltd) Pad dressing 10cm x 10cm = £2.13, 10cm x 20cm = £3.91, 5cm x 5cm = £0.89, Rope dressing 30cm = £2.79

Capillary-acting dressings
Advadraw
Non-adherent dressing consisting of a soft viscose and polyester absorbent pad with central wicking layer between two perforated permeable wound contact layers

Advadraw dressing (Advancis Medical) 10cm x 10cm = £0.88, 10cm x 15cm = £1.19, 15cm x 20cm = £1.57, 5cm x 7.5cm = £0.57

Advadraw Spiral
Advadraw (Advancis Medical) Spiral dressing 0.5cm x 40cm = £0.82

Cerdak Aerocloth
Non-adhesive wound contact sachet containing ceramic spheres, with non-woven fabric adhesive backing

Cerdak Aerocloth dressing (Apollo Medical Products Ltd) 5cm x 10cm = £1.94, 5cm x 5cm = £1.37

Cerdak Aerofilm
Non-adhesive wound contact sachet containing ceramic spheres, with waterproof transparent adhesive film backing

Cerdak Aerofilm dressing (Apollo Medical Products Ltd) 5cm x 10cm = £2.07, 5cm x 5cm = £1.51

Cerdak Basic
Non-adhesive wound contact sachet containing ceramic spheres

Cerdak Basic dressing (Apollo Medical Products Ltd) 10cm x 10cm = £1.56, 10cm x 15cm = £2.08, 5cm x 5cm = £0.70

Sumar Lite

Sumar Lite dressing (Lantor (UK) Ltd) 10cm x 10cm = £1.59, 10cm x 15cm = £2.12, 5cm x 5cm = £0.93

Sumar Max

Sumar Max dressing (Lantor (UK) Ltd) 10cm x 10cm = £1.61, 10cm x 15cm = £2.15, 5cm x 5cm = £0.95

Sumar Spiral

Sumar (Lantor (UK) Ltd) Spiral dressing 0.5cm x 40cm = £1.57

Vacutex

Low-adherent dressing consisting of two external polyester wound contact layers with central wicking polyester/cotton mix absorbent layer

Vacutex dressing (Haddenham Healthcare Ltd) 10cm x 10cm = £1.66, 10cm x 15cm = £2.23, 10cm x 20cm = £2.68, 5cm x 5cm = £0.94

Odour absorbent dressings

Dressings containing activated charcoal are used to absorb odour from wounds. The underlying cause of wound odour should be identified. Wound odour is most effectively reduced by debridement of slough, reduction in bacterial levels, and frequent dressing changes. Fungating wounds and chronic infected wounds produce high volumes of exudate which can reduce the effectiveness of odour absorbent dressings. Many odour absorbent dressings are intended for use in combination with other dressings; odour absorbent dressings with a suitable wound contact layer can be used as a primary dressing.

Askina Carbosorb dressing (B.Braun Medical Ltd) 10cm x 10cm = £2.89, 10cm x 20cm = £5.58

CarboFLEX
Dressing in 5 layers: wound-facing absorbent layer containing alginate and hydrocolloid; water-resistant second layer; third layer containing activated charcoal; non-woven absorbent fourth layer; water-resistant backing layer

CarboFLEX dressing (ConvaTec Ltd) 10cm x 10cm = £3.21, 15cm x 20cm = £7.30, 8cm x 15cm oval = £3.85

Carbolap VC
Activated charcoal non-absorbent dressing

Carbolap VC dressing (Synergy Health Plc) 10cm x 10cm = £1.62, 10cm x 20cm = £2.19

Clinisorb Odour Control Dressings
Activated charcoal cloth enclosed in viscose rayon with outer polyamide coating

Clinisorb dressing (CliniMed Ltd) 10cm x 10cm = £1.91, 10cm x 20cm = £2.54, 15cm x 25cm = £4.09

Sorbans Plus Carbon
Alginate dressing with activated carbon

Sorbans Plus Carbon dressing (Aspen Medical Europe Ltd) 10cm x 15cm = £4.96, 10cm x 20cm = £5.94, 15cm x 20cm = £6.84, 7.5cm x 10cm = £2.56

Antimicrobial dressings

Spreading infection at the wound site requires treatment with systemic antibacterials. For local wound infection, a topical antimicrobial dressing can be used to reduce the level of bacteria at the wound surface but will not eliminate a spreading infection. Some dressings are designed to release the antimicrobial into the wound, others act upon the bacteria after absorption from the wound. The amount of exudate present and the level of infection should be taken into account when selecting an antimicrobial dressing. Medical grade honey has antimicrobial and anti-inflammatory properties. Dressings impregnated with iodine can be used to treat clinically infected wounds. Dressings containing silver should be used only when clinical signs or symptoms of infection are present. Dressings containing other antimicrobials such as polyhexanide (polyhexamethylene biguanide) or dialkylcarbamoyl chloride are available for use on infected wounds. Although hypersensitivity is unlikely with chlorhexidine impregnated tulle dressing, the antibacterial efficacy of these dressings has not been established.

Honey
Medical grade honey has antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Medical grade honey has osmotic properties, producing an environment that promotes autolytic debridement; it can help control wound malodour. Honey dressings should not be used on patients with extreme sensitivity to honey, bee stings or bee products. Patients with diabetes should be monitored for changes in blood-glucose concentrations during treatment with topical honey or honey-impregnated dressings. For Activon Tulle®, where no size is stated by the prescriber the 5cm size is to be supplied. Medihoney® Antimicrobial Wound Gel is not recommended for use in deep wounds or body cavities where removal of waxes may be difficult.

Honey-based topical application

Activon Honey
Medical grade manuka honey

L-Mesitran SOFT ointment dressing
Honey (medical grade) 40%

L-Mesitran (Aspen Medical Europe Ltd) SOFT ointment dressing = £3.59

MANUKApli Honey
Medical grade manuka honey

MANUKApli (Manuka Medical Ltd) dressing = £5.90
**Medihoney Antibacterial Medical Honey**  
Medical grade, Leptospermum sp.  
**Medihoney** (Derma Sciences Europe, Ltd) Antibacterial Medical Honey dressing= £9.90

**Medihoney Antibacterial Wound Gel**  
Medical grade, Leptospermum sp. 80% in natural waxes and oils  
**Medihoney** (Derma Sciences Europe, Ltd) Antibacterial Wound Gel dressing= £4.02

**Melladerm Plus Honey**  
Medical grade; Bulgarian, mountain flower) 45% in basis containing polyethylene glycol

**Mesitran Ointment**  
Honey (medical grade) 47%  
**Excipients** include lanolin  
**Mesitran** (Aspen Medical Europe Ltd) ointment dressing= £9.90

**Actilite**  
Knitted viscose impregnated with medical grade manuka honey and manuka oil  
**Actilite gauze dressing** (Advancis Medical) 10cm x 10cm= £0.98, 10cm x 20cm= £1.90, 5cm x 5cm= £0.57

**Activon Tulle**  
Knitted viscose impregnated with medical grade manuka honey  
**Activon Tulle gauze dressing** (Advancis Medical) 10cm x 10cm= £2.97, 5cm x 5cm= £1.80

**Algivan**  
Absorbent, non-adherent calcium alginate dressing impregnated with medical grade manuka honey  
**Algivan dressing** (Advancis Medical) 10cm x 10cm= £3.40, 5cm x 5cm= £1.98

**Algivan Plus**  
Reinforced calcium alginate dressing impregnated with medical grade manuka honey  
**Algivan Plus** (Advancis Medical) Ribbon dressing 2.5cm x 20cm= £3.36, dressing 10cm x 10cm= £3.36, 5cm x 5cm= £1.96

**L-Mesitran Border**  
Hydrogel, semi-permeable dressing impregnated with medical grade honey, with adhesive border  
**L-Mesitran** (Aspen Medical Europe Ltd) Border sheet 10cm x 10cm square= £2.74

**L-Mesitran Hydro**  
Hydrogel, semi-permeable dressing impregnated with medical grade honey, without adhesive border  
**L-Mesitran Hydro sheet** (Aspen Medical Europe Ltd) 10cm x 10cm square= £2.63, 15cm x 20cm rectangular= £5.48

**L-Mesitran Net**  
Hydrogel, non-adherent wound contact layer, without adhesive border  
**L-Mesitran** (Aspen Medical Europe Ltd) Net sheet 10cm x 10cm square= £2.53

**Medihoney Antibacterial Honey Apinate**  
Non-adherent calcium alginate dressing, impregnated with medical grade honey  
**Medihoney Antibacterial Honey Apinate** (Derma Sciences Europe, Ltd) dressing 10cm x 10cm square= £3.40, 5cm x 5cm square= £2.00, rope dressing 1.9cm x 30cm= £4.20

**Medihoney Antibacterial Honey Tulle**  
Woven fabric impregnated with medical grade manuka honey  
**Medihoney** (Derma Sciences Europe, Ltd) Tulle dressing 10cm x 10cm= £2.98

**Medihoney Gel Sheet**  
Sodium alginate dressing impregnated with medical grade honey  
**Medihoney Gel Sheet dressing** (Derma Sciences Europe, Ltd) 10cm x 10cm= £4.20, 5cm x 5cm= £1.75

**MelMax**  
Acetate wound contact layer impregnated with buckwheat honey 75% in ointment basis  
**MelMax dressing** (CliniMed Ltd) 5cm x 5cm rectangular= £4.82, 8cm x 10cm rectangular= £9.90, 8cm x 20cm rectangular= £19.79

**Melladerm Plus Tulle**  
Knitted viscose impregnated with medical grade honey (Bulgarian, mountain flower) 45% in basis containing polyethylene glycol  
**Melladerm** (SanoMed Manufacturing BV) Plus Tulle dressing 10cm x 10cm= £2.10

**iodine**  
Cadoxem – iodine, like povidone–iodine, releases free iodine when exposed to wound exudate. The free iodine acts as an antiseptic on the wound surface, the cadoxem absorbs wound exudate and encourages de-sloughing. Two-component hydrogel dressings containing glucose oxidase and iodide ions generate a low level of free iodine in the presence of moisture and oxygen. Povidone–iodine fabric dressing is a knitted viscose dressing with povidone–iodine incorporated in a hydrophilic polyethylene glycol basis; this facilitates diffusion of the iodine into the wound and permits removal of the dressing by irrigation. The iodine has a wide spectrum of antimicrobial activity but it is rapidly deactivated by wound exudate. Systemic absorption of iodine may occur, particularly from large wounds or with prolonged use.  
**Iodoflex®** and **Iodosorb®** are used for the treatment of chronic exuding wounds; max. single application 50 g, max. weekly application 150 g; max. duration up to 3 months in any single course of treatment. They are contra-indicated in patients receiving lithium, in thyroid disorders, in pregnancy and breast feeding, and in children; they should be used with caution in patients with severe renal impairment or history of thyroid disorder.  
**Iodozyme®** is an antimicrobial dressing used for lightly to moderately exuding wounds. It is contra-indicated in thyroid disorders and in patients receiving lithium; it should be used with caution in children and in women who are pregnant or breast-feeding.  
**Oxodyne®** is used for non-infected, dry to moderately exuding wounds. It is contra-indicated in thyroid disorders and in patients receiving lithium; it should be used with caution in children and in women who are pregnant or breast-feeding.  
**Povidone-iiodine Fabric Dressing** is used as a wound contact layer for abrasions and superficial burns. It is contra-indicated in patients with severe renal impairment and in women who are pregnant or breast-feeding; it should be used with caution in patients with thyroid disease and in children under 6 months.  
**Iodosorb Ointment**  
Iodine 0.9% as cadoxem–iodine in a paste basis with gauze backing  
**Iodosorb®** (Smith & Nephew Healthcare Ltd) ointment dressing= £9.12

**Iodosorb Powder**  
Iodine 0.9% as cadoxem–iodine microbeads, 3-g sachet  
**Iodosorb®** (Smith & Nephew Healthcare Ltd) powder dressing sachets= £1.95

**Iodozyme Hydrogel**  
Hydrogel (two-component dressing containing glucose oxidase and iodide ions)  
**Iodozyme dressing** (Crawford Healthcare Ltd) 10cm x 10cm square= £12.62, 6.5cm x 5cm rectangular= £7.57

**Oxyzyme Hydrogel**  
Hydrogel (two-component dressing containing glucose oxidase and iodide ions)
Oxyzyme dressing (Crawford Healthcare Ltd) 10cm × 10cm square = £10.10, 6.5cm × 5cm rectangular = £6.06

Povidone-iodine fabric dressing

Inadine

(Drug Tariff specification 43). Knitted viscose primary dressing impregnated with povidone-iodine 10%

Inadine dressing (Systagenix Wound Management Ltd) 5cm × 5cm = £0.33, 9.5cm × 9.5cm = £0.49

Silver

Antimicrobial dressings containing silver should be used only when infection is suspected as a result of clinical signs or symptoms (see also notes above). Silver ions exert an antimicrobial effect in the presence of wound exudate; the volume of wound exudate as well as the presence of infection should be considered when selecting a silver-containing dressing. Silver-impregnated dressings should not be used routinely for the management of uncomplicated ulcers. It is recommended that these dressings should not be used on acute wounds as there is some evidence to suggest they delay wound healing. Dressings impregnated with silver sulfadiazine have broad antimicrobial activity; if silver sulfadiazine is applied to large areas, or used for prolonged periods, there is a risk of blood disorders and skin discoloration. The use of silver sulfadiazine-impregnated dressings is contra-indicated in neonates, in pregnancy, and in patients with significant renal or hepatic impairment, sensitivity to sulfonamides, or G6PD deficiency. Large amounts of silver sulfadiazine applied topically may interact with other drugs—see Appendix 1 (sulfonamides).

alginate dressings

Algisite Ag

Calcium alginate dressing, with silver

Algisite Ag dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm = £4.13, 10cm × 20cm = £7.65, 20cm × 5cm = £5.74, 5cm × 5cm = £1.66

Askina Calgitrol Ag

Calcium alginate and silver alginate dressing with polyurethane foam backing

Askina Calgitrol Ag dressing (B.Braun Medical Ltd) 10cm × 10cm square = £3.24, 15cm × 15cm square = £6.27, 20cm × 20cm square = £14.62

Askina Calgitrol Thin

Calcium alginate and silver alginate matrix, for use with absorptive secondary dressings

Askina Calgitrol Thin dressing (B.Braun Medical Ltd) 10cm × 10cm square = £4.08, 15cm × 15cm square = £9.16, 20cm × 20cm square = £16.18, 5cm × 5cm square = £1.97

Melgisorb Ag

Alginate and carboxymethylcellulose dressing, with ionic silver

Melgisorb Ag (Mohlycke Health Care Ltd) Cavity dressing 3cm × 4.4cm = £4.54, dressing 10cm × 10cm = £3.64, 15cm × 15cm = £7.71, 5cm × 5cm = £1.82

Silvercel

Alginate and carboxymethylcellulose dressing impregnated with silver

Silvercel dressing (Systagenix Wound Management Ltd) 10cm × 20cm rectangular = £7.68, 11cm × 11cm square = £4.14, 2.5cm × 30.5cm rectangular = £4.45, 5cm × 5cm square = £1.68

Silvercel Non-adherent

Alginate and carboxymethylcellulose dressing with film wound contact layer, impregnated with silver

Silvercel Non-Adherent (Systagenix Wound Management Ltd) cavity dressing 2.5cm × 30.5cm = £3.94, dressing 10cm × 20cm rectangular = £7.25, 11cm × 11cm square = £3.89, 5cm × 5cm square = £1.62

Sorbsan Silver Flat

Calcium alginate fibre, highly absorbent, flat non-woven pads, with silver

Sorbsan Silver Flat dressing (Aspen Medical Europe Ltd) 10cm × 10cm = £3.97, 10cm × 20cm = £7.26, 5cm × 5cm = £1.57

Sorbsan Silver Plus

Calcium alginate dressing with absorbent backing, with silver

Sorbsan Silver Plus dressing (Aspen Medical Europe Ltd) 10cm × 10cm = £5.56, 10cm × 20cm = £6.77, 15cm × 20cm = £9.08, 7.5cm × 10cm = £3.35

Sorbsan Silver Ribbon

With silver

Sorbsan (Aspen Medical Europe Ltd) Silver Ribbon dressing 1g = £4.15

Sorbsan Silver Surgical Packing

With silver

Sorbsan (Aspen Medical Europe Ltd) Silver Packing dressing 2g = £5.76

Suprasorb A + Ag

Calcium alginate dressing, with silver

Suprasorb A + Ag (Loehmann & Rauscher (UK) Ltd) dressing 10cm × 10cm = £4.11, 10cm × 20cm = £7.59, 5cm × 5cm = £1.63, rope dressing 2g = £6.08

Tegaderm Alginate Ag

Calcium alginate and carboxymethylcellulose dressing, with silver

Tegaderm Alginate Ag dressing (3M Health Care Ltd) 10cm × 10cm = £3.24, 3cm × 30cm = £3.70, 5cm × 5cm = £1.39

Urgosorb Silver

Alginate and carboxymethylcellulose dressing, impregnated with silver

Urgosorb Silver (Urgo Ltd) Rope dressing 2.5cm × 30cm = £3.71, dressing 10cm × 10cm = £3.68, 10cm × 20cm = £6.95, 5cm × 5cm = £1.54

Foam dressings

Acticoat Moisture Control

Three layer polyurethane dressing consisting of a silver coated layer, a foam layer, and a waterproof layer

Acticoat Moisture Control dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square = £16.95, 10cm × 20cm rectangular = £33.04, 5cm × 5cm square = £7.25

Allevyn Ag

Silver sulfadiazine impregnated polyurethane foam film dressing with or without adhesive border

Allevyn Ag (Smith & Nephew Healthcare Ltd) Adhesive dressing 10cm × 10cm = £5.50, 12.5cm × 12.5cm square = £7.23, 17.5cm × 17.5cm square = £13.90, 17cm × 17cm square = £10.85, 22cm × 22cm square = £14.54, 7.5cm × 7.5cm square = £3.49, Heal Non-Adhesive dressing 10.5cm × 13.5cm = £10.76, Non-Adhesive dressing 10cm × 10cm = £6.14, 15cm × 15cm square = £31.64, 20cm × 20cm square = £17.64, 5cm × 5cm square = £3.26

Biaitan Ag

Silver impregnated polyurethane foam film dressing, with or without adhesive border

Biaitan Ag (Coloplast Ltd) cavity dressing 5cm × 8cm = £4.07, dressing 10cm × 10cm square = £8.16, 10cm × 20cm rectangular = £15.00, 12.5cm × 12.5cm square = £9.34, 15cm × 15cm square = £16.38, 18cm × 18cm square = £18.73, 19cm × 20cm heel = £18.47, 20cm × 20cm square = £23.11, 23cm × 23cm square = £19.63, 5cm × 7cm rectangular = £3.35

PolyMem Silver

Silver impregnated polyurethane foam film dressing, with or without adhesive border

PolyMem Silver (Aspen Medical Europe Ltd) WIC dressing 8cm × 8cm = £7.05, dressing 10.8cm × 10.8cm = £8.86, 12.7cm × 8.8cm oval = £5.60, 17cm × 19cm rectangular = £17.76, 5cm × 7.6cm oval = £2.27

Urgocell Silver

Non-adherent, polyurethane foam film dressing with silver in wound contact layer

Urgocell Silver dressing (Urgo Ltd) 10cm × 10cm = £5.95, 15cm × 20cm = £10.90, 6cm × 6cm = £4.33
### Antimicrobial dressings

#### Hydrocolloid dressings

**Aquadel Ag**  
Soft non-woven pad containing hydrocolloid fibres, (silver impregnated)

**Aquadel Ag** (Convatec Ltd) Ribbon dressing 1cm x 45cm = £3.08, 2cm x 45cm = £4.76, dressing 10cm x 10cm square = £4.74, 15cm x 15cm square = £8.92, 20cm x 30cm rectangular = £22.12, 4cm x 10cm rectangular = £2.88, 4cm x 20cm rectangular = £3.76, 4cm x 30cm rectangular = £5.63

**Physioutil Ag**  
Non-adherent polyester fabric with hydrocolloid and silver sulfadiazine

**Physioutil** (Coloplast Ltd) dressing 10cm x 10cm = £2.28

#### Low adherence dressing

**Acticoat**  
Three-layer antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 3-day wear)

**Acticoat dressing** (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £6.65, 10cm x 20cm rectangular = £13.53, 20cm x 40cm rectangular = £46.28, 5cm x 5cm square = £3.54

**Acticoat 7**  
Five-layer antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 7-day wear)

**Acticoat 7 dressing** (Smith & Nephew Healthcare Ltd) 10cm x 12.5cm rectangular = £18.94, 15cm x 15cm square = £32.97, 5cm x 5cm square = £6.15

**Acticoat Flex 3**  
Conformable antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 3-day wear)

**Acticoat Flex 3 dressing** (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £6.64, 10cm x 20cm rectangular = £13.50, 20cm x 40cm rectangular = £46.21, 5cm x 5cm square = £3.54

**Acticoat Flex 7**  
Conformable antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 7-day wear)

**Acticoat Flex 7 dressing** (Smith & Nephew Healthcare Ltd) 10cm x 12.5cm rectangular = £18.31, 15cm x 15cm square = £32.92, 5cm x 5cm square = £6.15

**Atrauman Ag**  
Non-adherent polyamide fabric impregnated with silver and neutral triglycerides

**Atrauman Ag dressing** (Paul Hartmann Ltd) 10cm x 10cm = £1.26, 10cm x 20cm = £2.47, 5cm x 5cm = £0.52

#### Soft polymer dressings

**Allevyn Ag Gentle**  
Soft polymer wound contact dressing, with silver sulfadiazine impregnated polyurethane foam layer, with or without adhesive border

**Allevyn Ag Gentle** (Smith & Nephew Healthcare Ltd) Border dressing 10cm x 10cm = £6.43, 12.5cm x 12.5cm = £8.26, 17.5cm x 17.5cm = £15.75, 7.5cm x 7.5cm = £4.28, dressing 10cm x 10cm = £6.24, 10cm x 20cm = £10.31, 15cm x 15cm = £11.61, 20cm x 20cm = £17.19, 5cm x 5cm = £3.35

**Mepilex Ag**  
Soft silicone wound contact dressing with polyurethane foam film backing, with silver, with or without adhesive border

**Mepilex** (Mohlycke Health Care Ltd) Ag dressing 10cm x 10cm = £6.12, 10cm x 20cm = £10.09, 15cm x 15cm = £11.36, 20cm x 20cm = £16.84, 20cm x 50cm = £33.20, Border Ag dressing 10cm x 12.5cm = £6.16, 10cm x 20cm = £8.97, 10cm x 30cm = £13.46, 15cm x 15cm = £11.31, 17cm x 20cm = £14.66, 7cm x 7.5cm = £3.41, Border Sacrum Ag dressing 18cm x 18cm = £11.83, 20cm x 20cm = £14.38, 23cm x 23cm = £18.89, Heel Ag dressing 13cm x 20cm = £12.78, 15cm x 22cm = £14.32

**Urgotul Silver**  
Non-adherent soft polymer wound contact dressing, with silver

**Urgotul Silver dressing** (Urgo Ltd) 10cm x 12cm = £3.58, 15cm x 20cm = £9.75

**Urgotul Duo Silver**  
Non-adherent soft polymer wound contact dressing, with silver

**With charcoal**

**Actisorb Silver 220**  
Knitted fabric of activated charcoal, with one-way stretch, with silver residues, within spun-bonded nylon sleeve

**Actisorb Silver 220 dressing** (Systagenix Wound Management Ltd) 10.5cm x 10.5cm = £2.58, 10.5cm x 15cm = £4.70, 6.5cm x 9.5cm = £1.64

#### Other antimicrobials

**Cutimed Siltec Sorbact**  
Polyurethane foam dressing with acetate fabric coated with dialkylcarbamoyl chloride, with adhesive border

**Cutimed Siltec Sorbact dressing** (BSN medical Ltd) 12.5cm x 12.5cm = £6.44, 15cm x 15cm = £7.98, 17.5cm x 17.5cm = £11.17, 22.5cm x 22.5cm = £16.99, 7.5cm x 7.5cm = £2.51, 17.5cm x 17.5cm sacral = £8.07, 23cm x 23cm sacral = £12.14

**Cutimed Sorbact**  
Low adherence acetate tissue impregnated with dialkylcarbamoyl chloride; dressing pad, swabs, round swabs or ribbon gauze, cotton

**Cutimed Sorbact** (BSN medical Ltd) Ribbon dressing 2cm x 50cm = £4.93, 5cm x 200cm = £7.95, Round swab 3cm = £3.30, dressing pad 10cm x 10cm = £5.50, 10cm x 20cm = £8.58, 7cm x 9cm = £3.52, swab 4cm x 6cm = £1.65, 7cm x 9cm = £2.75

**Cutimed Sorbact Gel**  
Hydrogel dressing impregnated with dialkylcarbamoyl chloride

**Cutimed Sorbact Gel dressing** (BSN medical Ltd) 7.5cm x 15cm rectangular = £4.48, 7.5cm x 7.5cm square = £2.65

**Cutimed Sorbact Hydroactive**  
Non-adhesive gel dressing with hydrogel matrix and acetate fabric coated with dialkylcarbamoyl chloride

**Cutimed Sorbact Hydroactive dressing** (BSN medical Ltd) 14cm x 14cm = £5.37, 14cm x 24cm = £8.60, 19cm x 15cm = £10.10, 24cm x 24cm = £15.31, 7cm x 8.5cm = £3.68

**Cutimed Sorbact Hydroactive B**  
Gel dressing with hydrogel matrix and acetate fabric coated with dialkylcarbamoyl chloride, with adhesive border

**Cutimed Sorbact Hydroactive B dressing** (BSN medical Ltd) 10cm x 10cm = £7.08, 10cm x 20cm = £11.35, 15cm x 15cm = £13.34, 5cm x 6.5cm = £3.97

**Flaminial Forte gel**  
Alginate with glucose oxidase and lactoperoxidase, for moderately to heavily exuding wounds

**Flaminial Forte gel dressing** (Flan Health UK Ltd) 15g = £7.68, 50g = £25.42

**Flaminial Hydro gel**  
Alginate with glucose oxidase and lactoperoxidase, for lightly to moderately exuding wounds

**Flaminial Hydro gel dressing** (Flan Health UK Ltd) 15g = £7.68, 50g = £25.42

**Kendall AMD**  
Foam dressing with polihexanide, without adhesive border

**Kendall AMD Antimicrobial foam dressing** (Aria Medical Ltd) 10cm x 10cm square = £4.71, 10cm x 20cm rectangular = £8.92, 15cm x 15cm square = £8.92, 20cm x 20cm square = £13.07, 5cm x 5cm square = £2.50, 8.8cm x 7.5cm rectangular (fenestrated) = £4.23

**Kendall AMD Plus**  
Foam dressing with polihexanide, with adhesive border

**Kendall AMD Antimicrobial Plus foam dressing** (Aria Medical Ltd) 10cm x 10cm square = £4.94, 8.8cm x 7.5cm rectangular (fenestrated) = £4.43
Ocetinil Wound gel
Wound gel, hydroxyethylcellulose and propylene glycol, with octenidine hydrochloride
Ocetinil Wound Gel dressing (Schulke & Mayr Ltd) 20ml= £4.78

Prontosan Wound Gel
Hydrogel containing betaine surfactant and polihexanide
Prontosan Wound Gel dressing (B. Braun Medical Ltd) 30ml= £6.44

Suprasorb X + PHMB
Biosynthetic cellulose fibre dressing with polihexanide
Suprasorb X + PHMB dressing (Lohmann & Rauscher (UK) Ltd) 14cm x 20cm rectangular= £11.64, 2cm x 21cm rope= £7.25, 5cm x 5cm square= £2.97, 9cm x 9cm square= £5.12

Telfa AMD
Low adherence absorbent perforated plastic film faced dressing with polihexanide
Telfa AMD dressing (Aria Medical Ltd) 10cm x 7.5cm= £0.18, 20cm x 7.5cm= £0.28

Telfa AMD Island
Low adherence dressing with adhesive border and absorbent pad, with polihexanide
Telfa AMD Island dressing (Aria Medical Ltd) 10cm x 12.5cm= £0.59, 10cm x 20cm= £0.86, 10cm x 25.5cm= £0.98, 10cm x 35cm= £1.22

Chlorhexidine gauze dressing
Bactigras
Fabric of leno weave, wet and warp threads of cotton and/or viscose yarn, impregnated with ointment containing chlorhexidine acetate
Bactigras gauze dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm= no price available, 5cm x 5cm= no price available

Irrigation fluids
Ocetinil Wound Irrigation solution
Aqueous solution containing glycerol, ethelyxylglycerin and octenidine hydrochloride
Ocetinil irrigation solution (Schulke & Mayr Ltd) 350mL bottles= £4.60

Prontosan Wound Irrigation Solution
Aqueous solution containing betaine surfactant and polihexanide
Prontosan irrigation solution (B. Braun Medical Ltd) 350mL bottles= £4.78, 40ml unit dose= £14.18

Specialised dressings
Protease-modulating matrix dressings
Cadesorb Ointment
Cadesorb (Smith & Nephew Healthcare Ltd) ointment= £9.32

Catrix
Catrix dressing (Cranage Healthcare Ltd) sachets= £3.80

Promogran
Collagen and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing
Promogran dressing (Systagenix Wound Management Ltd) 123 square cm= £15.62, 28 square cm= £5.19

Promogran Prisma Matrix
Collagen, silver and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing
Promogran Prisma dressing (Systagenix Wound Management Ltd) 123 square cm= £17.98, 28 square cm= £6.31

UrgoStart
Soft adherent polymer matrix containing nano-oligosaccharide factor (NOSF), with polyurethane foam film backing
UrgoStart dressing (Urgo Ltd) 10cm x 10cm= £6.16, 15cm x 20cm= £11.08, 6cm x 6cm= £4.45, 12cm x 19cm heelp= £8.49

UrgoStart Contact
Non-adherent soft polymer wound contact dressing containing nano-oligosaccharide factor (NOSF)
UrgoStart (Urgo Ltd) Contact dressing 5cm x 7cm= £3.00

Silicone keloid dressings
Silicone gel and gel sheets are used to reduce or prevent hypertrophic and keloid scarring. They should not be used on open wounds. Application times should be increased gradually. Silicone sheets can be washed and reused.

Silicone gel
Bapsincare
Silicone gel
Bapsocrine (BAP Medical UK Ltd) gel= £17.00

Ciltech
Silicone gel
Ciltech (Su-Med International (UK) Ltd) gel= £50.00

Dermatix
Silicone gel
Dermatix gel (Meda Pharmaceuticals Ltd)= £60.53

Kelo-cote UV
Silicone gel with SPF 30 UV protection
Kelo-cote (Sinclair IS Pharma Plc) UV gel= £17.88

Kelo-cote gel
Silicone gel
Kelo-cote (Sinclair IS Pharma Plc) gel= £51.00

Kelo-cote spray
Silicone spray
Kelo-cote (Sinclair IS Pharma Plc) spray= £51.00

NewGel+E
Silicone gel with vitamin E
NewGel+E (Advantec Surgical Ltd) gel= £17.70

Scarsil
Silicone gel
Scarsil (Jobskin Ltd) gel= £15.19

Silgel STC-SE
Silicone gel
Silgel (Nagor Ltd) STC-SE gel= £19.00

Silicone sheets
Advasil Conform
Self-adhesive silicone gel sheet with polyurethane film backing
Advasil Conform sheet (Advancis Medical) 10cm x 10cm square= £5.20, 15cm x 10cm rectangular= £9.17

Bapsincare T
Self-adhesive silicone gel sheet
Bapsocrine T sheet (BAP Medical UK Ltd) 10cm x 15cm rectangular= £9.00, 5cm x 30cm rectangular= £9.00, 5cm x 7cm rectangular= £3.15

Cica-Care
Soft, self-adhesive, semi-occlusive silicone gel sheet with backing
Cica-Care sheet (Smith & Nephew Healthcare Ltd) 15cm x 12cm rectangular= £28.82, 6cm x 12cm rectangular= £14.79

Ciltech
Silicone gel sheet
Ciltech sheet (Su-Med International (UK) Ltd) 10cm x 10cm square= £7.50, 10cm x 20cm rectangular= £12.50, 15cm x 15cm square= £14.00

Dermatix
Self-adhesive silicone gel sheet (clear- or fabric-backed)
Dermatix (Meda Pharmaceuticals Ltd) Clear sheet 13cm x 13cm square= £15.79, 13cm x 25cm rectangular= £28.53, 20cm x 30cm rectangular= £51.97, 4cm x 13cm rectangular= £6.88, Fabric sheet 13cm x 13cm square= £15.79, 13cm x 25cm rectangular= £28.53, 20cm x 30cm rectangular= £51.97, 4cm x 13cm rectangular= £6.88

Mepiform
Self-adhesive silicone gel sheet with polyurethane film backing
Mepiform sheet (Molnycke Health Care Ltd) 4cm x 31cm rectangular= £10.90, 5cm x 7cm rectangular= £3.45, 9cm x 18cm rectangular= £13.49
Adjunct dressings and appliances

Surgical absorbents

Surgical absorbents applied directly to the wound have many disadvantages—dehydration of and adherence to the wound, shedding of fibres, and the leakage of exudate (‘strike through’) with an associated risk of infection. Gauze and cotton absorbent dressings can be used as secondary layers in the management of heavily exuding wounds (but see also Capillary-action dressings). Absorbent cotton gauze fabric can be used for swabbing and cleaning skin. Ribbon gauze can be used post-operatively to pack wound cavities, but adherence to the wound bed will cause bleeding and tissue damage on removal of the dressing—an advanced wound dressing (e.g. hydrocolloid-fibrous, foam, or alginate) layered into the cavity is often more suitable.

Cotton

Absorbent Cotton, BP
Carded cotton fibres of not less than 10 mm average staple length, available in rolls and balls

Absorbent (Robert Bailey & Son Plc) cotton BP 1988

Absorbent Cotton, Hospital Quality
As for absorbent cotton but lower quality materials, shorter staple length etc.

Absorbent (Robert Bailey & Son Plc) cotton hospital quality

Gauze and cotton tissue

Gamgee Tissue (blue)
Consists of absorbent cotton enclosed in absorbent cotton gauze type 12 or absorbent cotton and viscose gauze type 2 Gamgee (Robinson Healthcare) tissue blue label

Gamgee Tissue (pink)
Consists of absorbent cotton enclosed in absorbent cotton gauze type 12 or absorbent cotton and viscose gauze type 2 Gamgee (Robinson Healthcare) tissue pink label DT

Gauze and tissue

Absorbent Cotton Gauze, BP 1988
Cotton fabric of plain weave, in rolls and as swabs (see below), usually Type 13 light, sterile

Absorbent (Robert Bailey & Son Plc) cotton BP 1988

Alvita (Alliance Healthcare (Distribution) Ltd) absorbent cotton BP 1988

Clini (CliniSupplies Ltd) absorbent cotton BP 1988

Vernaid (Synergy Health Plc) absorbent cotton BP 1988

Absorbent Cotton and Viscose Ribbon Gauze, BP 1988
Woven fabric in ribbon form with fast selvedge edges, warp threads of cotton, weft threads of viscose or combined cotton and viscose yarn, sterile

Vernaid Fast Edge ribbon gauze sterile (Synergy Health Plc) 1.25cm, 2.5cm

Lint

Absorbent Lint, BPC
Cotton cloth of plain weave with nap raised on one side from warp yarns

Absorbent (Robinson Healthcare) lint

Alvita (Alliance Healthcare (Distribution) Ltd) absorbent lint BPC

Clini (CliniSupplies Ltd) absorbent lint BPC

Pads

Drisorb
Absorbent Dressing Pads, Sterile

Drisorb (Synergy Health Plc) dressing pad 10cm × 20cm= £0.17

PremierPad
Absorbent Dressing Pads, Sterile

PremierPad dressing pad (Shermond) 10cm × 20cm= £0.18, 20cm × 20cm= £0.25

XuPad
Absorbent Dressing Pads, Sterile

XuPad dressing pad (Richardson Healthcare Ltd) 10cm × 20cm= £0.17, 20cm × 20cm= £0.28, 20cm × 40cm= £0.40

Wound drainage pouches

Wound drainage pouches can be used in the management of wounds and fistulas with significant levels of exudate.

Biotrol Draina S
Wound drainage pouch

Biotrol Draina S wound drainage bag (B.Braun Medical Ltd) large (Transparent)= £95.45, medium (Transparent)= £77.61, mini (Transparent)= £77.84

Biotrol Draina S Vision
Wound drainage pouch

Draina S Vision (B.Braun Medical Ltd) 100 wound drainage bag= £123.94, 50 wound drainage bag= £101.11, 75 wound drainage bag= £106.82

Eakin Access window
For use with Eakin® pouches

Eakin (Pelican Healthcare Ltd) access window= £37.74

Eakin Wound pouch, bung closure
Wound pouch, bung closure

Eakin wound drainage bag with bung closure (Pelican Healthcare Ltd) large= £102.45, medium= £75.49, small= £53.92, and access window for horizontal wounds, extra large= £102.45, for horizontal wounds, extra large= £91.66, for vertical incision wounds, extra large= £91.66, wounds, extra large= £91.66

Eakin Wound pouch, fold and tuck closure
Wound pouch, fold and tuck closure

Eakin wound drainage bag with fold and tuck closure (Pelican Healthcare Ltd) large= £91.66, medium= £70.10, small= £48.53, extra large= £80.88

Option Wound Manager
Wound drainage bag

Option wound manager bag (Oakmed Ltd) large= £160.22, medium= £134.42, small= £131.50, square= £140.27, extra square= £118.23

Option Wound Manager with access port
Wound drainage bag with access port

Option wound manager bag with access port (Oakmed Ltd) large= £171.27, medium= £140.27, small= £137.34, square= £146.11, extra small= £129.28

Option Wound Manager, cut to fit
Wound drainage bag, cut to fit

Option wound manager bag (Oakmed Ltd) large= £84.23, medium= £80.42, small= £72.59

Welland Fistula bag
Wound drainage bag, cut-to-fit

Welland (Welland Medical Ltd) Fistula wound drainage bag= £28.07

Physical debridement pads

DebrisoSoft® is a pad that is used for the debridement of superficial wounds containing loose slough and debris, and for the removal of hyperkeratosis from the skin. DebrisoSoft® must be fully moistened with a wound cleansing solution before use and is not appropriate for use as a wound dressing.

DebrisoSoft Pad
Polyester fibres with bound edges and knitted outer surface coated with polyacrylate

DebrisoSoft (Lohmann & Rauscher (UK) Ltd) pad 10cm × 10cm= £6.45
Complex adjunct therapies

Topical negative pressure therapy

**Accessories**

**Renasyx**
Soft port and connector
Renasyx (Smith & Nephew Healthcare Ltd) Soft Port = £11.21

**V.A.C.**
Drape, gel for canister, Sensa T.R.A.C. Pad
SensaT.R.A.C. (KCI Medical Ltd) pad = £10.95
T.R.A.C. (KCI Medical Ltd) connector = £3.13
V.A.C. (KCI Medical Ltd) drape = £9.39, gel strips = £3.76

**Venturi**
Gel patches, adhesive, and connector
Venturi (Talley Group Ltd) adhesive gel patch = £15.00, connector = £15.00

**WoundASSIST gel strip**
WoundASSIST (Huntleigh Healthcare Ltd) TNP gel strip = £3.37

**Vacuum assisted closure products**

**Exsu-Fast kit 1**
Dressing Kit

**Exsu-Fast kit 2**
Dressing Kit

**Exsu-Fast kit 3**
Dressing Kit

**Exsu-Fast kit 4**
Dressing Kit

**V.A.C. GranuFoam**
Polyurethane foam dressing (with adhesive drapes and pad connector); with or without silver
V.A.C. GranuFoam (KCI Medical Ltd) Bridge dressing kit = £32.04
Silver with SensaiT.R.A.C. dressing kit medium = £38.04, small = £32.79, dressing kit large = £31.70, medium = £27.32, small = £22.95

**V.A.C. Simplace**
Spiral-cut polyurethane foam dressings, vapour-permeable adhesive film dressings (with adhesive drapes and pad connector)
V.A.C. Simplace EX dressing kit (KCI Medical Ltd) medium = £30.58, small = £26.60

**V.A.C. WhiteFoam**
Polyvinyl alcohol foam dressing or dressing kit
V.A.C. WhiteFoam dressing (KCI Medical Ltd) large = £17.04, medium = £10.64, kit large = £33.54, small = £25.91

**Venturi**
Wound sealing kit, flat drain; with or without channel drain
Venturi wound sealing kit with (Talley Group Ltd) channel drain = £15.00, flat drain, large = £17.50, standard = £15.00

**WoundASSIST**
Wound pack and channel drain
WoundASSIST TNP dressing pack (Huntleigh Healthcare Ltd) medium/large = £23.85, small/medium = £20.81, channel drain medium/large = £23.85, small/medium = £20.81, extra large = £34.95

**Wound drainage collection devices**

**ActiV.A.C.**
Canister with gel
ActiV.A.C. (KCI Medical Ltd) canister with gel = £28.42

**S-Canister**
Canister kit
S-Canister (Smith & Nephew Healthcare Ltd) kit = £19.00

**V.A.C. Freedom**
Canister with gel
V.A.C. (KCI Medical Ltd) Freedom Canister with gel = £28.85

**Venturi**
Canister kit with solidifier
Venturi (Talley Group Ltd) Compact canister kit = £12.50, canister kit = £12.50

**WoundASSIST wound pack**
Canister
WoundASSIST (Huntleigh Healthcare Ltd) TNP canister = £20.30

Wound care accessories

**Dressing packs**
The role of dressing packs is very limited. They are used to provide a clean or sterile working surface; some packs shown below include cotton wool balls, which are not recommended for use on wounds.

**Multiple Pack Dressing No. 1**
Consists of absorbent cotton, absorbent cotton gauze type 13 light (sterile), open-woven bandages (banded)

**Vernaid**
(Synergy Health Plc) multiple pack dressing

Non-drug tariff specification sterile dressing packs

**Dressit**
Vitrex gloves, large apron, disposable bag, paper towel, softswabs, adsorbent pad, sterile field

**Dressit sterile dressing pack** (Richardson Healthcare Ltd) with medium/large gloves = £0.60, small/medium gloves = £0.60

**Nurse It**
Contains latex-free, powder-free nitrile gloves, sterile laminated paper sheet, large apron, non-oven swabs, paper towel, disposable bag, compartmented tray, disposable forceps, paper measuring tape

**Nurse It sterile dressing pack** (Medicareplus International Ltd) with medium/large gloves = £0.55, small/medium gloves = £0.55

**Polynitrile Nitrile Patient Pack**
Consists of powder-free nitrile gloves, laminated paper sheet, non-oven swabs, towel, polythene disposable bag, apron

**Polynitrile Nitrile Patient Pack with** (Shermond) large gloves = £0.52, medium gloves = £0.52, small gloves = £0.52

Sterile Dressing Pack with Non-Woven Pads

**Vernaid**
(Drug Tariff specification 35). Contains non-oven fabric covered dressing pack, non-oven fabric swabs, absorbent cotton wool balls, absorbent paper towel, water repellent inner wrapper

**Sterile Dressing Pack with Non-Woven Pads**
Vernaid (Synergy Health Plc) sterile dressing pack with non-oven pads

**Styler dressing packs**

**Vernaid**
(Drug Tariff specification 10). Contains gauze and cotton tissue pad, gauze swabs, absorbent cotton wool balls, absorbent paper towel, water repellent inner wrapper

**Vernaid (Synergy Health Plc) sterile dressing pack**

**Woven and fabric swabs**

**Gauze Swab, PB 1988**
Consists of absorbent cotton gauze type 13 light or absorbent cotton and viscose gauze type 1 folded into squares or rectangles of 8-ply with no cut edges exposed, sterile or non-sterile

**Alvita gauze swab 8ply** (Alliance Healthcare (Distribution) Ltd) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm

**CS** (CliniSupplies Ltd) gauze swab 8ply non-sterile 10cm x 10cm

**Clini gauze swab 8ply** (CliniSupplies Ltd) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm

**Gauze** (Robert Bailey & Son Plc) swab 8ply non-sterile 10cm x 10cm

**McCoBo gauze swab 8ply** (McCoBo Ltd) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm

**Propox gauze** (BSN medical Ltd) swab 8ply sterile 7.5cm x 7.5cm

**Sovereign** (Waymade Healthcare Plc) gauze swab 8ply sterile 7.5cm x 7.5cm

**Steraid** (Robert Bailey & Son Plc) gauze swab 8ply sterile 7.5cm x 7.5cm

**Vernaid gauze swab 8ply** (Synergy Health Plc) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm
Non-woven Fabric Swab
(Drug Tariff specification 28). Consists of non-woven fabric folded 4-ply; alternative to gauze swabs, type 13 light, sterile or non-sterile
- CS (CliniSupplies Ltd) non-woven fabric swab 4ply non-sterile 10cm × 10cm
- Clini non-woven fabric swab 4ply (CliniSupplies Ltd) non-sterile 10cm × 10cm, sterile 7.5cm × 7.5cm
- CliniMed (CliniMed Ltd) non-woven fabric swab 4ply non-sterile 10cm × 10cm
- MeCoBo (MeCoBo Ltd) non-woven fabric swab 4ply non-sterile 10cm × 10cm
- Multisorb (BSN medical Ltd) non-woven fabric swab 4ply sterile 7.5cm × 7.5cm
- Sofsorb non-woven fabric swab 4ply (Synergy Health Plc) non-sterile 10cm × 10cm, sterile 7.5cm × 7.5cm
- Softswab non-woven fabric swab 4ply (Richardson Healthcare Ltd) non-sterile 10cm × 10cm, sterile 7.5cm × 7.5cm
- Topper 8 non-woven fabric swab 4ply (Systagenix Wound Management Ltd) non-sterile 10cm × 10cm, sterile 7.5cm × 7.5cm

Filamted non-woven Fabric Swab
Regal
(Drug Tariff specification 29). Film of viscose fibres enclosed within non-woven viscose fabric folded 8-ply, non-sterile
Regal (Systagenix Wound Management Ltd) filamated swab 8ply 10cm × 10cm

Surgical adhesive tapes
Adhesive tapes are useful for retaining dressings on joints or awkward body parts. These tapes, particularly those containing rubber, can cause irritant and allergic reactions in susceptible patients; synthetic adhesives have been developed to overcome this problem, but they, too, may sometimes be associated with reactions. Synthetic adhesive, or silicon adhesive, tapes can be used for patients with skin reactions to plasters and containing rubber, or undergoing prolonged treatment.
Adhesive tapes that are occlusive may cause skin maceration. Care is needed not to apply these tapes under tension, to avoid creating a tourniquet effect. If applied over joints they need to be orientated so that the area of maximum extensibility of the fabric is in the direction of movement of the limb.

Occlusive adhesive tapes
Blenderm
(Impermeable Plastic Adhesive Tape, BP 1988). Extensible water-impermeable plastic film spread with a polymeric adhesive mass
Blenderm tape (3M Health Care Ltd) 2.5cm = £1.77, 5cm = £3.37
Sleek
(Impermeable Plastic Adhesive Tape, BP 1988). Extensible water-impermeable plastic film spread with an adhesive mass
Leukoplast Sleek tape (BSN medical Ltd) 2.5cm = £1.19, 5cm = £2.99

3m Kind Removal Silicone Tape
Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape
3M Micropore Silicone tape (3M Health Care Ltd) 2.5cm = £3.58, 5cm = £6.48

Chemifix
Chemifix tape (Medicareplus International Ltd) 10cm = £2.10, 2.5cm = £0.90, 5cm = £1.40

Chemipore
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass
Chemipore tape (Medicareplus International Ltd) 1.25cm = £0.27, 2.5cm = £0.70, 5cm = £0.95

Clinipore
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass
Clinipore tape (CliniSupplies Ltd) 1.25cm = £0.35, 2.5cm = £0.73, 5cm = £0.99

Elastoplast
(Elastic Adhesive Tape, BP 1988). Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads, spread with adhesive mass containing zinc oxide
Tensoplast (BSN medical Ltd) elastic adhesive tape 2.5cm

Hypafix
Hypafix tape (BSN medical Ltd) 10cm = £6.67, 15cm = £6.92, 2.5cm = £1.69, 20cm = £9.18, 30cm = £13.27, 5cm = £2.68

Insil
Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape
Insil tape (Insight Medical Products Ltd) 2cm = £5.77, 4cm = £5.77

Leukokfix
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass
Leukokfix tape (BSN medical Ltd) 1.25cm = £0.55, 2.5cm = £0.90, 5cm = £1.57

Leukopor
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass
Leukopor tape (BSN medical Ltd) 1.25cm = £0.49, 2.5cm = £0.77, 5cm = £1.35

Mediplast
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass
Mediplast tape (Neomedic Ltd) 1.25cm = £0.30, 2.5cm = £0.50

Mepitac
Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape
Mepitac tape (Molynlycke Health Care Ltd) 2cm = £6.96, 4cm = £6.96

Micropore
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass
Micropore tape (3M Health Care Ltd) 1.25cm = £0.62, 2.5cm = £0.92, 5cm = £1.62

Omnifix
Omnifix tape (Paul Hartmann Ltd) 10cm = £4.08, 15cm = £6.02, 5cm = £2.42

OpSite Flexifix Gentle
Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape
OpSite Flexifix Gentle tape (Smith & Nephew Healthcare Ltd) 2.5cm = £10.30, 5cm = £19.31
Primafix

Primafix tape (Smith & Nephew Healthcare Ltd) 10cm = £2.36, 15cm = £3.48, 20cm = £4.29, 5cm = £1.61

Scantor
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

Scantor tape (Bio-Diagnostics Ltd) 1.25cm = £0.55, 2.5cm = £0.92, 5cm = £1.75, 7.5cm = £2.56

Siltape
Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape

Siltape (Advancis Medical) 2cm = £5.60, 4cm = £5.60

Strappal
Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide

Strappal adhesive tape (BSN medical Ltd) 2.5cm = £1.39, 5cm = £2.34, 7.5cm = £3.53

Transpor
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

Transpor tape (3M Health Care Ltd) 2.5cm = £0.84, 5cm = £1.48

Zinc Oxide Adhesive Tape, BP 1988
Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide

Fast Aid zinc oxide adhesive tape (Robinson Healthcare) 1.25cm, 2.5cm, 5cm, 7.5cm

Skin closure dressings
Skin closure strips are used as an alternative to sutures for minor cuts and lacerations. Skin tissue adhesive (section 13.10.5) can be used for closure of minor skin wounds and for additional suture support.

Skin closure strips, sterile

Leukostrip
Drug Tariff specifies that these are specifically for personal administration by the prescriber

Leukostrip (Smith & Nephew Healthcare Ltd) skin closure strips 6.4mm × 76mm = £6.38

Omnistrip
Drug Tariff specifies that these are specifically for personal administration by the prescriber

Omnistrip (Paul Hartmann Ltd) skin closure strips sterile 6mm × 76mm = £24.34

Steri-strip
Drug Tariff specifies that these are specifically for personal administration by the prescriber

Steri-strip (3M Health Care Ltd) skin closure strips 6mm × 75mm = £8.77

Bandages
Non-extensible bandages
Skin closure strips are used as an alternative to sutures for minor cuts and lacerations. Skin tissue adhesive can be used for closure of minor skin wounds and for additional suture support.

Open-wove Bandage, Type 1 BP 1988
Cotton cloth, plain weave, warp of cotton, weft of cotton, viscose, or combination, one continuous length

Clini open wove bandage Type 1 BP 1988 (CliniSupplies Ltd) 10cm × 5m, 2.5cm × 5m, 5cm × 5m, 7.5cm × 5m

Vernair white open wove bandage (Synergy Health Plc) 10cm × 5m, 2.5cm × 5m, 5cm × 5m, 7.5cm × 5m

White open wove bandage (Robert Bailey & Son Plc) 10cm × 5m, 2.5cm × 5m, 5cm × 5m, 7.5cm × 5m

Triangular Calico Bandage, BP 1980
Unbleached calico right-angled triangle

Clini (CliniSupplies Ltd) triangular calico bandage BP 1980 90cm × 127cm

Triangular (BSN medical Ltd) calico bandage 90cm × 127cm

Light-weight conforming bandages
Lightweight conforming bandages are used for dressing retention, with the aim of keeping the dressing close to the wound without inhibiting movement or restricting blood flow. The elasticity of conforming stretch bandages (also termed contour bandages) is greater than that of cotton conforming bandages.

Acti-Wrap
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched (all)

Acti-Wrap (cohesive/latex free) bandage (Activa Healthcare Ltd) 10cm × 4m = £0.81, 6cm × 4m = £0.47, 8cm × 4m = £0.69

Cotton Conforming Bandage, BP 1988
Cotton fabric, plain weave, treated to impart some elasticity to warp and weft

Easifix Crinx bandage (BSN medical Ltd) 10cm × 3.5m = £1.03, 15cm × 3.5m = £1.41, 5cm × 3.5m = £0.68, 7.5cm × 3.5m = £0.84

Easifix
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Easifix bandage (BSN medical Ltd) 10cm × 4m = £0.51, 15cm × 4m = £0.86, 5cm × 4m = £0.35, 7.5cm × 4m = £0.43

Easifix K
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched

Easifix K bandage (BSN medical Ltd) 10cm × 4m = £0.18, 15cm × 4m = £0.32, 2.5cm × 4m = £0.10, 5cm × 4m = £0.11, 7.5cm × 4m = £0.16

Hospiform
Fabric, plain weave, warp of polyamide, weft of viscose

Hospiform bandage (Paul Hartmann Ltd) 10cm × 4m = £0.19, 12cm × 4m = £0.24, 6cm × 4m = £0.14, 8cm × 4m = £0.17

K-Band
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched

K-Band (Burgos Ltd) 10cm × 4m = £0.28, 15cm × 4m = £0.50, 5cm × 4m = £0.20, 7cm × 4m = £0.26

Knit Fix
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched

Knit Fix bandage (Robert Bailey & Son Plc) 10cm × 4m = £0.17, 15cm × 4m = £0.33, 5cm × 4m = £0.12, 7cm × 4m = £0.17

Knit-Band
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched

Knit-Band bandage (CliniSupplies Ltd) 10cm × 4m = £0.17, 15cm × 4m = £0.30, 5cm × 4m = £0.10, 7cm × 4m = £0.15

Kontour
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched

Kontour bandage (Easigrab Ltd) 10cm × 4m = £0.40, 15cm × 4m = £0.66, 5cm × 4m = £0.28, 7.5cm × 4m = £0.35

Mollelast
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Mollelast (Lohmann & Rauscher (UK) Ltd) bandage 4cm × 4m = £0.30

Peha-haft
Polyamide and Cellulose Contour Bandage, cohesive, latex-free
Peha-haft bandage (Paul Hartmann Ltd) 10cm x 4m= £0.77, 12cm x 4m= £0.91, 2.5cm x 4m= £0.74, 4cm x 4m= £0.48, 6cm x 4m= £0.56, 8cm x 4m= £0.67

PremierBand
Polyamide and Cellulose Contour Bandage
PremierBand 4cm (Shermond) 10cm x 4m= £0.17, 15cm x 4m= £0.25, 5cm x 4m= £0.12, 7.5cm x 4m= £0.14

Slinky
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched (all)
Slinky bandage (Molynche Health Care Ltd) 10cm x 4m= £0.72, 15cm x 4m= £1.04, 7.5cm x 4m= £0.59

Stayform
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched (all)
Stayform bandage (Robinson Healthcare) 10cm x 4m= £0.40, 15cm x 4m= £0.68, 5cm x 4m= £0.29, 7.5cm x 4m= £0.36

Tubular bandages and garments
Tubular bandages are available in different forms, according to the function required of them. Some are used under orthopaedic casts and some are suitable for protecting areas to which creams or ointments (other than those containing potent corticosteroids) have been applied. The conformability of the elasticised versions makes them particularly suitable for retaining dressings on difficult parts of the body or for soft tissue injury, but their use as the only means of applying pressure to an oedematous limb or to a varicose ulcer is not appropriate, since the pressure they exert is inadequate. Compression hosiery reduces the recurrence of venous leg ulcers and should be considered for use after wound healing. Silk clothing is available as an alternative to elasticised viscose stockinettes, for use in the management of severe eczema and allergic skin conditions.

Elasticated Surgical Tubular Stockinette, Foam padded is used for relief of pressure and elimination of friction in relevant area; porosity of foam lining allows normal water loss from skin surface.
For Elasticated Tubular Bandage, BP 1993, where no size stated by the prescriber, the 50cm length should be supplied and width endorsed.
Non-elasticised Cotton Stockinette, Bleached, BP 1988 1m lengths is used as basis (with wadding) for plaster of Paris bandages etc., 6m length, compression bandage.
For Non Elasticated Ribbed Cotton and Viscose Surgical Tubular Stockinette, BP 1988, the Drug Tariff specifies various combinations of sizes to provide sufficient material for part or full body coverage. It is used as protective dressings with tar-based and other steroid ointments.

Elasticated

Acti-Fast
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage
Acti-Fast 2-way stretch stockinette (Activa Healthcare Ltd) 10.75cm= £0.04, 17.5cm= £1.83, 20cm= £3.20, 3.5cm= £0.56, 5cm= £0.58, 7.5cm= £0.77

Clinifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage; various colours and sizes
Clinifast stockinette (CliniSupplies Ltd) 10.75cm= £0.06, 17.5cm= £1.83, 3.5cm= £0.56, 5cm= £0.58, 7.5cm= £0.77, clava 5-14 years= £0.75, 6 months-5 years= £0.85, cycle shorts large adult= £16.25, medium adult= £14.25, small adult= £12.50, gloves large adult= £4.99, child/small adult= £4.99, gloves medium adult= £4.99, child= £4.99, gloves small child= £4.99, leggins (Blue, Pink, White) 11-14 years= £11.88, 2-5 years= £9.50, 5-8 years= £10.69, 6-24 months= £7.13, 8-11 years= £11.88, vest short sleeve large adult= £16.25, medium adult= £14.25, small adult= £12.50.

Comifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage; various colours and sizes
Comifast stockinette (Synergy Health Plc) 10.75cm= £0.04, 17.5cm= £1.83, 5cm= £0.56, 6cm= £0.58, 7.5cm= £0.77

Comifast Easywrap
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage; various colours and sizes
Comifast Easywrap stockinette (Synergy Health Plc) clava 5-14 years= £6.75, 6 months-5 years= £5.85, leggings 11-14 years= £11.88, 2-5 years= £9.50, 5-8 years= £10.69, 8-11 years= £11.88, mittens 2-8 years= £2.97, 8-14 years= £2.97, up to 24 months= £2.97, socks 8-14 years= £2.97, up to 8 years= £2.97, tights 6-24 months= £7.13, vest long sleeve 11-14 years= £11.88, 2-5 years= £9.50, 5-8 years= £10.69, 6-24 months= £7.13, 8-11 years= £11.88

Comifast Multistrong
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage; various colours and sizes
Comifast Multistrong 2-way stretch stockinette (Synergy Health Plc) 10.75cm= £0.45, 17.5cm= £2.45, 3.5cm= £0.61, 5cm= £0.63, 7.5cm= £0.83

Coverflex
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage; various colours and sizes
Coverflex stockinette (Paul Hartmann Ltd) 10.75cm= £0.59, 17.5cm= £2.53, 3.5cm= £0.83, 5cm= £0.86, 7.5cm= £5.68

Easifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticised tubular bandage; various colours and sizes
Easifast stockinette (Easigrip Ltd) 10.75cm= £7.23, 17.5cm= £1.91, 3.5cm= £0.65, 5cm= £0.69, 7.5cm= £0.94

Elasticated Surgical Tubular Stockinette, Foam padded or Tupipad
(Drug Tariff specification 25). Fabric as for Elasticated Tubular Bandage with polyurethane foam lining.

Elasticated Tubular Bandage, BP 1993
(Drug Tariff specification 25). Fabric as for Elasticated Tubular Bandage with polyurethane foam lining; lengths 50cm and 1m

Clinical Bandage (CliniSupplies Ltd) 10cm size F= £7.04, 12cm size G= £0.77, 6.25cm size B= £0.61, 6.75cm size C= £0.65, 7.5cm size D= £0.66, 8.75cm size E= £0.74

Comifast stockinette (Synergy Health Plc) 10cm size F= £0.74, 12cm size G= £0.77, 6.25cm size B= £0.61, 6.75cm size C= £0.65, 7.5cm size D= £0.66, 8.75cm size E= £0.74

Easihan EST Bandage (Easihan Ltd) 10cm size F= £1.80, 12cm size G= £2.09, 6.25cm size B= £0.87, 6.75cm size C= £0.95, 7.5cm size D= £0.95, 8.75cm size E= £1.80

Tubigrip bandage (Molynche Health Care Ltd) 10cm size F= £2.04, 12cm size G= £2.35, 6.25cm size B= £0.99, 6.75cm size C= £1.88, 7.5cm size D= £1.88, 8.75cm size E= £2.04

Easigrip bandage (Easigrip Ltd) 10cm size F= £0.75, 12cm size G= £0.78, 6.25cm size B= £0.62, 6.75cm size C= £0.66, 7.5cm size D= £0.68, 8.75cm size E= £0.75

Skinny
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Skinny stockinette (Dermacea Ltd) body suit (Blue, Ecri, Pink) 3-6 months= £16.18, 6-12 months= £18.21, premature= £16.18, up to 3 months= £16.18, clava (Blue, Ecri, Pink) 5-14 years= £7.73, 6 months-5 years= £6.74, gloves large (Beige, Blue, Ecri, Grey, Pink) adult= £5.34, child= £5.34, gloves medium (Beige, Blue, Ecri, Grey, Pink) adult= £5.34, child= £5.34, gloves small (Blue, Ecri, Grey, Pink) adult= £5.29, child= £5.29, knee socks extra (Black, Natural, White) large adult 11+ = £13.94, knee socks large (Black, Natural, White) adult 8-11 = £13.94, child 2-4 = £13.94, knee socks medium (Black, Natural, White) adult 6-8= £13.94, child 1-2 = £13.94, knee socks small (Black, Natural, White) adult
4-6= £13.94, child 0-1= £13.94, leggings (Beige, Blue, Ecru, Grey,
Pink) 11-14 years= £17.20, 2-5 years= £13.74, 5-8 years= £15.52,
6-24 months= £10.48, 8-11 years= £17.20, large adult= £25.13,
medium adult= £23.20, small adult= £21.27, mittens (Blue, Ecru,
Pink) 2-8 years= £3.87, 8-14 years= £3.87, up to 24 months=
£3.87, socks (Blue, Ecru, Pink) 6 months-8 years= £4.27, 814 years= £4.27, vest long sleeve (Beige, Blue, Ecru, Grey, Pink)
11-14 years= £17.20, 2-5 years= £13.74, 5-8 years= £15.52, 624 months= £10.48, 8-11 years= £17.20, large adult= £25.13,
medium adult= £23.20, small adult= £21.27, vest short sleeve
(White) 11-14 years= £17.09, 2-5 years= £13.63, 5-8 years=
£15.36, 6-24 months= £10.38, 8-11 years= £17.09, large adult=
£25.03, medium adult= £23.10, small adult= £21.16, vest
sleeveless (White) 11-14 years= £17.09, 2-5 years= £13.63,
5-8 years= £15.42, 6-24 months= £10.38, 8-11 years= £17.09,
large adult= £25.03, medium adult= £23.10, small adult= £21.16
Tubifast 2-way stretch
(Drug Tariff speciﬁcation 46). Lightweight plain-knitted
elasticated tubular bandage; various colours and sizes
Tubifast 2-way stretch stockinette (Molnlycke Health Care Ltd)
10.75cm= £6.45, 20cm= £3.42, 3.5cm= £0.61, 5cm= £0.63, 7.5cm=
£0.83, gloves extra small child= £5.69, medium/large adult=
£5.69, small child= £5.69, small/medium adult, medium/large
child= £5.69, leggings 2-5 years= £15.14, 5-8 years= £17.04,
8-11 years= £18.93, socks (one size)= £4.79, tights 6-24 months=
£11.36, vest long sleeve 11-14 years= £18.93, 2-5 years= £15.14,
5-8 years= £17.04, 6-24 months= £11.36, 8-11 years= £18.93

Non-elasticated
Cotton Stockinette, Bleached, BP 1988
Knitted fabric, cotton yarn, tubular length, 1m
Cotton stockinette bleached heavyweight (E Sallis Ltd) 10cm, 2.5cm,
5cm, 7.5cm

Silk Clothing
DermaSilk
Knitted silk fabric, hypoallergenic, sericin-free
DermaSilk (Espere Healthcare Ltd) medium/large= £41.63, mediumlarge= £30.97, body suit 0-3 months= £38.13, 12-18 months=
£40.40, 18-24 months= £41.41, 24-36 months= £41.49, 36 months= £38.21, 6-9 months= £39.31, 9-12 months= £40.32,
boxer shorts male adult extra large/XX large= £41.63,
small/small= £41.63, briefs female adult extra large-XX large=
£30.97, small-small= £30.97, facial mask adult= £20.91, child=
£16.40, infant= £16.40, teen= £20.91, gloves extra large adult=
£20.68, gloves large adult= £20.72, gloves medium adult=
£20.72, child= £14.76, gloves small adult= £20.72, child= £14.76,
leggings 0-3 months= £27.22, leggings 12-18 months= £29.47,
leggings 18-24 months= £30.51, leggings 3-4 years= £31.65,
leggings 3-6 months= £27.28, leggings 6-9 months= £28.37,
leggings 9-12 months= £29.41, leggings adult female XX large=
£78.31, extra large= £78.31, large= £78.31, medium= £78.31,
small= £78.31, leggings adult male XX large= £78.31, extra
large= £78.31, large= £78.31, medium= £78.31, small= £78.31,
pyjamas 10-12 years= £81.95, 3-4 years= £71.01, 5-6 years=
£75.39, 7-8 years= £78.67, roll neck shirt 10-12 years= £54.42, 34 years= £47.09, 5-6 years= £50.23, 7-8 years= £52.33, round neck
shirt adult female XX large= £77.40, extra large= £77.40, large=
£77.40, medium= £77.40, small= £77.40, round neck shirt adult
male XX large= £77.40, extra large= £77.40, large= £77.40,
medium= £77.40, small= £77.40, tubular sleeves= £33.67,
sleeves= £27.28, undersocks adult 11-13= £18.42, 5 1/2 - 6 1/2=
£18.42, 7 - 8 1/2= £18.42, 9 - 10 1/2= £18.42, undersocks child 25= £18.42, 3-8= £18.42, 9-1= £18.42, unisex roll neck shirt adult
XX large= £77.40, extra large= £77.40, large= £77.40, medium=
£77.40, small= £77.40
DreamSkin
Knitted silk fabric, hypoallergenic, sericin-free, with
methyacrylate copolymer and zinc-based antibacterial
DreamSkin (DreamSkin Health Ltd) baby leggings with foldaway feet
0-3 months= £25.19, 12-18 months= £28.07, 18-24 months=
£28.59, 3-4 years= £30.15, 3-6 months= £25.69, 6-9 months=
£27.03, 9-12 months= £27.55, body suit 0-3 months= £35.48, 1218 months= £38.49, 18-24 months= £39.01, 3-4 years= £40.57, 36 months= £35.99, 6-9 months= £37.44, 9-12 months= £37.99,
boxer shorts 11-12 years= £21.39, boxer shorts 3-4 years= £21.39,

Support bandages 1407
boxer shorts 5-6 years= £21.39, boxer shorts 7-8 years= £21.39,
boxer shorts 9-10 years= £21.39, boxer shorts male adult XX
large= £33.65, extra large= £33.65, large= £33.65, medium=
£33.65, small= £33.65, briefs 11-12 years= £21.39, briefs 3-4
years= £21.39, briefs 5-6 years= £21.39, briefs 7-8 years= £21.39,
briefs 9-10 years= £21.39, briefs female adult XX large= £31.60,
extra large= £31.60, large= £31.60, medium= £31.60, small=
£31.60, eye mask= £10.16, footless leggings 11-12 years boys=
£33.18, girls= £33.18, footless leggings 3-4 years boys= £30.15,
girls= £30.15, footless leggings 5-6 years boys= £31.64, girls=
£31.64, footless leggings 7-8 years boys= £32.15, girls= £32.15,
footless leggings 9-10 years boys= £32.67, girls= £32.67, footless
leggings adult female XX large= £76.32, extra large= £76.32,
large= £76.32, medium= £76.32, small= £76.32, footless leggings
adult male XX large= £76.32, extra large= £76.32, large= £76.32,
medium= £76.32, small= £76.32, gloves extra large adult=
£20.03, gloves large adult= £20.03, gloves medium adult=
£20.03, child= £14.28, gloves small adult= £20.03, child= £14.28,
head mask child= £15.62, infant= £15.62, teenager= £20.38,
heel-less undersocks= £23.61, liner socks adult female 4 - 5 1/2=
£17.95, 6 - 8 1/2= £17.95, liner socks adult male 6 - 8 1/2= £17.95,
9 - 11= £17.95, liner socks child 12 1/2 - 3 1/2= £17.95, 3 - 5 1/2=
£17.95, 4 - 5 1/2= £17.95, 6 - 8 1/2= £17.95, 9 - 12= £17.95, polo
neck shirt 11-12 years boy= £53.04, girl= £53.04, polo neck shirt
3-4 years boy= £45.89, girl= £45.89, polo neck shirt 5-6 years
boy= £48.95, girl= £48.95, polo neck shirt 7-8 years boy= £50.99,
girl= £50.99, polo neck shirt 9-10 years boy= £52.02, girl= £52.02,
polo neck shirt adult female XX large= £75.43, extra large=
£75.43, large= £75.43, medium= £75.43, small= £75.43, polo neck
shirt adult male XX large= £75.43, extra large= £75.43, large=
£75.43, medium= £75.43, small= £75.43, pyjamas 11-12 years
boy= £78.06, girl= £78.06, pyjamas 3-4 years boy= £67.65, girl=
£67.65, pyjamas 5-6 years boy= £71.81, girl= £71.81, pyjamas 78 years boy= £74.94, girl= £74.94, pyjamas 9-10 years boy=
£76.53, girl= £76.53, round neck shirt 3-4 years= £45.90, round
neck shirt 5-6 years= £47.94, round neck shirt 7-8 years= £49.98,
round neck shirt 9-10 years= £51.00, round neck shirt adult
female XX large= £75.43, extra large= £75.43, large= £75.43,
medium= £75.43, small= £75.43, round neck shirt adult male XX
large= £75.43, extra large= £75.43, large= £75.43, medium=
£75.43, small= £75.43, tubular sleeves= £26.38, sleeves= £32.81

Support bandages
Light support bandages, which include the various forms of
crepe bandage, are used in the prevention of oedema; they
are also used to provide support for mild sprains and joints
but their effectiveness has not been proven for this purpose.
Since they have limited extensibility, they are able to provide
light support without exerting undue pressure. For a warning
against injudicious compression see Compression bandages.
CliniLite
Knitted fabric, viscose and elastomer yarn. Type 2 (light
support bandage)
CliniLite bandage (CliniSupplies Ltd) 10cm 6 4.5m= £0.80, 15cm 6
4.5m= £1.16, 5cm 6 4.5m= £0.44, 7.5cm 6 4.5m= £0.61
CliniPlus
Knitted fabric, viscose and elastomer yarn. Type 2 (light
support bandage)
CliniPlus (CliniSupplies Ltd) bandage 10cm 6 8.7m= £1.80
Cotton Crepe Bandage
Light support bandage, 4.5 m stretched (all)
Hospicrepe 239 bandage (Paul Hartmann Ltd) 10cm 6 4.5m= £0.81,
15cm 6 4.5m= £1.18, 5cm 6 4.5m= £0.44, 7.5cm 6 4.5m= £0.63
Cotton Crepe Bandage, BP 1988
Fabric, plain weave, warp of crepe-twisted cotton threads,
weft of cotton and/or viscose threads; stretch bandage. 4.5 m
stretched (both)
Elastocrepe bandage (BSN medical Ltd) 10cm 6 4.5m, 7.5cm 6 4.5m
Flexocrepe bandage (Robinson Healthcare) 10cm 6 4.5m, 7.5cm 6
4.5m
Sterocrepe bandage (Steroplast Healthcare Ltd) 10cm 6 4.5m, 7.5cm
6 4.5m

A4
Wound management | Appendix 4

BNF 73


Cotton Suspensory Bandage

(Drug Tariff) Type 1: cotton net bag with draw tapes and webbing waistband; small, medium, and large (all)

Crepe Bandage, BP 1988

Fabric, plain weave, warp of wool threads and crepe-twisted cotton threads, weft of cotton threads; stretch bandage; 4.5 m stretched

Alvita crepe bandage (Alliance Healthcare (Distribution) Ltd) 10 cm × 4.5 m, 15 cm × 4.5 m, 5 cm × 4.5 m, 7.5 cm × 4.5 m

Clinicrepe bandage (CliniSupplies Ltd) 10 cm × 4.5 m, 15 cm × 4.5 m, 5 cm × 4.5 m, 7.5 cm × 4.5 m

Crepe bandage (Robert Bailey & Son Plc) 10 cm × 4.5 m, 15 cm × 4.5 m, 5 cm × 4.5 m, 7.5 cm × 4.5 m

Propax crepe bandage (BSN medical Ltd) 10 cm × 4.5 m, 15 cm × 4.5 m, 5 cm × 4.5 m, 7.5 cm × 4.5 m

Vernaid crepe bandage (Synergy Health Plc) 10 cm × 4.5 m, 15 cm × 4.5 m, 5 cm × 4.5 m, 7.5 cm × 4.5 m

Elset

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

Elset (Molinlycke Health Care Ltd) S bandage 15 cm × 12 m = £5.60, bandage 10 cm × 6 m = £2.61, 10 cm × 8 m = £3.34, 15 cm × 6 m = £2.80.

Hospicare 233

Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe, 4.5 m stretched (all)

Hospicare 233 bandage (Paul Hartmann Ltd) 10 cm × 4.5 m = £0.96, 15 cm × 4.5 m = £1.36, 5 cm × 4.5 m = £0.52, 7.5 cm × 4.5 m = £0.72

Hospilite

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Hospilite bandage (Paul Hartmann Ltd) 10 cm × 4.5 m = £0.62, 15 cm × 4.5 m = £0.91, 5 cm × 4.5 m = £0.37, 7.5 cm × 4.5 m = £0.51

K-Lite

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

K-Lite (Urgo Ltd) Long bandage 10 cm × 5.25 m = £1.16, bandage 10 cm × 4.5 m = £1.01, 15 cm × 4.5 m = £1.46, 5 cm × 4.5 m = £0.55, 7 cm × 4.5 m = £0.77

K-Plus

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

K-Plus (Urgo Ltd) Long bandage 10 cm × 10.25 m = £2.65, bandage 10 cm × 8.7 m = £2.29

Knit-Firm

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

Knit-Firm bandage (Millpledge Healthcare) 10 cm × 4.5 m = £0.66, 15 cm × 4.5 m = £0.96, 5 cm × 4.5 m = £0.36, 7 cm × 4.5 m = £0.51

L3

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

L3 (Smith & Nephew Healthcare Ltd) bandage 10 cm × 8.6 m = £2.22

Neosport

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Neosport bandage (Neomedic Ltd) 10 cm × 4.5 m = £0.91, 15 cm × 4.5 m = £1.12, 5 cm × 4.5 m = £0.54, 7.5 cm × 4.5 m = £0.73

PremierBand

Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe, 4.5 m stretched (all)

PremierBand bandage (Shermond) 10 cm × 4.5 m = £0.79, 15 cm × 4.5 m = £1.18, 5 cm × 4.5 m = £0.45, 7.5 cm × 4.5 m = £0.63

Profore #2

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Profore #2 (Smith & Nephew Healthcare Ltd) bandage 10 cm × 4.5 m = £1.36, latex free bandage 10 cm × 4.5 m = £1.44

Profore #3

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

Profore #3 (Smith & Nephew Healthcare Ltd) bandage 10 cm × 8.7 m = £3.96, latex free bandage 10 cm × 8.7 m = £4.31

Setocrepe

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Setocrepe (Molinlycke Health Care Ltd) bandage 10 cm × 4.5 m = £1.20

Soffcrepe

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Soffcrepe bandage (BSN medical Ltd) 10 cm × 4.5 m = £1.24, 15 cm × 4.5 m = £1.80, 5 cm × 4.5 m = £0.69, 7.5 cm × 4.5 m = £0.98

Adhesive bandages

Adhesive bandages are used to provide compression in the treatment of varicose veins and for the support of injured joints; they should no longer be used for the support of fractured ribs and clavicles. They have also been used with zinc paste bandage in the treatment of venous ulcers, but they can cause skin reactions in susceptible patients and may not produce sufficient pressures for healing (significantly lower than those provided by other compression bandages).

Elastic Adhesive Bandage, BP 1993

Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads spread with adhesive mass containing zinc oxide. 4.5 m stretched

Tensoplast bandage (BSN medical Ltd) 10 cm × 4.5 m, 5 cm × 4.5 m, 7.5 cm × 4.5 m

Cohesive bandages

Cohesive bandages adhere to themselves, but not to the skin, and are useful for providing support for sports use where ordinary stretch bandages might become displaced and adhesive bandages are inappropriate. Care is needed in their application, however, since the loss of ability for movement between turns of the bandage to equalise local areas of high tension carries the potential for creating a tourniquet effect. Cohesive bandages can be used to support sprained joints and as an outer layer for multi-layer compression bandaging; they should not be used if arterial disease is suspected.

Cohesive extensible bandages

Coban

Bandage

Coban (3M Health Care Ltd) self-adherent bandage 10 cm × 6 m = £2.93

K Press

Bandage

K Press bandage (Urgo Ltd) 10 cm × 6.5 m = £2.93, 10 cm × 7.5 m = £3.42, 12 cm × 7.5 m = £4.31, 8 cm × 7.5 cm = £3.22

Profore #4

Bandage

Profore #4 (Smith & Nephew Healthcare Ltd) bandage 10 cm × 2.5 m = £3.28, latex free bandage 10 cm × 2.5 m = £3.56

Ultra Fast

Bandage

Ultra (Robinson Healthcare) Fast cohesive bandage 10 cm × 6.3 m = £2.59

Compression bandages

High compression products are used to provide the high compression needed for the management of gross varices, post-thrombotic venous insufficiency, venous leg ulcers, and gross oedema in average-sized limbs. Their use calls for an expert knowledge of the elastic properties of the products and experience in the technique of providing careful graduated compression. Incorrect application can lead to uneven and inadequate pressures or to hazardous levels of pressure. In particular, injudicious use of compression in limbs with arterial disease has been reported to cause severe skin and tissue necrosis (in some instances calling for
amputation). Doppler testing is required before treatment with compression. Oral pentoxifylline p. 222 can be used as adjunct therapy if a chronic venous leg ulcer does not respond to compression bandaging [unlicensed indication].

**High compression bandages**

**High Compression Bandage**
Cotton, viscose, nylon, and Lycra® extensible bandage, 3m (unstretched)

- K-Threec (Urgo Ltd) bandage 10cm × 3m= £2.85
- SurePress (Convatec Ltd) bandage 10cm × 3m= £3.65

**PEC High Compression Bandages**
Polyamide, elastane, and cotton compression (high) extensible bandage, 3.5 m unstretched

- Setospread (Mohlycke Health Care Ltd) bandage 10cm × 3.5m= £3.55

**VEC High Compression Bandages**
Viscose, elastane, and cotton compression (high) extensible bandage, 2 m unstretched (both)

- Tensopress bandage (BSN medical Ltd) 10cm × 3m= £3.49, 7.5cm × 3m= £2.71

**Short stretch compression bandages**

**Actico**
Bandage

- Actico bandage (Activa Healthcare Ltd) 10cm × 6m= £3.38, 12cm × 6m= £4.31, 4cm × 6m= £2.42, 6cm × 6m= £2.83, 8cm × 6m= £3.25

**Comprilan**
Bandage

- Comprilan bandage (BSN medical Ltd) 10cm × 5m= £3.41, 12cm × 5m= £4.15, 6cm × 5m= £2.70, 8cm × 5m= £3.17

**Rosidal K**
Bandage

- Rosidal K bandage (Lohmann & Rauscher (UK) Ltd) 10cm × 10m= £6.02, 10cm × 5m= £3.46, 12cm × 5m= £4.20, 6cm × 5m= £2.65, 8cm × 5m= £3.17

**Silkolan**
Bandage

**Sub-compression wadding bandage**

**Cellona Undercast Padding**
Padding

- Cellona Undercast padding bandage (Lohmann & Rauscher (UK) Ltd) 10cm × 2.75m= £0.47, 15cm × 2.75m= £0.60, 5cm × 2.75m= £0.31, 7.5cm × 2.75m= £0.38

**Flexi-Ban**
Padding

- Flexi-Ban (Activa Healthcare Ltd) bandage 10cm × 3.5m= £0.50

**K Tech Reduced**
Padding

- K Tech Reduced bandage 10cm × (Urgo Ltd) 6m= £4.75, 7.3m= £5.18

**K-Soft**
Padding

- K-Soft (Urgo Ltd) Long bandage 10cm × 4.5m= £0.57, bandage 10cm × 3.5m= £0.46

**K-Tech (K Tech in DMD)**
Padding

- K Tech (Urgo Ltd) Reduced bandage 10cm × 7.3m= £5.18, bandage 10cm × 5m= £3.96, 10cm × 6m= £4.75, 12cm × 6m= £5.99, 12cm × 7.3m= £6.54, 8cm × 6m= £4.49, 8cm × 7.3m= £4.89

**Ortho-Band Plus**
Padding

- Ortho-Band (Millipede Healthcare) Plus bandage 10cm × 3.5m= £0.37

**Profores #1**
Padding

- Profores #1 (Smith & Nephew Healthcare Ltd) bandage 10cm × 3.5m= £0.71, latex free bandage 10cm × 3.5m= £0.77

**Softexe**
Padding

- Softexe (Mohlycke Health Care Ltd) bandage 10cm × 3.5m= £0.62

**SurePres**
Padding

- SurePres (Convatec Ltd) bandage 10cm × 3m= £3.65

**Ultra Soft**
Padding

- Ultra (Robinson Healthcare) Soft wadding bandage 10cm × 3.5m= £0.39

**Velband**
Padding

- Velband (BSN medical Ltd) absorbent bandage 10cm × 4.5m= £0.73

**Multi-layer compression bandaging**

Multi-layer compression bandaging systems are an alternative to High Compression Bandages for the treatment of venous leg ulcers. Compression is achieved by the combined effects of two or three extensible bandages applied over a layer of orthopaedic wadding and a wound contact dressing.

**Four layer systems**

**K-Four**
Padding

- K-Four multi-layer compression bandaging kit, four layer system

**Profores**
Wound contact layer

**Ultra Four**
Wound contact layer

**Two layer systems**

**Coban 2**
Multi-layer compression bandaging kit, two layer system (latex-free, foam bandage and cohesive compression bandage)

**K Two**
Multi-layer compression bandaging kit, two layer system

**UrgoKTwo** (Urgo Ltd) Reduced latex free multi-layer compression bandage kit (10cm) 18cm-25cm ankle circumference= £8.68, 25cm-32cm ankle circumference= £8.93, Reduced multi-layer compression bandage kit 18cm-25cm ankle circumference= £8.18, 25cm-32cm ankle circumference= £8.93, latex free multi-layer compression bandage kit (10cm) 18cm-25cm ankle circumference= £8.17, 25cm-32cm ankle circumference= £8.93, multi-layer compression bandage kit (12cm) 18cm-25cm ankle circumference= £10.30, 25cm-32cm ankle circumference= £11.26, multi-layer compression bandage kit (6cm) 18cm-25cm ankle circumference= £7.71, 25cm-32cm ankle circumference= £8.93.
£8.39, multi-layer compression bandage kit size 0 short 18cm-25cm ankle circumference= £6.50, with UrgoStart multi-layer compression bandage kit 18cm-25cm ankle circumference= £10.19, 25cm-32cm ankle circumference= £10.86

**Medicated bandages**

Zinc Paste Bandage has been used with compression bandaging for the treatment of venous leg ulcers. However, paste bandages are associated with hypersensitivity reactions and should be used with caution. Zinc paste bandages are also used with coal tar or ichthammol in chronic lichenified skin conditions such as chronic eczema (ichthammol often being preferred since its action is considered to be milder). They are also used with calamine in milder eczematous skin conditions. Zipzoc® can be used under appropriate compression bandages or hosiery in chronic venous insufficiency.

**Zinc Paste Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide; requires additional bandaging

*Excipients: may include* cetostearyl alcohol, hydroxybenzoates

**Viscopaste** (Smith & Nephew Healthcare Ltd) PB7 bandage 7.5cm × 6m= £3.69

**Zinc Paste and Ichthammol Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide and ichthammol; requires additional bandaging

*Excipients: may include* cetostearyl alcohol

**Ichthopaste** (Smith & Nephew Healthcare Ltd) bandage 7.5cm × 6m= £3.72

**Medicated stocking**

**Zipzoc**

Sterile rayon stocking impregnated with ointment containing zinc oxide 20%

**Zipzoc** (Smith & Nephew Healthcare Ltd) stockings= £31.26

**Compression hosiery and garments**

Compression (elastic) hosiery is used to treat conditions associated with chronic venous insufficiency, to prevent recurrence of thrombosis, or to reduce the risk of further venous ulceration after treatment with compression bandaging. Doppler testing to confirm arterial sufficiency is required before recommending the use of compression hosiery.

Before elastic hosiery can be dispensed, the quantity (single or pair), article (including accessories), and compression class must be specified by the prescriber. There are different compression values for graduated compression hosiery and lymphoedema garments (see table below). All dispensed elastic hosiery articles must state on the packaging that they conform with Drug Tariff technical specification No. 40, for further details see Drug Tariff.

**Graduated Compression hosiery, Class 1 Light Support** is used for superficial or early varices, varicosity during pregnancy.

**Graduated Compression hosiery, Class 2 Medium Support** is used for varices of medium severity, ulcer treatment and prophylaxis, mild oedema, varicosity during pregnancy.

**Graduated Compression hosiery, Class 3 Strong Support** is used for gross varices, post thrombotic venous insufficiency, gross oedema, ulcer treatment and prophylaxis.

**Compression values for hosiery and lymphoedema garments**

Class 1: Compression hosiery (British standard) 14–17 mmHg, lymphoedema garments (European classification) 18–21 mmHg; Class 2 Compression hosiery (British standard) 18–24 mmHg, lymphoedema garments (European classification) 23–32 mmHg; Class 3 Compression hosiery (British standard) 25–35 mmHg, lymphoedema garments (European classification) 34–46 mmHg; Class 4 Compression hosiery (British standard)—not available, lymphoedema garments (European classification) 49–70 mmHg; Class 4 *super* Compression hosiery (British standard)—not available, lymphoedema garments (European classification) 60–90 mmHg.

**Graduated compression hosiery**

**Class 1 Light Support**

Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel

**Class 2 Light Support**

Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel

**Accessories**

**Suspender**

Suspender, for thigh stockings

**Anklets**

**Class 2 Medium Support**

Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Class 3 Strong Support**

Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Knee caps**

**Class 2 Medium Support**

Knee caps, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Class 3 Strong Support**

Knee caps, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Lymphoedema garments**

Lymphoedema compression garments are used to maintain limb shape and prevent additional fluid retention. Either flat-bed or circular knitting methods are used in the manufacture of elasticated compression garments. Seamless, circular-knitted garments (in standard sizes) can be used to prevent swelling if the lymphoedema is well controlled and if the limb is in good shape and without skin folds. Flat-knitted garments (usually made-to-measure) with a seam, provide greater rigidity and stiffness to maintain reduction of lymphoedema following treatment with compression bandages. A standard range of light, medium, or high compression garments are available, as well as low compression (12–16 mmHg) armsleeves, made-to-measure garments up to compression 50 mmHg, and accessories—see Drug Tariff for details. Note There are different compression values for lymphoedema garments and graduated compression hosiery, see above.
Dental Practitioners’ Formulary

List of Dental Preparations

The following list has been approved by the appropriate Secretaries of State, and the preparations therein may be prescribed by dental practitioners on form FP10D (GP14 in Scotland, WP10D in Wales).

Licensed sugar-free versions, where available, are preferred. Licensed alcohol-free mouthwashes, where available, are preferred.

Aciclovir Cream, BP
Aciclovir Oral Suspension, BP, 200 mg/5 mL
Aciclovir Tablets, BP, 200 mg
Aciclovir Tablets, BP, 800 mg
Amoxicillin Capsules, BP
Amoxicillin Oral Powder, DPF
Amoxicillin Oral Suspension, BP
Artificial Saliva Gel, DPF
Artificial Saliva Oral Spray, DPF
Artificial Saliva Pastilles, DPF
Artificial Saliva Protective Spray, DPF
Artificial Saliva Substitutes as listed below (to be prescribed only for indications approved by ACBS (patients suffering from dry mouth as a result of having or, having undergone, radiotherapy or sicca syndrome):

BioXtra® Gel Mouthspray
BioXtra® Moisturising Gel
Glandosane® Saliveze®
Artificial Saliva Substitute Spray, DPF
Aspirin Tablets, Dispersible, BP
Azithromycin Capsules, 250 mg, DPF
Azithromycin Oral Suspension, 200 mg/5 mL, DPF
Azithromycin Tablets, 250 mg, DPF
Azithromycin Tablets, 500 mg, DPF
Beclometasone Pressurised Inhalation, BP,
50 micrograms/metered inhalation, CFC-free, as: Clen modulite®
Benzylamine Mouthwash, BP 0.15%
Benzylamine Oromucosal Spray, BP 0.15%
Betamethasone Soluble Tablets, 500 micrograms, DPF
Carbamazine Tablets, BP
Cefalexin Capsules, BP
Cefalexin Oral Suspension, BP
Cefalexin Tablets, BP
Cefradine Capsules, BP
Cetirizine Oral Solution, BP, 5 mg/5 mL
Cetirizine Tablets, BP, 10 mg
Chlorhexidine Gluconate Gel, BP
Chlorhexidine Mouthwash, BP
Chlorhexidine Oral Spray, BP
Chlorphenamine Oral Solution, BP
Chlorphenamine Tablets, BP
Choline Salicylate Dental Gel, BP
Clarithromycin Oral Suspension, 125 mg/5 mL, DPF
Clarithromycin Oral Suspension, 250 mg/5 mL, DPF
Clarithromycin Tablets, BP
Clindamycin Capsules, BP
Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)
Co-amoxiclav Oral Suspension, BP, 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL
Co-amoxiclav Oral Suspension, BP, 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL
Diazepam Oral Solution, BP, 2 mg/5 mL

Diazepam Tablets, BP
Diclofenac Sodium Tablets, Gastro-resistant, BP
Dihydrocodeine Tablets, BP, 30 mg
Doxycline Tablets, Dispersible, BP
Doxycline Capsules, BP, 100 mg
Doxycline Tablets, 20 mg, DPF
Ephedrine Nasal Drops, BP
Erythromycin Ethyl Succinate Oral Suspension, BP
Erythromycin Ethyl Succinate Tablets, BP
Erythromycin Stearate Tablets, BP
Erythromycin Tablets, Gastro-resistant, BP
Fluconazole Capsules, 50 mg, DPF
Fluconazole Oral Suspension, 50 mg/5 mL, DPF
Hydrocortisone Cream, BP, 1%
Hydrocortisone Oromucosal Tablets, BP
Hydrogen Peroxide Mouthwash, BP, 6%
Ibuprofen Oral Suspension, BP, sugar-free
Ibuprofen Tablets, BP
Lansoprazole Capsules, Gastro-resistant, BP
Lidocaine Ointment, BP, 5%
Lidocaine Spray 10%, BP
Loratadine Syrup, 5 mg/5 mL, DPF
Loratadine Tablets, BP, 10 mg
Menthol and Eucalyptus Inhalation, BP 1980
Metronidazole Oral Suspension, BP
Metronidazole Tablets, BP
Miconazole Cream, BP
Miconazole Oromucosal Gel, BP
Miconazole and Hydrocortisone Cream, BP
Miconazole and Hydrocortisone Ointment, BP
Nystatin Oral Suspension, BP
Omeprazole Capsules, Gastro-resistant, BP
Oxycycline Tablets, BP
Paracetamol Oral Suspension, BP
Paracetamol Tablets, BP
Paracetamol Tablets, Soluble, BP
Phenoxybenzylpenicillin Oral Solution, BP
Phenoxybenzylpenicillin Tablets, BP
Promethazine Hydrochloride Tablets, BP
Promethazine Oral Solution, BP
Saliva Stimulating Tablets, DPF
Sodium Chloride Mouthwash, Compound, BP
Sodium Fluoride Toothpaste
Sodium Fluoride Tablets, BP
Sodium Fluoride Oral Drops, BP
Sodium Fluoride Tablets, BP
Sodium Fluoride Toothpaste 0.619%, DPF
Sodium Fluoride Toothpaste 1.1%, DPF
Sodium Fusidate Ointment, BP
Temazepam Oral Solution, BP
Temazepam Tablets, BP
Tetracycline Tablets, BP

Preparations in this list which are not included in the BP or BPC are described under Details of DPF preparations. For details of preparations that can be prescribed, see individual entries under the relevant drug monographs throughout the BNF publications.

Details of DPF preparations

Preparations on the List of Dental Preparations which are specified as DPF are described as follows in the DPF. Although brand names have sometimes been included for identification purposes preparations on the list should be prescribed by non-proprietary name.

Amoxicillin Oral Powder
amoxicillin (as trihydrate) 3 g sachet
Artificial Saliva Gel
(proprietary product: Biotene Oralbalance), lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis

Artificial Saliva Oral Spray
(proprietary product: Xerotin) consists of water, sorbitol, carmellose (carboxymethylcellulose), potassium chloride, sodium chloride, potassium phosphate, magnesium chloride, calcium chloride and other ingredients, pH neutral

Artificial Saliva Pastilles
(proprietary product: Salivix), consists of acacia, malic acid, and other ingredients

Artificial Saliva Protective Spray
(proprietary product: Aquoral) consists of oxidised glycerol triesters, silicon dioxide, flavouring agents, aspartame

Artificial Saliva Substitute Spray
(proprietary product: AS Saliva Orthana Spray) consists of mucin, methylparaben, benzalkonium chloride, EDTA, xylitol, peppermint oil, spearmint oil, mineral salts

Azithromycin Capsules
azithromycin 250 mg

Azithromycin Oral Suspension 200 mg/5 mL
azithromycin 200 mg/5 mL when reconstituted with water

Azithromycin Tablets
azithromycin 250 mg and 500 mg

Betamethasone Soluble Tablets 500 micrograms
betamethasone (as sodium phosphate) 500 micrograms

Chlorhexidine Oral Spray
(proprietary product: Corsodyl Oral Spray), chlorhexidine gluconate 0.2%

Clarithromycin Oral Suspension 125 mg/5 mL
clarithromycin 125 mg/5 mL when reconstituted with water

Clarithromycin Oral Suspension 250 mg/5 mL
clarithromycin 250 mg/5 mL when reconstituted with water

Doxycycline Tablets 20 mg
(proprietary product: Periostat), doxycycline (as hyclate) 20 mg

Fluconazole Capsules 50 mg
fluconazole 50 mg

Fluconazole Oral Suspension 50 mg/5 mL
(proprietary product: Diflucan), fluconazole 50 mg/5 mL when reconstituted with water

Lidocaine Spray 10%
(proprietary product: Xylocaine Spray), lidocaine 10% supplying 10 mg lidocaine/spray

Loratadine Syrup 5 mg/5 mL
loratadine 5 mg/5 mL

Saliva Stimulating Tablets
(proprietary product: SST), citric acid, malic acid and other ingredients in a sorbitol base

Sodium Fluoride Toothpaste 0.619%
(proprietary product: Duraphat '2800 ppm' Toothpaste), sodium fluoride 0.619%

Sodium Fluoride Toothpaste 1.1%
(proprietary product: Duraphat '5000 ppm' Toothpaste), sodium fluoride 1.1%
Nurse Prescribers’ Formulary

Nurse Prescribers’ Formulary for Community Practitioners

List of preparations approved by the Secretary of State which may be prescribed on form FP10P (form HS21(N) in Northern Ireland, form GP10(N) in Scotland, forms WP10CN and WP10PN in Wales) by Nurses for National Health Service patients.

Community practitioners who have completed the necessary training may only prescribe items appearing in the nurse prescribers’ list set out below. Community Practitioner Nurse Prescribers are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved generic name.

Medicinal Preparations

Preparations on this list which are not included in the BP or BPC are described under Details of NPF preparations.

Almond Oil Ear Drops, BP
Arachis Oil Enema, NPF
Aspirin Tablets, Dispersible, 300 mg, BP (max. 96 tablets; max. pack size 32 tablets)
Bisacodyl Suppositories, BP (includes 5-mg and 10-mg strengths)
Bisacodyl Tablets, BP
Catheter Maintenance Solution, Sodium Chloride, NPF
Catheter Maintenance Solution, 'Solution G', NPF
Catheter Maintenance Solution, 'Solution R', NPF
Chlorhexidine Gluconate Alcoholic Solutions containing at least 0.05%
Chlorhexidine Gluconate Aqueous Solutions containing at least 0.05%
Choline Salicylate Dental Gel, BP
Clotrimazole Cream 1%, BP
Co-danthrane Capsules, NPF
Co-danthramer Capsules, Strong, NPF
Co-danthramer Capsules, Strong, NPF
Co-danthrusate Capsules, NPF
Co-danthrusate Oral Suspension, Strong, NPF
Crotamiton Cream, BP
Crotamiton Lotion, BP
Dimeticone barrier creams containing at least 10%
Dimeticone Lotion, NPF
Docusate Capsules, BP
Docusate Enema, NPF
Docusate Oral Solution, BP
Docusate Oral Solution, Paediatric, BP
Econazole Cream 1%, BP
Emollients as listed below:
  Aquadrate® 10% w/w Cream
  Arachis Oil, BP
  Balneum® Plus Cream
  Cetraben® Emollient Cream
  Dermamist®
  Diprobse® Cream
  Diprobse® Ointment
  Doublebase®
  Doublebase® Dayleve Gel
  E45® Cream
  E45® Itch Relief Cream
  Emulsifying Ointment, BP
  Eucerin® Intensive 10% w/w Urea Treatment Cream
  Eucerin® Intensive 10% w/w Urea Treatment Lotion
  Hydromol® Cream
  Hydromol® Intensive
  Hydrosol Ointment, BP
  Lipobase®
  Liquid and White Soft Paraffin Ointment, NPF
  Neutrogena® Norwegian Formula Dermatological Cream
  Nutraplus® Cream
  Oilatum® Cream
  Oilatum® Junior Cream
  Paraffin, White Soft, BP
  Paraffin, Yellow Soft, BP
  Ultrabase®
  Unguentum M®

Emollient Bath and Shower Preparations as listed below:
Aqueous Cream, BP
Balneum® (except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff))
Balneum Plus® Bath Oil (except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff))
Cetraben® Emollient Bath Additive
Dermalo® Bath Emollient
Doublebase® Emollient Bath Additive
Doublebase® Emollient Shower Gel
Doublebase® Emollient Wash Gel
Hydromol® Bath and Shower Emollient
Oilatum® Emollient
Oilatum® Gel
Oilatum® Junior Bath Additive
Zerolatum® Emollient Medicinal Bath Oil
Folic Acid Tablets 400 micrograms, BP
Glycerol Suppositories, BP
Ibuprofen Oral Suspension, BP (except for indications and doses that are prescription-only)
Ibuprofen Tablets, BP (except for indications and doses that are prescription-only)
Isophagula Husk Granules, BP
Isophagula Husk Granules, Effervescent, BP
Isophagula Husk Oral Powder, BP
Lactulose Solution, BP
Lidocaine Ointment, BP
Lidocaine and Chlorhexidine Gel, BP
Macrogol Oral Liquid, Compound, NPF
Macrogol Oral Powder, Compound, NPF
Macrogol Oral Powder, Compound, Half-strength, NPF
Magnesium Hydroxide Mixture, BP
Magnesium Sulfate Paste, BP
Malathion aqueous lotions containing at least 0.5%
Mebendazole Oral Suspension, NPF
Mebendazole Tablets, NPF
Methylcellulose Tablets, BP
Miconazole Cream 2%, BP
Miconazole Oromucosal Gel, BP
Mouthwash Solution-tablets, NPF
Nicotine Inhalation Cartridge for Oromucosal Use, NPF
Nicotine Lozenge, NPF
Nicotine Medicated Chewing Gum, NPF
Nicotine Nasal Spray, NPF
Nicotine Oral Spray, NPF
Nicotine Sublingual Tablets, NPF
Nicotine Transdermal Patches, NPF
Nystatin Oral Suspension, BP
Olive Oil Ear Drops, BP
Paracetamol Oral Suspension, BP (includes 120 mg/5 mL and 250 mg/5 mL strengths—both of which are available as sugar-free formulations)
Paracetamol Tablets, BP (max. 96 tablets; max. pack size 32 tablets)
Paracetamol Tablets, Soluble, BP (includes 120-mg and 500-mg tablets; max. 96 tablets; max. pack size 32 tablets)
Permethrin Cream, NPF
Phosphates Enema, BP
Povidone–Iodine Solution, BP
Senna Oral Solution, NPF
Senna Tablets, BP
Senna and Ispaghula Granules, NPF
Sodium Chloride Solution, Sterile, BP
Sodium Citrate Compound Enema, NPF
Sodium Picosulfate Capsules, NPF
Sodium Picosulfate Elixir, NPF
Spermicidal contraceptives as listed below: Gygel® Contraceptive Jelly
Sterculia Granules, NPF
Sterculia and Frangula Granules, NPF
Titanium Oxidation, BP
Water for Injections, BP
Zinc and Castor Oil Ointment, BP
Zinc Oxide and Dimeticon Spray, NPF
Zinc Oxide Impregnated Medicated Bandage, NPF
Zinc Oxide Impregnated Medicated Stocking, NPF
Zinc Paste Bandage, BP 1993
Zinc Paste and Ichthammol Bandage, BP 1993

Appliances and Reagents (including Wound Management Products)

Community Practitioner Nurse Prescribers in England, Wales and Northern Ireland can prescribe any appliance or reagent in the relevant Drug Tariff. In the Scottish Drug Tariff, Appliances and Reagents which may not be prescribed by Nurses are annotated Nx.

Appliances (including Contraceptive Devices) as listed in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 (Appliances) and Part 2 (Dressings) of the Scottish Drug Tariff). (Where it is not appropriate for nurse prescribers in family planning clinics to prescribe contraceptive devices using form FP1(P) (forms WP10CN and WP10PN in Wales), they may prescribe using the same system as doctors in the clinic.)

Incontinence Appliances as listed in Part IXB of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 5 of the Scottish Drug Tariff).

Stoma Appliances and Associated Products as listed in Part IXC of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 6 of the Scottish Drug Tariff).

Chemical Reagents as listed in Part IXR of the Drug Tariff (Part II of the Northern Ireland Drug Tariff, Part 9 of the Scottish Drug Tariff).
The Drug Tariffs can be accessed online at:
National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm
Health and Personal Social Services for Northern Ireland Drug Tariff: www.hscbusiness.hscni.net/services/2034.htm
Scottish Drug Tariff: www.isdscotland.org/Health-topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

Details of NPF preparations

Preparations on the Nurse Prescribers’ Formulary which are not included in the BP or BPC are described as follows in the Nurse Prescribers’ Formulary. Although brand names have sometimes been included for identification purposes, it is recommended that non-proprietary names should be used for prescribing medicinal preparations in the NPF except where a non-proprietary name is not available.

Arachis Oil Enema
arachis oil 100%

Catheter Maintenance Solution, Sodium Chloride
(proprietary products: OptiFlo S; Uro-Tainer Sodium Chloride; Uriflex-S), sodium chloride 0.9%

Catheter Maintenance Solution, ‘Solution G’
(proprietary products: OptiFlo G; Uro-Tainer Suby G; Uriflex G), citric acid 3.23%, magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01%

Catheter Maintenance Solution, ‘Solution R’
(proprietary products: OptiFlo R; Uro-Tainer Solution R; Uriflex R), citric acid 6%, gluconolactone 0.6%, magnesium carbonate 2.8%, disodium edetate 0.01%

Chlorhexidine gluconate alcoholic solutions
(proprietary products: ChlorPrep; Hydrex Solution; Hydrex spray), chlorhexidine gluconate in alcoholic solution

Chlorhexidine gluconate aqueous solutions
(proprietary product: Unisept), chlorhexidine gluconate in aqueous solution

Co-danthramer Capsules
co-danthramer 25/200 (dantron 25 mg, poloxamer ‘188’ 200 mg)

Co-danthramer Capsules, Strong
co-danthramer 37.5/500 (dantron 37.5 mg, poloxamer ‘188’ 500 mg)

Co-danthramer Oral Suspension
(proprietary product: Codalax), co-danthramer 25/200 in 5 mL (dantron 25 mg, poloxamer ‘188’ 200 mg/L)

Co-danthramer Oral Suspension, Strong
(proprietary product: Codalax Forte), co-danthramer 75/1000 in 5 mL (dantron 75 mg, poloxamer ‘188’ 1 g/L)

Co-danthrusate Oral Suspension
(proprietary product: Normax), co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg/L)

Dimeticone barrier creams
(proprietary products Conotranse Cream, dimeticone ‘350’ 22%; Silopel Barrier Cream, dimeticone ‘1000’ 10%), dimeticone 10–22%

Dimeticone Lotion
(proprietary product: Hedrin), dimeticone 4%

Docusate Enema
(proprietary product: Norgalax Micro-enema), docusate sodium 120 mg in 10 g

Liquid and White Soft Paraffin Ointment
liquid paraffin 50%, white soft paraffin 50%

Macrogol Oral Liquid, Compound
(proprietary product: Movicol Liquid), macrocol ‘3350’ (polyethylene glycol ‘3350’) 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/25 mL

Macrogol Oral Powder, Compound
(proprietary products: Lasido Orange, Molaxole, Movicol), macrocol ‘3350’ (polyethylene glycol ‘3350’) 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet; (amount of potassium chloride varies according to flavour of Movicol® as follows: plain-flavour (sugar-free) = 50.2 mg/sachet; lime and lemon flavour = 46.6 mg/sachet; chocolate flavour = 31.7 mg/sachet. 1 sachet when reconstituted with 125 mL water provides K+ 5.4 mmol/litre)

Macrogol Oral Powder, Compound, Half-strength
(proprietary product: Movicol-Half), macrocol ‘3350’ (polyethylene glycol ‘3350’) 6.563 g, sodium bicarbonate 89.3 g, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet

Malathion aqueous lotions
(proprietary products: Derbac-M Liquid), malathion 0.5% in an aqueous basis

Mebendazole Oral Suspension
(proprietary product: Vermox), mebendazole 100 mg/5 mL
Mebendazole Tablets (proprietary products: Ovex, Vermox), mebendazole 100 mg (can be supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg)

Mouthwash Solution-tablets consist of tablets which may contain antimicrobial, colouring and flavouring agents in a suitable soluble effervescent basis to make a mouthwash

Nicotine Inhalation Cartridge for Oromucosal Use (proprietary products: NicAssist Inhalator, Nicorette Inhalator), nicotine 15 mg (for use with inhalation mouthpiece; to be prescribed as either a starter pack (6 cartridges with inhalator device and holder) or refill pack (42 cartridges with inhalator device)

Nicotine Lozenge nicotine (as bitartrate) 1 mg or 2 mg (proprietary product: Nicorette Mint Lozenge, Nicotinell Mint Lozenge), or nicotine (as resinate) 1.5 mg, 2 mg, or 4 mg (proprietary product: NiQuitin Lozenges, NiQuitin Minis, NiQuitin Pre-quit)

Nicotine Medicated Chewing Gum (proprietary products: NicAssist Gum, Nicorette Gum, Nicotinell Gum, NiQuitin Gum), nicotine 2 mg or 4 mg

Nicotine Nasal Spray (proprietary product: NicAssist Nasal Spray, Nicorette Nasal Spray), nicotine 500 micrograms/metered spray

Nicotine Oral Spray (proprietary product: Nicorette Quickmist), nicotine 1 mg/metered spray

Nicotine Sublingual Tablets (proprietary product: NicAssist Microtab, Nicorette Microtab), nicotine (as a cyclodextrin complex) 2 mg (to be prescribed as either a starter pack (2 × 15-tablet discs with dispenser) or refill pack (7 × 15-tablet discs))

Nicotine Transdermal Patches releasing in each 16 hours, nicotine approx. 5 mg, 10 mg, or 15 mg (proprietary products: Boots NicAssist Patch, Nicorette Patch), or releasing in each 16 hours approx. 10 mg, 15 mg, or 25 mg (proprietary products: NicAssist Translucent Patch, Nicorette Invisi Patch), or releasing in each 24 hours nicotine approx. 7 mg, 14 mg, or 21 mg (proprietary products: Nicopatch, Nicotinell TTS, NiQuitin, NiQuitin Clear) (prescriber should specify the brand to be dispensed)

Permethrin Cream (proprietary product: Lyclear Dermal Cream), permethrin 5%

Senna Oral Solution (proprietary product: Senokot Syrup), sennosides 7.5 mg/5 mL

Senna and Ispaghula Granules (proprietary product: Manevac Granules), senna fruit 12.4%, ispaghula 54.2%

Sodium Citrate Compound Enema (proprietary products: Micolette Micro-ename; Micralax Micro-ename; Relaxit Micro-ename), sodium citrate 450 mg with glycerol, sorbitol and an anionic surfactant

Sodium Picosulfate Capsules (proprietary products: Dulcolax Perles), sodium picosulfate 2.5 mg

Sodium Picosulfate Elixir (proprietary product: Dulcolax Liquid), sodium picosulfate 5 mg/5 mL

Sterculia Granules (proprietary product: Normacol Granules), sterculia 62%

Sterculia and Frangula Granules (proprietary product: Normacol Plus Granules), sterculia 62%, frangula (standardised) 8%

Zinc Oxide Impregnated Medicated Bandage (proprietary product: Steripaste), sterile cotton bandage impregnated with paste containing zinc oxide 15%

Zinc Oxide Impregnated Medicated Stocking (proprietary product: Zipzoc), sterile rayon stocking impregnated with ointment containing zinc oxide 20%
Non-medical prescribing

Overview
A range of non-medical healthcare professionals can prescribe medicines for patients as either Independent or Supplementary Prescribers.

Independent prescribers are practitioners responsible and accountable for the assessment of patients with previously undiagnosed or diagnosed conditions and for decisions about the clinical management required, including prescribing. They are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved non-proprietary name.

Supplementary prescribing is a partnership between an independent prescriber (a doctor or a dentist) and a supplementary prescriber to implement an agreed Clinical Management Plan for an individual patient with that patient’s agreement.

Independent and Supplementary Prescribers are identified by an annotation next to their name in the relevant professional register.

Information and guidance on non-medical prescribing is available on the Department of Health website at www.dh.gov.uk/health/2012/04/prescribing-change.

For information on the mixing of medicines by Independent and Supplementary Prescribers, see Mixing of medicines prior to administration in clinical practice—responding to legislative changes, National Prescribing Centre, May 2010 (available at www.npc.nhs.uk/improving_safety/mixing_meds/resources/mixing_of_medicines.pdf).

For information on the supply and administration of medicines to groups of patients using Patient Group Directions see Guidance on prescribing p. 1.

Nurses
Nurse Independent Prescribers (formerly known as Extended Formulary Nurse Prescribers) are able to prescribe any medicine for any medical condition.

Nurse Independent Prescribers are able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Nurse Independent Prescribers must work within their own level of professional competence and expertise.

The Nurse Prescribers’ Formulary p. 1413 for Community Practitioners provides information on prescribing.

Pharmacists
Pharmacist Independent Prescribers can prescribe any medicine for any medical condition.

They are also able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Pharmacist Independent Prescribers must work within their own level of professional competence and expertise.

Optometrists
Optometrist Independent Prescribers can prescribe any licensed medicine for ocular conditions affecting the eye and the tissues surrounding the eye, except Controlled Drugs or medicines for parenteral administration. Optometrist Independent Prescribers must work within their own level of professional competence and expertise.
Index of proprietary manufacturers

The following is an alphabetical list of manufacturers and other companies referenced in the BNF, with their medicines information or general contact details. For information on ‘special-order’ manufacturers and specialist importing companies see ‘Special-order manufacturers’.

3M Health Care Ltd, Tel: (01509) 611 611
Allen & Hanbury Ltd, Tel: 0800 221 441, customercntactuk@gsk.com
A1 Pharmaceuticals Plc, Tel: (01708) 528 900, sales@atpl.co.uk
AAbbott, Tel: (01628) 773 355
Abbott Healthcare Products Ltd, Tel: (01628) 773 355, medinfo.shl@abbott.com
AbbVie Ltd, Tel: (01628) 561 090, ukmedinfo@abbvie.com
Abrasix BioScience Ltd, Tel: (020) 7081 0850, abraxismedical@idipharma.com
Acorus Therapeutics Ltd, Tel: (01244) 625 152
Actavis UK Ltd, Tel: (01271) 385 267, medinfo@actavis.co.uk
Acelion Pharmaceuticals UK Ltd, Tel: (020) 8978 3333, medinfo.uk@acelion.com
Activia Healthcare, Tel: 0845 060 6707, advice@activiahealthcare.co.uk
Adienne Pharma and Biotech, Tel: 0039 (0) 335 873 8731
ADI Medical UK, Tel: (01628) 485159, info@adimedia.co.uk
Advanced Medical Solutions Group Plc, Tel: (01606) 863 500
Adovance Medical Ltd, Tel: (01623) 751 500, info@advanceds.co.uk
Advantech Surgical Ltd, Tel: 0845 130 5866, customerservice@newgcl.co.uk
Aegerion Pharmaceuticals Ltd, Tel: 00800 2343 7466, medinfo.emea@aegerion.com
AstraZeneca Capital Europe Ltd, Tel: (01235) 838 639, info@astrazeneca.co.uk
Agema GmbH, Tel: (020) 3239 6241, uk@aegerion.com
Aguettant Ltd, Tel: (01275) 463 691, info@aguettant.co.uk
Air Products plc, Tel: 0800 373 580
Alan Pharmaceuticals, Tel: (020) 7284 2887, info@alanpharmaceuticals.com
Alcon Laboratories (UK) Ltd, Tel: 0345 266 9363, gmedicaledepartment@alcon.com
Alexion Pharma UK Ltd, Tel: (01932) 359 220, alexion.uk@alexion.com
Alimera Sciences Limited, Tel: 0800 019 1253, medicalinformation@alimerasciences.com
Alissa Healthcare, Tel: (01489) 80 759, enquiries@alisahcarehealth.com
ALK-Albelô (UK) Ltd, Tel: (0118) 903 7940, info.uk@alk-albelo.com
Alkopharma Sarl, Tel: (0041) 277 206 969, regulator@alkopharma.com
Allergan Ltd, Tel: (01628) 494 026
Allergy Therapeutics Ltd, Tel: (01903) 844 702
Alliance Pharmaceuticals Ltd, Tel: (01249) 466 966, info@alliancepharma.co.uk
Almirall Ltd, Tel: 0800 008 7399, medinfo@almirall.com
AltaCord Ltd, Tel: (01223) 421 411, info@altacor-pharma.com
Amidpharm Mercury Company Ltd, Tel: 08700 70 30 33, medicalinformation@amcolimited.com
Amen Ltd, Tel: (01223) 420 305, gbinfoline@amen.com
Abbot Medical Optics, Tel: 0800 376 7950
Amrmed Healthcare Ltd, Tel: (0330) 333 0079, info@amrmedhealthcare.co.uk
Apollo Medical Technologies Ltd, Tel: (01636) 7202, supercheck2@blinternet.com
Archimde, Tel: 0800 756 9951, enquiries@archimed.co.uk
Archimedes Pharma UK Ltd, Tel: (0118) 931 5094, medicalinformation@archimedescopharma.com
Arctic Medical Ltd, Tel: (01303) 277 751, sales@arcticmedical.co.uk
Ardana Bioscience Ltd, Tel: (0313) 226 8550
ARIAD Pharmaceuticals Ltd, Tel: 0800 0002 7423, eumed@ariad.com
Ark Therapeutics Group Plc, Tel: (020) 7388 7722, info@arkearthapeutics.com
Aspen, Tel: 0800 008 7392, aspenmedinfo@professionalinformation.co.uk
Aspen Medical Europe Ltd, Tel: (01527) 587 728, customers@aspent-medica-europe.co.uk
AS Pharma Ltd, Tel: 0870 066 4117, info@aspharma.co.uk
Aspire Pharma Ltd, Tel: (01730) 231 148, info@aspir pharmapharma.co.uk
Astellas Pharma Ltd, Tel: (020) 3379 8000, medinfo.gb@stellas.com
AstraZeneca UK Ltd, Tel: 0800 783 0032, medicalinformationuk@astraZeneca.com
Auden Mckenzie (Pharma Division) Ltd, Tel: (01985) 627 420
Auxilium, Tel: 0845 017 2315, auxilium@pilglobal.com
Axcan Pharma SA, Tel: (0033) 130 461 900
AYMES International Ltd, Tel: 0845 6805 496, info@aymes.com
Ayrton Saunders Ltd, Tel: (0151) 709 2074, info@ayrtons.com
BAP Medical UK Ltd, Tel: 0844 879 7689
Bard Ltd, Tel: (01293) 527 888
Basilea Pharmaceutica Ltd, Tel: (01483) 790 023, ukmedinfo@basilea.com
Bausch & Lomb UK Ltd, Tel: (01748) 828 864, medicalinformationuk@bausch.com
Baxter Healthcare Ltd, Tel: (01635) 206 345, surecall@baxter.com
Bayer Healthcare Pharmaceuticals, Tel: (01635) 563 000, medicalinformation@bayer.co.uk
Bayer Healthcare Pharmaceuticals, Tel: (01635) 563 000, medicalinformation@bayer.co.uk
Bayer Healthcare Pharmaceuticals, Tel: (01635) 563 000, medicalinformation@bayer.co.uk
BBI Healthcare, Tel: (01792) 229 333, info@bbihealthcare.com
B. Braun Medical Ltd, Tel: (0114) 225 9000, info.bbnuke@bbraun.com
Beacon Pharmaceuticals Ltd, Tel: (01892) 600 930, info@beaconpharma.co.uk
Beiersdorf UK Ltd, Tel: (021) 329 8800
Besins Healthcare (UK) Ltd, Tel: (01748) 828 789, information@besins-healthcare.com
BGP Products Ltd, Tel: (01707) 853 000, medinfo.shl@mylan.com
BHR Pharmaceuticals Ltd, Tel: (024) 7637 7210, info@bhr.co.uk
Biogen Idec Ltd, Tel: 0800 008 7401
Biolitec Pharma Ltd, Tel: (00353) 1463 7415
BioMarin Europe Ltd, Tel: (020) 7420 0800, biomarin-europe@bmn.com
BioMondo, Tel: 0845 230 1810, info@biomondo.com
Biostek (UK) Ltd, Tel: (0121) 733 3393, medicinesinformation@biostek.com
Blackwell Supplies Ltd, Tel: (01634) 877 620
BOC Medical, Tel: 0800 111 333
Boehringer Ingelheim Ltd, Tel: (01344) 424 600, medinfo@bba.boehringer-ingelheim.com
The Boots Company PLC, Tel: (0115) 959 5165
BPC 100 Ltd, Tel: 01942 852085
Bio Products Laboratory Ltd, Tel: (020) 8957 2255, medinfo@bpl.co.uk
Brancaster Pharma Ltd, Tel: (01737) 243 407, enquiries@brancasterpharma.com
Bray Healthcare, Tel: (01367) 240 736, info@bray-healthcare.com
Bristol-Myers Squibb Pharmaceuticals Ltd, Tel: (01895) 523 000, medicalinformation@bms.com
Britannia Pharmaceuticals, Tel: 0870 851 0207, enquiries@medinformation.co.uk
BSN Medical Ltd, Tel: 0845 122 3600
BTG International Ltd, Tel: (0207) 575 0000, medical.services@btgplc.com
Bullen Healthcare, Tel: 0800 269 327
Cambridge Medical Aesthetics Ltd, Tel: (01733) 396171, info@cambridgemeaesthetics.com
Cambridge Sensors Ltd, Tel: (01480) 482 920, sales-orders@cs-limited.co.uk
CareFusion UK 244 Ltd, Tel: 0800 043 7546, enquiries@chlororapre.co.uk
Cazen-Fleet, Tel: (0034) 913 518 800
C D Medical Ltd, Tel: (01942) 816 184
Celgene Ltd, Tel: 0844 801 0045, medinfo.uk.ire@celgene.com
Chanelle Medical UK Ltd, Tel: (01233) 822 297
Chattem UK Ltd, Tel: (01256) 844 144

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PGR Health Foods Ltd, Tel: (01992) 581 715, info@pgrhealthfoods.co.uk
Pfizer Ltd, Tel: (01304) 616 161, eumedinfo@pfizer.com
Pharmacosmos UK Ltd, Tel: (01844) 269 007, info@vitalineuk.com
Pharma Nord (UK) Ltd, Tel: (01670) 519 989, uksales@pharmanord.co.uk
Pharmasure Ltd, Tel: (01923) 233 466, info@pharmasure.co.uk
Pharmaxis Pharmaceuticals Ltd, Tel: (01628) 902 053, med.info@pharmaxis.com
Phasar Associates Ltd, Tel: 01483 212151, medinfoenquiries@phasar.com
Phoenix Labs, Tel: (00353) 1468 8917, medicalinformation@phoenixlabs.ie
Pierre Fabre Ltd, Tel: (01962) 874 435, medicalinformation@pierre-fabre.co.uk
Pinewood Healthcare, Tel: (00353) 523 6253, info@pinewood.ie
Pinnacle Biologics Inc., Tel: 1-866-248-2039, pinnaclemedinformation@optum.com
Potters Herbal Medicines, Tel: (01942) 219 960
Procelli, Tel: (01226) 713 044, admin@procelli.co.uk
Procter & Gamble (Health and Beauty Care) Ltd, Tel: (0191) 297 5000
Profile Pharma Ltd, Tel: 0800 1300 855, info@profilepharma@zambongroup.com
Protex Healthcare (UK) Ltd, Tel: 0870 011 4112, orders@protexhealthcare.co.uk
Qdem, Tel: (01223) 426 929, medicalinformationukqdem@qdem.co.uk
RPH Pharmaceuticals, Tel: (01483) 212 151, medinfoenquiries@phasar.com
Smith & Nephew Healthcare Ltd, Tel: (01482) 222 200, advice@smith-nephew.com
Sallis Healthcare Ltd, Tel: (0115) 978 7841
Sandoz Ltd, Tel: (01276) 698 020, sandoz@professionalinformation.co.uk
Sanochemia Diagnostics UK Ltd, Tel: (0117) 906 3962
Sanofi-Aventis Ltd, Tel: 0845 372 7101, uk-medicalinformation@sanofi-aventis.co.uk
Sanofi Pasteur MSD Ltd, Tel: (01628) 785 291
SANOMED Manufacturing BV, Tel: +32 503 93627, sanomed.nl
Santen UK Limited, Tel: (0345) 075 4863, medinfo@santen.co.uk
Merck Sharp & Dohme Ltd, Tel: (01992) 467 272, medicalinformation@merck.co.uk
Schuco International Ltd, Tel: (020) 8368 1642, sales@schuco.co.uk
Schülke UK, Tel: (0114) 254 3500, mail.uk@schuelke.com
Scope Ophthalmics Ltd, Tel: (01293) 897 209, info@scopeophthalmics.com
SD Biosensor, Inc., Tel: 0082 31 300 0475, sales@sdbiosensor.com
SD Healthcare, Tel: (0161) 776 7626, sales@sdhealthcare.com
Seahorse Laboratories Ltd, Tel: (020) 8257 8412, info@seahorse-labs.com
Septodont Ltd, Tel: (01622) 695 520
Serveri Laboratories Ltd, Tel: (01753) 666 409, medicalinformation-uk@serveri.com
Seven Seas Ltd, Tel: (01482) 375 234
Shermondd, Tel: 0870 242 7701, sales@shermomdd.com
Shire Pharmaceuticals Ltd, Tel: 0800 055 6114, medinfo@shire.com
Shire Human Genetic Therapies, Tel: (01256) 894 000, bgm@shire.com
SHS International Ltd, Tel: (0151) 228 8161
Siemens Healthcare Diagnostics Ltd, Tel: 0845 600 1966, dx-diag-sales-uk@med-siemens.com
Sigma-Tau Pharma UK Ltd (Medi), Tel: 0800 043 1268, medicalinformation@sigmatau-uk.co.uk
SilDerm Ltd, Tel: (01260) 271 666
Sinclair IS Pharma, Tel: (01244) 625 152, enquiries@ispharma.plc.uk
The Skin Camouflage Company Ltd, Tel: (01507) 343 091, sjmgcovermark@aol.com
Skinnies UK, Tel: (01562) 546 123, info@skinniesuk.com
SLO Drinks Ltd, Tel: 0345 222 205, info@slo-drinks.com
Wyeth Pharmaceuticals, Tel: (01260) 604 737, eumedinfo@wyeth.com
Scottish National Blood Transfusion Service, Tel: (0131) 536 5700, contact.pfc@snbts.csc.sct.nhs.uk
Sound Opinion, Tel: 0870 192 3283, enquiries@medicalinformation.co.uk
Speciality European Pharma Ltd, Tel: (020) 7421 7400, info@speedepharma.co.uk
SPEPharm UK Ltd, Tel: 0844 800 7579, medinfo@spepharm.co.uk
Spirit Healthcare Ltd, Tel: 0800 881 5423, cs@spirit-healthcare.co.uk
Bristol-Myers Squibb Pharmaceuticals Ltd, Tel: (01895) 523 000, medicalinformation@bms.com
SSL International plc, Tel: 0870 122 2690
Stanningley Pharma Ltd, Tel: (01159) 124 253, medinfo@stanningleypharma.co.uk
STD Pharmaceutical Products Ltd, Tel: (01432) 373 555, enquiries@stdpharm.co.uk
Steraid (Gainsborough) Ltd, Tel: (01427) 677 559
St George's Medical, Tel: (020) 7582 1015
Stiefel (a GSK company), Tel: 0800 221 441
Stiletto Foods UK Ltd, Tel: 0845 130 0869
Stragen UK Ltd, Tel: 0870 351 8744, info@stragenuk.com
Sucampo Pharma, Tel: 0800 756 3416, info@ sucampo.com
Su-Med International UK Ltd Ltd, Tel: (01457) 890 980, sales@sumed.co.uk
Sunovion Pharmaceuticals Europe Ltd, Tel: 020) 7821 2840, medinfo@sunovion.eu
Sutherland Health Ltd, Tel: (01635) 874 488
Swedish Orphan Biovitrum Ltd, Tel: (01638) 722 380, medical.info@sobi.com
Synergy Healthcare (UK) Ltd, Tel: (0161) 624 5641, healthcare resolutions@synergyhealthplc.com
Syner-Med (Pharmaceutical Products) Ltd, Tel: 0845 634 2100, mail@syner-med.com
Systagenix Wound Management, Tel: (01293) 842 000
Takeda UK Ltd, Tel: (01628) 537 900, medinfo@takeda.co.uk
Talley Group Ltd, Tel: (01794) 503 500
Taro Pharmaceuticals (UK) Ltd, Tel: 0870 736 9544, customerservice@taropharma.co.uk
Teofarma S.r.l., servizioclienti@teofarma.it
TEVA UK Ltd, Tel: 0870 502 0304, medinfo@tevauk.com
TEVA UK Ltd, Tel: (020) 7540 7117, medinfo@tevauk.com
The Medicines Company, Tel: 00800 8436 3326, medicalinformation@themedco.com
Thea Pharmaceuticals, Tel: 0870 192 3283, thea-pharma@medicalinformation.co.uk
Therabel Pharma UK Ltd, Tel: 0800 066 5446, info@therabel.co.uk
The Urology Company Ltd, Tel: (020) 3077 5411, info@theurologyco.com
Thomas Blake Cosmetic Creams Ltd, Tel: (01207) 272 311, sales@veilcover.com
Thornton & Ross Ltd, Tel: (01484) 842 217
Tilomed Laboratories Ltd, Tel: (01480) 402 400, info@tilomed.co.uk
Tillotts Pharma UK Ltd, Tel: 01255 813 500, ukmedinfo@tillotts.co.uk
TMC Pharma Services Ltd, Tel: (01252) 842 255, info@tmcpharma.com
Tobia Teff UK Ltd, Tel: (020) 7328 2045, info@tobiatheff.co.uk
Torbet Laboratories Ltd, Tel: (01953) 607 856, customerservices@cambridge-healthcare.co.uk
Transdermal Ltd, Tel: (020) 8654 2251, info@transdermal.co.uk
TRB Chemedica (UK) Ltd, Tel: 0845 330 7556
Typharm Ltd, Tel: (01603) 722 480, customerservices@typharm.com
UCB Pharma Ltd, Tel: (01753) 534 655, medicinalinformation@ucb.com
Ultrapr furnish, Tel: (01491) 578 016
Univar Ltd, Tel: (01908) 362 200, trientine@univareurope.com
Unomedical Ltd, Tel: (01527) 587 700

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<table>
<thead>
<tr>
<th>Company</th>
<th>Phone/Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgo Ltd</td>
<td>Tel: (01509) 502 051, <a href="mailto:woundcare@uk.urgo.com">woundcare@uk.urgo.com</a></td>
</tr>
<tr>
<td>Vegenat c/o Archaeis Ltd</td>
<td>Tel: 0870 803 2484</td>
</tr>
<tr>
<td>Vertex Pharmaceuticals (UK) Ltd</td>
<td>Tel: 0800 028 2616, <a href="mailto:eumedicalinfo@VRTX.com">eumedicalinfo@VRTX.com</a></td>
</tr>
<tr>
<td>Vifor Pharma UK Ltd</td>
<td>Tel: (01276) 853 633, <a href="mailto:medicalinfo.uk@viforpharma.com">medicalinfo.uk@viforpharma.com</a></td>
</tr>
<tr>
<td>Viiv Healthcare UK Ltd</td>
<td>Tel: 0800221441, <a href="mailto:customercontactuk@gsk.com">customercontactuk@gsk.com</a></td>
</tr>
<tr>
<td>Viridian Pharma Ltd</td>
<td>Tel: (01633) 400 335, <a href="mailto:info@viridianpharma.co.uk">info@viridianpharma.co.uk</a></td>
</tr>
<tr>
<td>ViroPharma Ltd</td>
<td>Tel: (020) 7572 1222</td>
</tr>
<tr>
<td>Vitafl International Ltd</td>
<td>Tel: (0151) 709 9020, <a href="mailto:vitafl@vitafl.co.uk">vitafl@vitafl.co.uk</a></td>
</tr>
<tr>
<td>Vitalograph Ltd</td>
<td>Tel: (01280) 827 110, <a href="mailto:sales@vitalograph.co.uk">sales@vitalograph.co.uk</a></td>
</tr>
<tr>
<td>Wallace Cameron Ltd</td>
<td>Tel: (01698) 354 600, <a href="mailto:sales@wallacecameron.com">sales@wallacecameron.com</a></td>
</tr>
<tr>
<td>Wallace Manufacturing Chemists Ltd</td>
<td>Tel: (01235) 358 700, <a href="mailto:info@allinter.co.uk">info@allinter.co.uk</a></td>
</tr>
<tr>
<td>Warburtons</td>
<td>Tel: (01204) 513 004</td>
</tr>
<tr>
<td>Warner Chilcott UK Ltd</td>
<td>Tel: (01932) 824 700</td>
</tr>
<tr>
<td>Welsh Blood Service</td>
<td>Tel: (01443) 622 000, <a href="mailto:donor.care@wales.nhs.uk">donor.care@wales.nhs.uk</a></td>
</tr>
<tr>
<td>Wellfoods Ltd</td>
<td>Tel: (01226) 381 712, <a href="mailto:wellfoods@wellfoods.co.uk">wellfoods@wellfoods.co.uk</a></td>
</tr>
<tr>
<td>Williams Medical Supplies Ltd</td>
<td>Tel: (01685) 844 739</td>
</tr>
<tr>
<td>Wockhardt UK Ltd</td>
<td>Tel: (01978) 661 261</td>
</tr>
<tr>
<td>Wyeth Pharmaceuticals</td>
<td>Tel: (01628) 604 377, <a href="mailto:eumedinfo@pfizer.com">eumedinfo@pfizer.com</a></td>
</tr>
<tr>
<td>Wynil Laboratories</td>
<td>Tel: (07903) 370 130</td>
</tr>
<tr>
<td>Wyvern Medical Ltd</td>
<td>Tel: (01531) 631 105</td>
</tr>
<tr>
<td>Zentiva</td>
<td>Tel: (01483) 554 101, <a href="mailto:gb-zentivamedicalinformation@sanofi.com">gb-zentivamedicalinformation@sanofi.com</a></td>
</tr>
<tr>
<td>Zeroderma Ltd</td>
<td>Tel: (01858) 525 643</td>
</tr>
</tbody>
</table>
Special-order manufacturers

Unlicensed medicines are available from ‘special-order’ manufacturers and specialist-importing companies; the MHRA maintains a register of these companies at tinyurl.com/cdslike.

Licensed hospital manufacturing units also manufacture ‘special-order’ products as unlicensed medicines, the principal NHS units are listed below. A database (Pro-File: www.pro-file.nhs.uk) provides information on medicines manufactured in the NHS; access is restricted to NHS pharmacy staff.

The Association of Pharmaceutical Specials Manufacturers may also be able to provide further information about commercial companies (www.apsm-uk.com).

The MHRA recommends that an unlicensed medicine should only be used when a patient has special requirements that cannot be met by use of a licensed medicine.

As well as being available direct from the hospital manufacturer(s) concerned, many NHS-manufactured Specials may be bought from the Oxford Pharmacy Store, owned and operated by Oxford Health NHS Foundation Trust.

England

London

Barts and the London NHS Trust
Mr J. A. Rickard, Head of Barts Health Pharmaceuticals
Barts Health NHS Trust
The Royal London Hospital
Pathology and Pharmacy Building
80 Newark St
Whitechapel
London
E1 2ES
(020) 3246 0394 (order/enquiry)
barts.pharmaceuticals@bartshealth.nhs.uk

Guy’s and St. Thomas’ NHS Foundation Trust
Mr P. Forsay, Associate Chief Pharmacist
Guy’s and St. Thomas’ NHS Foundation Trust
Guy’s Hospital
Pharmacy Department
Great Maze Pond
London
SE1 9RT
(020) 7188 4992 (order)
(020) 7188 5003 (enquiry)
Fax: (020) 7188 5013
paul.forsay@gstt.nhs.uk

Moorfields Pharmaceuticals
Mr. T. Record, Technical Director
Moorfields Pharmaceuticals
25 Provost St
London
N1 7NH
(020) 7684 9090 (order/enquiry)
Fax: (020) 7502 2332

London North West Healthcare NHS Trust
Mr. K. Wong,
London North West Healthcare NHS Trust
Northwick Park Hospital
Watford Rd
Harrow
Middlesex
HA1 3UJ
(020) 8869 2295 (order)
(020) 8869 2204/2223 (enquiry)
kwong@nhs.net

Royal Free Hampstead NHS Trust
Ms. C. Trehan, Production Manager
Royal Free Hampstead NHS Trust
Pond St
London
NW3 2OG
(020) 7830 2424 (order)
(020) 7830 2282 (enquiry)
Fax: (020) 7794 1875
christine.trehane@nhs.net

St George’s Healthcare NHS Trust
Mr. V. Kumar, Assistant Chief Pharmacist
St George’s Hospital
Technical Services
Blackshaw Rd
Tooting
London
SW17 0QT
(020) 8725 1770/1768
Fax: (020) 8725 3947
vinodh.kumar@stgeorges.nhs.uk

University College Hospital NHS Foundation Trust
Mr. T. Murphy, Production Manager
University College Hospital
235 Euston Rd
London
NW1 2BU
(020) 7380 9723 (order)
(020) 7380 9726 (enquiry)
Fax: (020) 7380 9726
tony.murphy@uclh.nhs.uk

Midlands and Eastern

Barking, Havering and Redbridge University Hospital
Mr. N. Fisher, Senior Principal Pharmacist
Queen’s Hospital
Pharmacy Department
Romford
Essex
RM7 0AG
(01708) 435 463 (order)
(01708) 435 042 (enquiry)
neil.fisher@bhrrhospitals.nhs.uk

Burton Hospitals NHS Foundation Trust
Mr. D. Raynor, Head of Pharmacy Manufacturing Unit
Queens Hospital
Burton Hospitals NHS Foundation Trust
Pharmacy Manufacturing Unit
Belvedere Rd
Burton-on-Trent
DE13 0RB
(01283) 511 511 ext: 5275 (order/enquiry)
Fax: (01283) 593 036
david.raynor@burtonft.nhs.uk

Colchester Hospital University NHS Foundation Trust
Mr. S. Pullen, Pharmacy Production Manager
Colchester General Hospital
Main Pharmacy
Turner Rd
Colchester
Essex
CO4 5JL
(01206) 742 007 (order)
(01206) 744 208 (enquiry)
Fax: (01206) 841 249
pharmacy.stores@colchesterhospital.nhs.uk
(enquiry)

Ipswich Hospital NHS Trust
Dr. J. Harwood, Production Manager
Ipswich Hospital NHS Trust
Pharmacy Manufacturing Unit
Health Rd
Ipswich
IP4 5PD
(01473) 703 440 (order)
(01473) 703 603 (enquiry)
Fax: (01473) 703 609
john.harwood@ipswichhospital.nhs.uk

Nottingham University Hospitals NHS Trust
Mr. J. Graham, Senior Pharmacist, Production
Nottingham University Hospitals NHS Trust
Pharmacy Production Units
Queens Medical Centre Campus
Nottingham
NG7 2UH
(0115) 924 9924 ext: 66521 (enquiry/order)
Fax: (0115) 970 9780
jeff.graham@nuh.nhs.uk

University Hospital of North Staffordshire NHS Trust
Ms K. Ferguson, Chief Technician
University Hospital of North Staffordshire NHS Trust
Pharmacy Technical Services
City General Site
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ST4 6GQ
(01782) 674 568 (order)
(01782) 674 568 (enquiry)
Fax: (01782) 674 575
caroline.ferguson@uhns.nhs.uk

The Newcastle upon Tyne Hospitals NHS Foundation Trust
Mr Y. Hunter-Blair, Production Manager
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Newcastle Specials
Pharmacy Production Unit
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Newcastle-upon-Tyne
NE1 4LP
(0191) 282 0395 (order)
(0191) 282 0389 (enquiry)
Fax: (0191) 282 0469
yan.hunter-blair@nuth.nhs.uk
North West
Preston Pharmaceuticals
Ms A. Bolch, Deputy Chief Pharmacist (PMU)
Preston Pharmaceuticals
Royal Preston Hospital
Fulwood
Preston
PR2 9HT
(01772) 523 617 (order)
(01772) 522 593 (enquiry)
Fax: (01772) 523 645
angela.bolch@lthtr.nhs.uk

Stockport Pharmaceuticals
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Stepping Hill Hospital
Stockport NHS Foundation Trust
Stockport Pharmaceuticals
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SK2 7JE
(0161) 419 5666 (order)
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Fax: (0161) 419 5426
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South
Portsmouth Hospitals NHS Trust
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Pharmacy Manufacturing Unit
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Portsmouth
PO6 1TF
(02392) 389 078 (order)
(02392) 316 312 (enquiry)
Fax: (02392) 316 316
robert.lucas@porthosp.nhs.uk

South East
East Sussex Healthcare NHS Trust
Mr P. Keen, Business Manager
Eastbourne District General Hospital
East Sussex Hospitals NHS Trust
Eastbourne Pharmaceuticals
Kings Drive
Eastbourne
BN21 2UD
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It’s easy to report online at: www.mhra.gov.uk/yellowcard

REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See ‘Adverse reactions to drugs’ section in BNF or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

**PATIENT DETAILS**

<table>
<thead>
<tr>
<th>Patient Initials:</th>
<th>Sex: M / F</th>
<th>Is the patient pregnant? Y / N</th>
<th>Ethnicity:</th>
</tr>
</thead>
</table>

Age (at time of reaction): | Weight (kg): | Identification number (e.g. Practice or Hospital Ref): |
--------------------------|--------------|---------------------------------------------------|

**SUSPECTED DRUG(S)/VACCINE(S)**

<table>
<thead>
<tr>
<th>Drug/Vaccine (Brand if known)</th>
<th>Batch</th>
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**SUSPECTED REACTION(S)**

Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

<table>
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Date reaction(s) started: Date reaction(s) stopped:

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- [ ] Patient died due to reaction
- [ ] Life threatening
- [ ] Congenital abnormality
- [ ] Involved or prolonged inpatient hospitalisation
- [ ] Involved persistent or significant disability or incapacity
- [ ] Medically significant; please give details:

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

- [ ] Mild
- [ ] Unpleasant, but did not affect everyday activities
- [ ] Bad enough to affect everyday activities
OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No
If yes, please give the following information if known:

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Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS
Name and Professional Address: ________________________________

Postcode: _________________ Tel No: _______________________
Email: ____________________
Speciality: __________________
Signature: __________________ Date: ____________________

CLINICIAN (if not the reporter)
Name and Professional Address: ________________________________

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Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps
Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin Drug Safety Update at: www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)
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Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)
Adult Advanced Life Support Algorithm

Unresponsive and not breathing normally

Call resuscitation team

CPR 30:2
Attach defibrillator/monitor
Minimise interruptions

Assess rhythm

Shockable (VF/Pulseless VT)

1 Shock
Minimise interruptions

Immediately resume CPR for 2 min
Minimise interruptions

Return of spontaneous circulation

Immediate post cardiac arrest treatment
- Use ABCDE approach
- Aim for SpO2 of 94-96%
- Aim for normal PaCO2
- 12-lead ECG
- Treat precipitating cause
- Targeted temperature management

Non-shockable (PEA/Asystole)

Immediately resume CPR for 2 min
Minimise interruptions

During CPR
- Ensure high quality chest compressions
- Minimise interruptions to compressions
- Give oxygen
- Use waveform capnography
- Continuous compressions when advanced airway in place
- Vascular access (intravenous or intracessous)
- Give adrenaline every 3-5 min
- Give amiodarone after 3 shocks

Treat Reversible Causes
- Hypoxia
- Hypovolaemia
- Hypo-/hyperkalaemia/metabolic
- Hypothermia
- Thrombosis - coronary or pulmonary
- Tension pneumothorax
- Tamponade – cardiac
- Toxins

Consider
- Ultrasound imaging
- Mechanical chest compressions to facilitate transfer/treatment
- Coronary angiography and percutaneous coronary intervention
- Extracorporeal CPR

Reproduced with the kind permission of the Resuscitation Council (UK) from Resuscitation Guidelines, 2015
Medical emergencies in the community

Overview
Drug treatment outlined below is intended for use by appropriately qualified healthcare professionals. Only drugs that are used for immediate relief are shown; advice on supporting care is not given. Where the patient’s condition requires investigation and further treatment, the patient should be transferred to hospital promptly.

Acute coronary syndromes

▶ ANGINA: UNSTABLE
Aspirin dispersible tablets p. 114 (75 mg, 300 mg)
BY MOUTH (DISPERSED IN WATER OR CHEWED)
  ▶ Adult: 300 mg

▶ PLUS
▶ EITHER Glyceryl trinitrate aerosol spray p. 207
(400 micrograms/metered dose)
SUBLINGUALLY
  ▶ Adult: 1–2 sprays, repeated as required
▶ OR Glyceryl trinitrate tablets (300 micrograms, 500 micrograms, 600 micrograms)
SUBLINGUALLY
  ▶ Adult: 0.3–1 mg, repeated as required

▶ MYOCARDIAL INFARCTION: NON-ST-SEGMENT ELEVATION
Treat as for Angina: unstable

▶ MYOCARDIAL INFARCTION: ST-SEGMENT ELEVATION
Aspirin dispersible tablets (75 mg, 300 mg)
BY MOUTH (DISPERSED IN WATER OR CHEWED)
  ▶ Adult: 300 mg
Glyceryl trinitrate aerosol spray (400 micrograms/metered dose)
SUBLINGUALLY
  ▶ Adult: 1–2 sprays, repeated as required
▶ OR Glyceryl trinitrate tablets (300 micrograms, 500 micrograms, 600 micrograms)
SUBLINGUALLY
  ▶ Adult: 0.3–1 mg, repeated as required
Metoclopramide hydrochloride injection p. 403 (5 mg/mL)
BY INTRAVENOUS INJECTION
  ▶ Adult 18-19 years (body-weight up to 60 kg): 5 mg
  ▶ Adult 18-19 years (body-weight 60 kg and over): 10 mg
  ▶ Adult over 19 years: 10 mg
Diamorphine hydrochloride injection p. 423 (5 mg powder for reconstitution)
BY SLOW INTRAVENOUS INJECTION (1-2 mg/minute)
  ▶ Adult: 5 mg followed by a further 2.5–5 mg if necessary
  ▶ Elderly or frail patients: reduce dose by half
▶ OR Morphine sulfate injection p. 429 (10 mg/mL)
BY SLOW INTRAVENOUS INJECTION (1-2 mg/minute)
  ▶ Adult: 5–10 mg followed by a further 5–10 mg if necessary
  ▶ Elderly or frail patients: reduce dose by half
Oxygen, if appropriate

Airways disease, obstructive

▶ ASThma: ACUTE
Regard each emergency consultation as being for severe acute asthma until shown otherwise; failure to respond adequately at any time requires immediate transfer to hospital

▶ EITHER Salbutamol aerosol inhaler p. 239
(100 micrograms/metered inhalation)
BY AEROsOL INHALATION VIA LARGE-VOLUME SPACER (AND A CLOSE-FITTING FACE MASK IF CHILD UNDER 3 YEARS)
  ▶ Adult and Child: 2–10 puffs each inhaled separately, repeated every 10–20 minutes or as necessary
▶ OR Salbutamol nebuliser solution (1 mg/mL, 2 mg/mL)
BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)
  ▶ Child 4 years and below: 2.5 mg every 20–30 minutes or as necessary
  ▶ Child 5–11 years: 2.5–5 mg every 20–30 minutes or as necessary
  ▶ Child 12-17 years: 5 mg every 20–30 minutes or as necessary
  ▶ Adult: 5 mg every 20–30 minutes or as necessary
▶ OR Terbutaline sulfate nebuliser solution p. 241 (2.5 mg/mL)
BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)
  ▶ Child 4 years and below: 5 mg every 20–30 minutes or as necessary
  ▶ Child 5–11 years: 5–10 mg every 20–30 minutes or as necessary
  ▶ Child 12-17 years: 10 mg every 20–30 minutes or as necessary
  ▶ Adult: 10 mg every 20–30 minutes or as necessary

▶ PLUS (in all cases)
▶ EITHER Prednisolone tablets p. 622 (or prednisolone soluble tablets) (5 mg)
BY MOUTH
  ▶ Child 11 years and below: 1–2 mg/kg (max. 40 mg) once daily for up to 3 days or longer if necessary; if child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily
  ▶ Child 12-17 years: 40–50 mg once daily for at least 5 days
  ▶ Adult: 40–50 mg once daily for at least 5 days
▶ OR Hydrocortisone p. 620 (preferably as sodium succinate)
BY INTRAVENOUS INJECTION
  ▶ Child 17 years and below: 4 mg/kg (max.100 mg) every 6 hours until conversion to oral prednisolone is possible; alternative dose if weight unavailable:
    ▶ Child 1 year and below: 25 mg
    ▶ Child 2-4 years: 50 mg
    ▶ Child 5-17 years: 100 mg
  ▶ Adult: 100 mg every 6 hours until conversion to oral prednisolone is possible
High-flow oxygen should be given if available (via face mask in children)
Monitor response 15 to 30 minutes after nebulisation; if any signs of acute asthma persist, arrange hospital admission.
While awaiting ambulance, repeat nebulised β₂ agonist (as above) and give with
Ipratropium bromide nebuliser solution p. 234
(250 micrograms/mL)
*BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)*
- Child 11 years and below: 250 micrograms, repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary
- Child 12-17 years: 500 micrograms every 4–6 hours as necessary
- Adult: 500 micrograms every 4–6 hours as necessary

**CROUP**
Dexamethasone oral solution p. 618 (2 mg/5 mL)
*BY MOUTH*
- Child 1 month-2 years: 150 micrograms/kg as a single dose

**Anaphylaxis**

**ANAPHYLAXIS**
Adrenaline/epinephrine injection p. 211 (1 mg/mL (1 in 1000))
*BY INTRAMUSCULAR INJECTION*
- Child 5 years and below: 150 micrograms (0.15 mL), repeated every 5 minutes if necessary
- Child 6-11 years: 300 micrograms (0.3 mL), repeated every 5 minutes if necessary
- Child 12-17 years: 500 micrograms (0.5 mL), repeated every 5 minutes if necessary; 300 micrograms (0.3 mL) should be given if child is small or prepubertal
- Adult: 500 micrograms (0.5 mL), repeated every 5 minutes if necessary
High-flow oxygen and intravenous fluids should be given as soon as available.

Chlorphenamine maleate injection p. 266
*BY INTRAMUSCULAR OR INTRavenous INJECTION*
May help counter histamine-mediated vasodilation and bronchoconstriction.

Hydrocortisone (preferably as sodium succinate)
*BY INTRavenous INJECTION*
Has delayed action but should be given to severely affected patients to prevent further deterioration.

**Bacterial infection**

**MENINGOCOCCAL DISEASE**
Benzylenicillin sodium injection p. 504 (600 mg, 1.2 g)
*BY INTRavenous INJECTION (OR BY INTRamuscular INJECTION IF VENous ACCESS NOT AVAILABLE)*
- Neonate: 300 mg
- Child 1 month-11 months: 300 mg
- Child 1-9 years: 600 mg
- Child 10-17 years: 1.2 g
- Adult: 1.2 g
*NOTE* A single dose should be given before urgent transfer to hospital, so long as this does not delay the transfer.

**OR** if history of allergy to penicillin

Cefotaxime injection p. 487 (1 g)
*BY INTRavenous INJECTION (OR BY INTRamuscular INJECTION IF VENous ACCESS NOT AVAILABLE)*
- Neonate: 50 mg/kg
- Child 1 month-11 years: 50 mg/kg (max. 1 g)
- Child 12-17 years: 1 g
- Adult: 1 g
*NOTE* A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer.

**OR** if history of immediate hypersensitivity reaction (including anaphylaxis, angioedema, urticaria, or rash immediately after administration) to penicillin or to cephalosporins

Chloramphenicol injection p. 524 (1 g)
*BY INTRavenous INJECTION*
- Child: 12.5–25 mg/kg
- Adult: 12.5–25 mg/kg
*NOTE* A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer. See also Central nervous system infections, bacterial p. 473.

**Hypoglycaemia**

**DIABETIC HYPOGLYCAEMIA**
Glucose or sucrose
*BY MOUTH*
- Adult and Child over 2 years: approx. 10–20 g
  - (55–110 mL Lucozade® Energy Original or 100–200 mL Coca-Cola®—both non-diet versions or 2–4 teaspoonfuls of sugar or 3–6 sugar lumps) repeated after 10–15 minutes if necessary
- **OR** if hypoglycaemia unresponsive or if oral route cannot be used

Glucagon injection p. 660 (1 mg/mL)
*BY SUBCUTANEOUS OR INTRamuscular INJECTION*
- Child body-weight up to 25 kg: 500 micrograms (0.5 mL)
- Child body-weight 25 kg and over: 1 mg (1 mL)
- Adult: 1 mg (1 mL)
- **OR** if hypoglycaemia prolonged or unresponsive to glucagon after 10 minutes

Glucose intravenous infusion p. 915 (10%)
*BY INTRavenous INJECTION INTO LARGE VEIN*
- Child: 5 mL/kg (glucose 500 mg/kg)
- Glucose intravenous infusion p. 915 (20%)
*BY INTRavenous INJECTION INTO LARGE VEIN*
- Adult: 50 mL

**Seizures**

**CONVULSIVE (INCLUDING FEBRILE) SEIZURES LASTING LONGER THAN 5 MINUTES**

**EITHER** Diazepam rectal solution p. 321 (2 mg/mL, 4 mg/mL)
*BY RECTUM*
- Neonate: 1.25–2.5 mg, repeated once after 10–15 minutes if necessary
- Child 1 month-1 year: 5 mg, repeated once after 10–15 minutes if necessary
- Child 1-4 years: 5 mg
- Child 5–9 years: 7.5 mg
- Child 10–17 years: 10 mg
- Adult: 10 mg [unlicensed]

**OR** Midazolam oromucosal solution p. 318
*BY BUCCAL ADMINISTRATION, REPEATED ONCE AFTER 10 MINUTES IF NECESSARY*
- Neonate: 300 micrograms/kg [unlicensed]
- Child 1-2 months: 300 micrograms/kg [max. 2.5 mg] [unlicensed]
- Child 3 months–11 months: 2.5 mg
- Child 1-4 years: 5 mg
- Child 5–9 years: 7.5 mg
- Child 10–17 years: 10 mg
- Adult: 10 mg [unlicensed]
Approximate Conversions and Units

**Conversion of pounds to kilograms**

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<tr>
<th>lb</th>
<th>kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
</tr>
<tr>
<td>3</td>
<td>1.36</td>
</tr>
<tr>
<td>4</td>
<td>1.81</td>
</tr>
<tr>
<td>5</td>
<td>2.27</td>
</tr>
<tr>
<td>6</td>
<td>2.72</td>
</tr>
<tr>
<td>7</td>
<td>3.18</td>
</tr>
<tr>
<td>8</td>
<td>3.63</td>
</tr>
<tr>
<td>9</td>
<td>4.08</td>
</tr>
<tr>
<td>10</td>
<td>4.54</td>
</tr>
<tr>
<td>11</td>
<td>4.99</td>
</tr>
<tr>
<td>12</td>
<td>5.44</td>
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<tr>
<td>13</td>
<td>5.90</td>
</tr>
<tr>
<td>14</td>
<td>6.35</td>
</tr>
</tbody>
</table>

**Conversion of stones to kilograms**

<table>
<thead>
<tr>
<th>stones</th>
<th>kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.35</td>
</tr>
<tr>
<td>2</td>
<td>12.70</td>
</tr>
<tr>
<td>3</td>
<td>19.05</td>
</tr>
<tr>
<td>4</td>
<td>25.40</td>
</tr>
<tr>
<td>5</td>
<td>31.75</td>
</tr>
<tr>
<td>6</td>
<td>38.10</td>
</tr>
<tr>
<td>7</td>
<td>44.45</td>
</tr>
<tr>
<td>8</td>
<td>50.80</td>
</tr>
<tr>
<td>9</td>
<td>57.15</td>
</tr>
<tr>
<td>10</td>
<td>63.50</td>
</tr>
<tr>
<td>11</td>
<td>69.85</td>
</tr>
<tr>
<td>12</td>
<td>76.20</td>
</tr>
<tr>
<td>13</td>
<td>82.55</td>
</tr>
<tr>
<td>14</td>
<td>88.90</td>
</tr>
<tr>
<td>15</td>
<td>95.25</td>
</tr>
</tbody>
</table>

**Conversion from millilitres to fluid ounces**

<table>
<thead>
<tr>
<th>mL</th>
<th>fl oz</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1.8</td>
</tr>
<tr>
<td>100</td>
<td>3.5</td>
</tr>
<tr>
<td>150</td>
<td>5.3</td>
</tr>
<tr>
<td>200</td>
<td>7.0</td>
</tr>
<tr>
<td>500</td>
<td>17.6</td>
</tr>
<tr>
<td>1000</td>
<td>35.2</td>
</tr>
</tbody>
</table>

**Mass**

- 1 kilogram (kg) = 1000 grams (g)
- 1 gram (g) = 1000 milligrams (mg)
- 1 milligram (mg) = 1000 micrograms
- 1 microgram = 1000 nanograms
- 1 nanogram = 1000 picograms

**Volume**

- 1 litre = 1000 millilitres (mL)
- 1 millilitre (1 mL) = 1000 microlitres
- 1 pint = 568 mL

**Other units**

- 1 kilocalorie (kcal) = 4186.8 joules (J)
- 1000 kilocalories (kcal) = 4.1868 megajoules (MJ)
- 1 megajoule (MJ) = 238.8 kilocalories (kcal)
- 1 millimetre of mercury (mmHg) = 133.3 pascals (Pa)
- 1 kilopascal (kPa) = 7.5 mmHg (pressure)

**Plasma-drug concentrations**

Plasma-drug concentrations in BNF publications are expressed in mass units per litre (e.g. mg/litre). The approximate equivalent in terms of amount of substance units (e.g. micromol/litre) is given in brackets.

**Prescribing for children: weight, height, and gender**

The table below shows the mean values for weight, height, and gender by age; these values have been derived from the UK-WHO growth charts 2009 and UK1990 standard centile charts, by extrapolating the 50th centile, and may be used to calculate doses in the absence of measurements. However, an individual’s weight and height might vary considerably from the values in the table and it is important to ensure that the value chosen is appropriate. In most cases the actual measurement should be obtained as soon as possible and the dose re-calculated.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-term neonate</td>
<td>3.5</td>
<td>51</td>
</tr>
<tr>
<td>1 month</td>
<td>4.3</td>
<td>55</td>
</tr>
<tr>
<td>2 months</td>
<td>5.4</td>
<td>58</td>
</tr>
<tr>
<td>3 months</td>
<td>6.1</td>
<td>61</td>
</tr>
<tr>
<td>4 months</td>
<td>6.7</td>
<td>63</td>
</tr>
<tr>
<td>6 months</td>
<td>7.6</td>
<td>67</td>
</tr>
<tr>
<td>1 year</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>3 years</td>
<td>14</td>
<td>96</td>
</tr>
<tr>
<td>5 years</td>
<td>18</td>
<td>109</td>
</tr>
<tr>
<td>7 years</td>
<td>23</td>
<td>122</td>
</tr>
<tr>
<td>10 years</td>
<td>32</td>
<td>138</td>
</tr>
<tr>
<td>12 years</td>
<td>39</td>
<td>149</td>
</tr>
<tr>
<td>14 year old boy</td>
<td>49</td>
<td>163</td>
</tr>
<tr>
<td>14 year old girl</td>
<td>50</td>
<td>159</td>
</tr>
<tr>
<td>Adult male</td>
<td>68</td>
<td>176</td>
</tr>
<tr>
<td>Adult female</td>
<td>58</td>
<td>164</td>
</tr>
</tbody>
</table>

**Length**

- 1 metre (m) = 1000 millimetres (mm)
- 1 centimetre (cm) = 10 mm
- 1 inch (in) = 25.4 mm
- 1 foot (ft) = 12 inches
- 12 inches = 304.8 mm
Recommended wording of cautionary and advisory labels

For details including Welsh Language translation see p. 1383

1. **Warning:** This medicine may make you sleepy
2. **Warning:** This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol
3. **Warning:** This medicine may make you sleepy. If this happens, do not drive or use tools or machines
4. **Warning:** Do not drink alcohol
5. **Do not take indigestion remedies 2 hours before or after you take this medicine**
6. **Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine**
7. **Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine**
8. **Warning:** Do not stop taking this medicine unless your doctor tells you to stop
9. Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop
10. **Warning:** Read the additional information given with this medicine
11. Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds
12. **Do not take anything containing aspirin while taking this medicine**
13. **Dissolve or mix with water before taking**
14. **This medicine may colour your urine. This is harmless**
15. **Caution:** flammable. Keep your body away from fire or flames after you have put on the medicine
16. **Dissolve the tablet under your tongue—do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening**
17. **Do not take more than... in 24 hours**
18. **Do not take more than... in 24 hours. Also, do not take more than... in any one week**
19. **Warning:** This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol
20. **Take with or just after food, or a meal**
21. **Take 30 to 60 minutes before food**
22. **Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food**
23. **Suck or chew this medicine**
24. **Swallow this medicine whole. Do not chew or crush**
25. **Dissolve this medicine under your tongue**
26. **Take with a full glass of water**
27. **Spread thinly on the affected skin only**
28. **Do not take more than 2 at any one time. Do not take more than 8 in 24 hours**
29. **Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well**
30. **Contains aspirin. Do not take anything else containing aspirin while taking this medicine**
Abbreviations and Symbols

Internationally recognised units and symbols are used in the BNF publications where possible.

- **ACBS**: Advisory Committee on Borderline Substances
- **ACE**: Angiotensin-converting enzyme
- **ADHD**: Attention deficit hyperactivity disorder
- **AIDS**: Acquired immunodeficiency syndrome
- **approx.**: approximately
- **AV**: atroventricular
- **AV**: atrioventricular
- **BP**: British Pharmacopoeia
- **BMI**: body mass index
- **BNP**: British National Formulary
- **BPC**: British Pharmaceutical Codex 1973 and Supplement 1976
- **BRECA**: breast cancer gene
- **CAPD**: Continuous ambulatory peritoneal dialysis
- **CD**: Continuous Dependent
- **CD2**: preparation in Schedule 2 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 8.
- **CD3**: preparation in Schedule 3 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 8.
- **CD4**: preparation in Schedule 4 (Part I) of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 8.
- **CD5**: preparation in Schedule 5 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 8.
- **CHM**: Commission on Human Medicines
- **CHMP**: Committee for Medicinal Products for Human Use
- **CNS**: central nervous system
- **CSM**: Committee on Safety of Medicines (now subsumed under Commission on Human Medicines)
- **d. c.**: direct current
- **DMARD**: Disease-modifying antirheumatic drug
- **DPF**: Dental Practitioners’ Formulary
- **e/c**: enteric-coated (termed gastro-resistant in BP)
- **EEG**: electroencephalogram
- **eGFR**: estimated glomerular filtration rate, see Prescribing in renal impairment p. 19
- **f/c**: film-coated
- **G6PD**: glucose-6-phosphate dehydrogenase
- **HIV**: Human immunodeficiency virus
- **HRT**: Hormone replacement therapy
- **i/m**: intramuscular
- **i/v**: intravenous
- **INR**: international normalised ratio
- **MAOI**: Monoamine-oxidase inhibitor
- **max.**: maximum
- **MHRA**: Medicines and Healthcare products Regulatory Agency
- **m/r**: modified-release
- **NCL**: no cautionary labels (prescription endorsement made by prescriber when recommended cautionary labels are not required)
- **NHS**: National Health Service
- **NICE**: National Institute for Health and Care Excellence
- **NPF**: Nurse Prescribers’ Formulary
- **NSAID**: Non-steroidal anti-inflammatory drug
- **NSTEMI**: non-ST-segment elevation myocardial infarction
- **PARP**: poly (ADP-ribose) polymerase
- **PGD**: patient group direction
- **PHE**: Public Health England (formerly Health Protection Agency (HPA))
- **PoM**: prescription-only medicine, see Fig. 1 How to use BNF publications
- **rINN**: Recommended International Non-proprietary Name
- **RSV**: respiratory syncytial virus
- **s/c**: sugar-coated
- **SLS**: Selected List Scheme
- **SMC**: Scottish Medicines Consortium
- **SPC**: Summary of Product Characteristics
- **SSRI**: Selective serotonin reuptake inhibitor
- **STEMI**: ST-segment elevation myocardial infarction
- **UK**: United Kingdom
- **WHO**: World Health Organization
- **GSL**: General Sales List
- **p. r. n.**: pro re nata (when required)
- **q. d.**: quater die sumendum (to be taken four times daily)
- **q. h.**: quarta hora (four times daily)
- **q. d. s.**: quatuor die sumendum (to be taken four times daily)
- **r. c.**: pre cibum (before food)
- **r. d.**: re die sumendum (to be taken three times daily)
- **r. c.**: post cibum (after food)
- **r. m.**: omni mane (every morning)
- **r. n.**: omni nocte (every night)
- **r. c.**: pro re nata (when required)
- **t. d. s.**: ter die sumendum (to be taken three times daily)
- **t. i. d.**: ter in die (three times daily)

**Latin abbreviations**

Directions should be in English without abbreviation. However, Latin abbreviations have been used when prescribing.

The following is a list of appropriate abbreviations. It should be noted that the English version is not always an exact translation.

- **a. c.**: ante cibum (before food)
- **b. d.**: bis die (twice daily)
- **o. d.**: omni die (every day)
- **o. m.**: omni mane (every morning)
- **o. n.**: omni nocte (every night)
- **p. c.**: post cibum (after food)
- **p. r. n.**: pro re nata (when required)
- **q. d. s.**: quater die sumendum (to be taken four times daily)
- **q. h.**: quarta hora (four times daily)
- **stat.**: immediately
- **t. d. s.**: ter die sumendum (to be taken three times daily)
- **t. i. d.**: ter in die (three times daily)

**E numbers**

The following is a list of common E numbers and the inactive ingredients to which they correspond.

- **E102**: Tartrazine
- **E121**: Sodium Benzoate
- **E104**: Quinoline Yellow
- **E223**: Sodium Metabisulfi te
- **E222**: Sodium Benzoate
- **E121**: Tartrazine
- **E421**: Mannitol
- **E132**: Indigo Carmine
- **E123**: Erythrosine BS
- **E322**: Lecithins
- **E127**: Erythrosine B5
- **E420**: Sorbitol
- **E223**: Sodium Metabisulfi te
- **E110**: Sunset Yellow FCF
- **E320**: Butylated Hydroxyani sole
- **E123**: Amaranth
- **E321**: Butylated Hydroxytoluene
- **E124**: Ponceau 4R
- **E322**: Lecithins
- **E127**: Erythrosine B5
- **E420**: Sorbitol
- **E422**: Glycerol
- **E171**: Titanium Dioxide
- **E901**: Beeswax (white and yellow)
- **E172**: Iron oxides, iron hydroxides
- **E1520**: Propylene Glycol